**Name of journal:** *World Journal of Gastroenterology*

**ESPS Manuscript NO: 5986**

**Columns: TOPIC HIGHLIGHT**

WJG 20th Anniversary Special Issues (5): Colorectal cancer

**Pharmacogenetics research on chemotherapy resistance in colorectal cancer from the perspective of last 20 years**

Panczyk M. Chemoresistance in colorectal cancer

Mariusz Panczyk

**Mariusz Panczyk,** Laboratory of Molecular Diagnostics and Pharmacogenomics, Department of Pharmaceutical Biochemistry, Medical University of Lodz, 90-151 Lodz, Poland

**Mariusz Panczyk,** Division of Teaching and Outcomes of Education, Faculty of Health Science, Medical University of Warsaw, 02-091 Warsaw, Poland

**Author contributions:** Panczyk M designed and wrote the manuscript.

**Correspondence to: Mariusz Panczyk, PharmD, PhD,** Division of Teaching and Outcomes of Education, Faculty of Health Science, Medical University of Warsaw, Zwirki i Wigury 61, 02-091 Warsaw, Poland. mariusz.panczyk@wum.edu.pl

**Telephone:** +48-225-720490 **Fax:** +48-225-720491

**Received:** September 28, 2013 **Revised:** January 17, 2014

**Accepted:** April 21, 2014

**Published online:**

**Abstract**

During past two decades was performed first sequencing of the human genome showing its high degree of inter-individual differentiation, as a result of works of large international research projects (Human Genome Project, the 1000 Genomes Project International HapMap Project, and Programs for Genomic Applications NHLBI-PGA). This period is also a time of intensive development of molecular biology techniques and enormous knowledge growth in biology of cancer. For clinical use in the treatment of patients with colorectal cancer (CRC) apart from fluoropyrimidines other two new cytostatic drugs were allowed: irinotecan and oxaliplatin. An intensive research into new treatment regimens and new generation of drugs used in targeted therapy has also been conducted. Last 20 years was a time of numerous *in vitro* and *in vivo* studies on molecular basis of drug resistance. Still one of the most important factors limiting effectiveness of chemotherapy is the primary and secondary resistance of cancer cells. Understanding the genetic factors and mechanisms that contribute to the lack of or low sensitivity to the tumour tissue for cytostatics is the key element in the currently developing trend of personalized medicine. Scientists hope to increase the percentage of positive treatment response in CRC patients due to practical applications of pharmacogenetics/pharmacogenomics. Over past 20 years clinical usability of different predictive markers has been tested among which only a few have confirmed a high application potential. This review is an attempt of a synthetic presentation of drug resistance in the context of CRC patient chemotherapy. Certainly, multifactorial nature and volume of the issues do not allow creation of a comprehensive study on this subject in one review.

© 2014 Baishideng Publishing Group Co., Limited. All rights reserved.

**Key words:** Pharmacogenetics; Pharmacogenomics; Drug resistance; Colorectal cancer; Chemoresistance; Individualized medicine

**Core tip:** Insufficient effectiveness of chemotherapy is still the most important factor limiting the successful treatment of patients with colorectal cancer (CRC). Drug resistance phenomenon in anticancer therapy is recognized virtually from the very beginning, since cytostatic drugs were first used in oncology practice. Intensive research on causes of low sensitivity in colorectal cancer cells on such drugs as fluoropyrimidines, irinotecan and oxaliplatin, brought a number of evidence on importance of genetic factors in phenotype conditioning of drug resistance. This review is an attempt of a synthetic presentation of drug resistance in the context of its role in chemotherapy, and the potential clinical use of different biomarkers in individualization of CRC patient treatment.

Panczyk M.Pharmacogenetics research on chemotherapy resistance in colorectal cancer from the perspective of last 20 years.*World J Gastroenterol* 2014; In press

**Available from:** URL: http://www.wjgnet.com/esps/

**DOI:** http://dx.doi.org/10.3748/wjg.v20.i0.0000

**RESEARCH ON THE EFFECTIVENESS OF CYTOTOXICANTINEOPLASTICDRUGS FOR THE TREATMENT OF COLORECTAL CANCER**

Since the beginning of the 21st century, we observe a very rapid development of high-throughput research techniques described by the term 'omics' (genomics, transcriptomics, proteomics and metabolomics). Pharmacogenomics uses advanced research techniques “omics”, which allow researchers to identify genetic basis of inter-individual differences in the pharmacodynamics and pharmacokinetics of drugs[1,2]. An important objective of this research is to search for biomarkers for predicting treatment outcomes, as well as giving the opportunity to avoid the toxic effects arising in the course of pharmacotherapy (prognostic and predictive markers)[3]. The terms of pharmacogenetics and pharmacogenomics are closely related and are often used interchangeably, although there are some historical differences between them. Today pharmacogenomics is commonly used synonymously with “individualized” or “personalized” medicine, although the latter term is often understood to stratify medical treatment by the use of genomic biomarkers rather than to treat an individual. Accordingly, the Personalized Medicine Coalition defined personalized medicine as “the application of genomic and molecular data to better target the delivery of health care, facilitate the discovery and clinical testing of new products, and help determine a person's predisposition to a particular disease or condition"[4,5].

Environmental factors such as age, sex or health condition of the patient are the classical groups of factors which affect onto the treatment results has been studied for decades. Influence of genetic factors on the response variability is far greater than sex, age, or interactions with other drugs could have. Therefore, it seems advisable to seek the basis of all abnormal body reactions in relation to the used treatment. It should also be noted that the distribution frequency of correct answers for a drug usage in a population is far from a normal distribution, that means the presence of treatment non-responders and over-responders (increased toxicity) is much more common than we have assumed so far[6]. The first studies on pharmacogenomics and colorectal cancer (CRC) outcome were conducted and published approximately 20 years ago[7]. Since then, hundreds of possible biodeterminants have been studied with many expectations. The technology, and its spread, has improved incredibly, and the importance with which this subject is regarded by many research groups throughout the world has grown relentlessly. The reproducibility of some results was, initially, promising, as also were some confirmatory clues derived from deeper biological studies, but the final step of clinical validation has remained an unmet objective for almost all putative biomarkers[8].

Treatment options in CRC have systematically advanced over the last several years with the introduction of effective chemotherapeutic and targeted drugs. But providing individual treatment with low toxicity and significant benefit is still an unsolved problem[9]. This part of review focuses on pharmacogenomic knowledge of substances routinely administrated in patients with CRC: fluoropyrimidines, irinotecan (CPT-11), and oxaliplatin (OX).

**5-FLUOROURACIL AND FLUOROPYRIMIDINES**

In 1957 Heidelberger *et al*[10] reported antitumour activity of 5-fluorouracil. Charles Heidelberger makes the synthesis of 5-FU as a result of experiments which showed the ability of tumour cells to acquire uracil for DNA synthesis[11]. 50 years after the first synthesis of 5-FU it is still a standard component of adjuvant and palliative therapy having a proven impact on survival time of patients with CRC[12]. Experimental studies have shown that 5-FU is converted to an active metabolite, FdUMP (fluorodeoxyuridine monophosphate), which is a potent inhibitor of DNA synthesis (Figure 1). FdUMP forms a ternary complex together with thymidylate synthaseenzyme (TS) and 5,10-methylenetetrahydrofolate (CH2THF) cofactor, responsible for the catalytic conversion of deoxyuridine monophosphate (dUMP) to deoxythymidine monophosphate (dTMP). dTMP is a substrate for deoxythymidine triphosphate (dTTP) necessary for the process of DNA synthesis (Figure 2). Furthermore, on the basis of fundamental and clinical research it has been proven that the addition to a exogenous therapy source of folic acid, such as leucovorin (LV) increases the degree of inhibition of TS supporting the formation of active complexes of 5-FU with the enzyme[13]. 5-FU/LV combination therapy in patients with diagnosed CRC is much more effective than monotherapy with 5-FU[14].

The purpose of individualization of therapy is to choose the most effective treatment and the optimal dosage for each patient, while minimizing toxicity and side effects of the therapy. This objective is particularly important in case of new generation of anticancer drugs which include expensive targeted therapies using antibodies such as cetuximab and bevacizumab. Much cheaper 5-FU therapy also can be individualized and selection of CRC diagnosed patients with potentially best response to the administration of 5-FU appears to be justified medically and financially. Despite the significant progress in understanding the 5-FU activity mechanisms, the identification of molecular markers potentially clinically useful in predicting 5-FU treatment efficacy is still the subject of research.

***TS***

TS is an important enzyme involved in metabolism of folic acid and catalyze of dUMP methylation to dTMP, what is a critical reaction in maintaining balance of available dNTPs (deoxynucleotides) in cells, substrates necessary for the synthesis and repair of DNA. TS is the main interaction aim of such cytostatic drugs as 5-FU, and the level of *TYMS* gene expression and TS protein is a prognostic marker in the treatment of several types of cancer. Thus, the 5-FU cell sensitivity profile may be affected by genetic variants of *TYMS* gene, expression level of *TYMS*/TS gene/ protein, and intracellular concentration of dNTP and CH2THF[15]. Expression of TS as a sensitivity determinant for fluoropyrimidines has been shown *in vitro*[16] as well as *in vivo* where intratumour TS expression level was associated with the chemosensitivity of tumour tissue exposed to 5-FU. The most important data collected during past few years indicate that TS expression varies considerably between different types of cancers and that the degree of tumour response to 5-FU treatment is inversely proportional to the measured level of intratumour mRNA and protein expression[17]. Leichman *et al*[18] as first proved that there is an inverse relationship between intratumoural *TYMS* gene expression and the degree of response to 5-FU treatment. CRC patients with low levels of *TYMS* gene expression had a significantly higher rate of response to therapy and longer survival median compared to patients with the tumour tissue indicating higher *TYMS* expression (13.6 mo *vs* 8.2 mo, *P* = 0.02)[19]. Meta-analysis of 13 clinical trials of patients with advanced CRC (total number of patients: 887 cases) carried by Popat *et al*[20] showed that patients with low TS expression have longer overall survival (OS) than patients with higher TS expression in tumour tissue. Recently there was also published a meta-analysis including 24 clinical trials with total of more than 1100 CRC patients[21]. The pooled relative risk of overall response rate (ORR) indicates that the group of lower TS expression has greater sensitivity to fluoropyrimidine-based chemotherapy than patients with high TS expression level[21]. Numerous studies were also carried out on studying different TS expression levels in tissue deriving from primary tumours and metastases[22,23]. Analyzing the two subgroups it was demonstrated that predictive TS expression levels determined in tissue derived from metastases is more pronounced than determined in primary tumours[21]. Furthermore, during the assessment of the predictive values of TS expression level, the results obtained using RT-PCR techniques are statistically more significant than those in which the expression was determined using immunohistochemistry (IHC) technique[21].

The results indicate that the low TS expression in tumours of advanced CRC patients is associated with increased individual sensitivity to 5-FU therapy[7,17,19,24-39]. Furthermore, *in vitro* studies using cell lines and tumour tissues demonstrated that 5-FU therapy contributes to the induction of TS expression[40,41]. This increase in TS expression upon 5-FU exposure seems to be a result of a negative feedback loop in which ligand-free TS binds to its own mRNA and inhibits its own translation[42]. When stably bound by FdUMP, TS can no longer bind its own mRNA and suppress translation, resulting in increased protein expression. This constitutes a potentially important resistance mechanism, as acute increases in TS would facilitate recovery of enzyme activity[41].

Although, the reason of ontogenetic variation in TS expression is still not clear, one of the main examined hypotheses is possible influence of *TYMS* gene polymorphisms onto the TS expression. As it is now known, some of the described polymorphisms affect inter-individual differences in patient sensitivity to 5-FU treatment (Figure 3 and Table 1)[43-52]. Polymorphism of variable number of tandem repetition (VNTR) located in *TYMS* gene sequence is one of the studied genetic variants that may have clinical relevance as a predictive marker for the effectiveness of 5-FU treatment. Horie *et al*[53] reported 28-nucleotide sequence in 5'-region of the *TYMS* gene, which occurs in the population with a variable number of iterations: two (2R) or three (3R). According to the classification proposed by Kawakami and Watanabe, it is assumed that VNTR in this region is responsible for the occurrence of two alleles, 2R and 3R, and three different genotypes (2R/2R, 2R/3R and 3R/3R)[54]. The results of various studies suggest that the 3R allele is responsible for four times higher mRNA level of *TYMS* gene marked in tissue tumours obtained from patients with metastatic CRC compared to patients who are carriers of the 2R variant (*P* < 0.004)[55]. Homozygous patients having both alleles with a double repeat (2R/2R) show significantly higher percentage of favourable response to 5-FU treatment as compared to those who have 3R/3R genotype (50% *vs* 9%, *P* = 0.04)[55]. In addition to the predictive values for 5-FU chemotherapy, in retrospective studies demonstrated that this polymorphism also has properties of toxicity marker for fluoropyrimidine-based chemotherapy. Patients who are carriers of the 3R/3R genotype exhibited reduced toxicity as compared to patients with 2R variant. A high TS expression level related to the presence of 3R/3R genotype accounts for less effective inhibition of TS, which contributes to both increased likelihood of survival of cancer cells (drug resistance), but also to reduced loss of healthy cells and less toxic therapy[55]. Moreover, a single nucleotide polymorphism (SNP) of a guanine instead of a cytosine (G/C) in 3R determines two different alleles (3C or 3G)[55]. Based on the presence of this polymorphism two different groups of patients can be distinguished with two levels of TS expression: a high expression group with (2R/3G, 3C/3G and 3G/3G genotypes carriers) and low expression group (2R/2R, 2R/3C and 3C/3C genotypes). Taking into account the study results published by Mandola *et al*[56], it is believed that the presence of the 28-bp G>C SNP within the second repeat of the 3R allele *TYMS* promoter enhancer region (TSER) tandem repeats is associated with a weaker bond in the promoter region of USF-1 transcription factor leading to a decreased transcriptional activity of *TYMS* gene. A lower transcription rate of the TSER 3RC allele *in vitro* is also observable upon comparison with TSER 3RG, comparable with the TSER 2R/2R genotype[56,57]. These results may at least partly explain why some patients with 3R/3R genotype have low TS expression and a good response to 5-FU chemotherapy.

The third described polymorphism is an insertion/deletion of hexanucleotide TTAAAG sequence at 1494 position on the 3'-UTR (1494del6)[58]. This polymorphism may contribute to stability changes of secondary mRNA structure as it has been demonstrated for alterations of the 3'-region in other genes[59]. Ulrich *et al*[58] analysed the mRNA expression level of *TYMS* gene in 43 patients and showed that homozygous patients with 6-dp deletion were three times lower level of steady-state TS mRNA compared with patients who were homozygous for the 6-bp insertion alleles (*P* = 0.017). Furthermore, it was shown that homozygous patients with deletion (del/del) had significantly lower mRNA levels for *TYMS* gene which was also associated with greater sensitivity to 5-FU based therapy as compared to homozygous patients with (ins/ins) insertion (*P* = 0.017)[57,60]. There is a need for further analyses allowing identification of *TYMS* transcription regulatory mechanisms including role played by combinations of different genetic variants, such as polymorphisms, SNPs and VTNR in *TYMS*/TS expression variability in population.

A major limitation of correlational research on pharmacogenetic importance of polymorphisms and *TYMS*/TS expression is an increasing proportion of patients who are treated with combined therapy, for which 5-FU is not the only component in the chemotherapy. Therefore, it is often difficult to determine whether the observed greater sensitivity in a small number of patients to a treatment is associated with the presence of genetic determinants (*e.g.,* 2R/2R homozygous status, 6 bp– /6 bp– 3’‑UTR, allele G of the G>C SNP) or is it a result of drugs other than 5-FU used in combination therapy[50].

***Methylenetetrahydrofolate reductase***

Usage of folic acid in combination with 5-FU is a standard in the treatment of advanced CRC for more than 30 years[61]. Intracellular metabolic balance of folic acid is regulated by methylenetetrahydrofolate reductase(MTHFR), critical enzyme in the folic acid pathway catalysing irreversible conversion of CH2THF to 5-methyltetrahydrofolate (CH3THF) (Figure 2). 677C>T is one of numerous polymorphisms of gene *MTHFR* described in literature,whichmay contribute to activity changes of this enzyme. 677TT genotype responsible for about 30% reduction of enzymatic activity in respect to 677CC genotype is associated with observed *in vitro* reduced thermolability[62], which results in a decreased erythrocyte concentration of CH3THF and accumulation of CH2THF[63]. The frequency of specific genetic variants of *MTHFR* for SNP 677C>T is diversed ethnically. Analyses of Caucasian and Asian populations suggest that the prevalence of 677TT genotype oscillates from 12%-15% at a frequency of 677CT homozygotes at 50% level. Whereas, in population of African-Americans there was a very low frequency of 677TT genotype[64]. An important consequence of *MTHFR* 677T variant presence is a possibility of accumulation of CH2THF in the cells, which may have a significant effect on the pharmacological efficacy of 5-FU. This is due to the fact that the effect of 5-FU is largely dependent on the concentration of foliants. The 5-FU–5-FdUMP metabolite irreversibly forms a stable complex with TS and CH2THF. Creation this complex inhibits the activity of TS what leads to intracellular drop of dTMP concentration and finally inhibition of DNA synthesis. Increased concentration of CH2THF as a consequence of *MTHFR* 677C>T polymorphism presence may therefore contribute to changes in chemosensitivity of cancer cells exposed to 5-FU by increasing the amount and stability of CH2THF-TS-FdUMP ternary complex and thus a stronger inhibition of DNA synthesis. Sohn *et al*[65] *in vitro* and *in vivo* studies observed that the presence of 677T allele of *MTHFR* gene is responsible for greater chemosensitivity in colon cancer cells, this suggests that the genetic variant 677C>T may be a pharmacogenetic factor used to assess the effectiveness of 5-FU based chemotherapy. However, clinical studies published in recent years lead to contradictory and inconsistent conclusions[64]. In advanced CRC patient group undergoing 5-FU based therapy, in three published studies the presence of 677T variant of *MTHFR* gene was associated with a higher percentage of positive responses[66-68], while the results of another study did not confirm the existence of such a relationship (Table 1)[69].

Another frequent polymorphism of *MTHFR* gene is SNP 1298A>C, which results in substitution of glutamine amino acid by alanine an in enzyme protein sequence[70,71]. Similar to SNP 677C>T, 1298A>C polymorphism contributes to the reduction of enzymatic activity of MTHFR but has no connection with the thermolabile proteins. Observed frequency of mutated 1298C allele is approximately 33%[70,71]. Some of the published studies on SNP 1298A>C suggest that the presence of 1298C variant of *MTHFR* gene has no impact on the percentage of positive responses to 5-FU treatment[68,69,72], while two studies suggest that it is associated with significantly decreased patient survival time[67,73]. So contrary conclusions concerning both polymorphic variants of 677C>T and 1298A>C of *MTHFR* gene call into question their practical application as response predictors to 5-FU based therapy[74]. However, recent reports suggest that the simultaneous assessment of several markers, such as *MTHFR* 1298A>C and *TYMS* 3'UTR ins/del polymorphisms makes it possible to obtain accurate assessment to predict toxic effects of 5-FU treatment in CRC treated patients[75]. Large-scale and well-planned clinical trials are necessary to determine if practical application of *MTHFR* 677C>T and 1298>C gene polymorphisms would be possible to predict treatment efficacy. It is also necessary to assess whether these SNPs may be used as prognostic markers for use in patients undergoing CRC treatment based on 5-FU.

***Dihydropyrimidine dehydrogenase***

5-FU as prodrug, in order to achieve its intracellular cytotoxic activity, requires metabolic activation (with over 80% of the administered dose of 5-FU degrading rapidly)[76]. Considering 5-FU metabolic pathways in cells, it seems important to conduct pharmacogenetic analysis of molecular factors that are associated with biotransformation of the drug. Inter-individual variability in the response of patients to 5-FU treatment may in fact be associated with a activity decrease of enzymes responsible for the catabolism, which will result in an increase in drug concentration and longer half-life, and thus an increased risk of serious toxic influence[77]. Dihydropyrimidine dehydrogenase (DPD) is acting as a regulatory enzyme in 5-FU catabolic pathway responsible for conversion of 5-FU to 5-fluorodihydrouracil (5-FUH2). After this conversion, 5-FUH2 is further metabolized to its final metabolite 5-fluoro-β-alanine, which is excreted in the urine (Figure 1)[78].

Partial DPD activity deficiency in general population is about 5%, and its total loss is very rare, about 0.2%[79]. Partial or total loss of DPD activity may be associated with the presence of genetic determinants influencing the function of *DPYD* gene including SNPs[80], deletion mutations[81,82] and methylation[83]. DPD deficit was first described in the autosomal recessive conditioned disease in patients with various neurological symptoms and an accumulation of uracil and thymine in the urine[84]. In recent years, several research groups have investigated the genetic variations present in *DPYD* gene, and DPD expression levels in tumour cells with respect to their use as a predictive marker for predicting both the effectiveness and toxicity of 5-FU treatment[85]. So far, more than 15000 genetic polymorphisms have been recorded in NCBI dbSNP in the coding, intronic and untranslated 3´ and 5´ regions of *DPYD*. Conditions resulting in a mutant *DPYD* allele include base substitutions, splicing deficits and frameshift mutations[85-87]. Taking into account the effect of catabolic processes on the pharmacokinetics of 5-FU and toxicity resulting from dosage, patients with low DPD activity are at an increased risk of serious or even fatal side effects when using standard 5-FU dose. Also, case reports of severe and fatal toxicity in patients with marked low DPD activity and treated with capecitabine suggest that DPD deficiency increases the risk of toxicity after application of 5-FU in oral form[88].

Meinsma *et al*[89] described molecular basis of observed DPD activity deficiency by testing the phenotype and genotype of patients with no DPD activity. Among analysed cases, there was no 165 nucleotide fragment of mRNA sequence as a result of ejection of one of the exons, moreover, no enzyme DPD protein was detected in these patients[89]. Wei *et al*[90] identified a heterozygous deletion case of 165 nucleotides, which was a British cancer patient, in whom there was no partial DPD activity and who had serious toxicity following administration of 5-FU. They found that a G to A transition within the 5’ splice site of intron 14 resulted in exon skipping and an inactive *DPYD* allele (IVS14+1G>A, *DPYD\*2A*) (Figure 4)[90]. Also other rare (frequency < 0.1%) polymorphisms and mutations have been identified (85T>C, 496A>G, 1627A>G, 2194G>A, 2846G>T) as factors possibly affecting the appearance of toxic symptoms after standard 5-FU treatment (Table 1). DPD activity deficiency is observed in approximately 60% of cases occurring in patients with severe toxicity, and *DPYD\*2A* polymorphism is found in 50% of patients with 4th stage of neutropenia as a result of 5-FU treatment[91]. In total, more than 40 *DPYD* polymorphisms were described of a potential use in 5-FU treatment prediction. In addition to single polymorphism changes it has also been demonstrated that the presence of a haplotype consisting of three new intronic SNPs (IVS5+18G>A, IVS6+139G>A, IVS9-51T>G), and synonymous mutation (1236G>A) may be associated with a decrease in DPD activity[92]. Moreover, hypermethylation phenomenon of the promoter region of *DPYD* gene is described as a possible mechanism of variable DPD activity[83,93]. It is believed that only a few of the reasons listed above are responsible for drug resistance and/or toxicity of fluoropyrimidines[94].

Low DPD expression level should lead to reduced catabolism of 5-FU and therefore contribute to a more effective accumulation of the drug inside cells. On the other hand, high DPD activity in tumour tissue should be responsible for development of drug resistance by reducing cytotoxic effects of 5-FU. Also, genetic changes in functioning of other genes encoding enzymatic proteins of 5-FU metabolic pathway, such as *DPYS* (dihydropyrimidinase)[95]or *UPB1* (β-ureidopropionase)[96] may contribute to a decrease in therapy effectiveness. Furthermore, it was proved that the patients with low expression of three genes, *TYMS*, *DPYD* and thymidine phosphorylase(*TYMP*) have a significantly longer survival time compared to patients with high expression of any of these genes[17]. A similar correlation between low expression of *DPYD* gene determined using RT-PCR technique and better response to 5-FU based therapy were found in patients with advanced CRC treated with first-line therapy capecitabine[97]. On the other hand, the results of recent studies of patients with metastatic CRC treated with fluoropyrimidine suggest that this correlation is weak or there is no evidence between the expression of *DPYD* and effectiveness of chemotherapy[37,98,99]. Acquired uncertain evidence derives mostly from retrospective clinical studies suggesting that low expression of *DPYD* gene may be a sensitivity marker for tumour cells for fluoropyrimidines and thus allow us to predict the degree of response to treatment. However, currently only little good quality clinical data confirms the predictive value of *DPYD* expression determination in order to predict the efficacy of 5-FU therapy in CRC patients[94].

***TYMP***

*TYMP* is the gene encoding thymidine phosphorylase (TP), an enzyme that catalyses phosphorylation of thymidine or deoxyuridine to thymine or uracil, and thus is essential for the nucleotide salvage pathway, that recovers pyrimidine nucleosides formed during RNA or DNA degradation[100]. Several studies suggest that TP is promoter of tumour growth and metastasis by inhibition of apoptosis and induction of angiogenesis[100]. There is evidence that the level of TP expression is connected with angiogenesis, growth and progression of certain types of cancer[101]. Observed increase in TP expression in tumour tissues as compared to that occurring in normal tissues is visible inter alia in CRC disease[102]. The most of the analysed cases, high TP expression is related to aggressiveness of cancer and bad prognosis, although there are conflicting reports in this regard (Table 2)[100].

TP is involved in metabolism of 5-FU, where catalysed by TP, 5-FU is converted to 5-fluoro-2'-deoxyuridine (5-FUDR) (Figure 1). It is first stage of 5-FU activation in tumour cells consequently leading to inhibition of DNA synthesis by reducing the pool of available dTTP to the substrate of this reaction. Capecitabine, an oral form of 5-FU prodrug, is designed to reduce the gastrointestinal toxicity of 5’-deoxy-5-fluorouridine (5’DFUR) and to generate 5-FU preferentially at the tumour site[103]. 5'DFUR may be transformed in cancer cells in a reaction catalysed by TP or uridine phosphorylase[103,104]. Since TP expression is significantly higher in tumour cells, it allows targeted activation which minimizes the toxicity of such therapy[105]. In III phase of clinical trials, metastatic CRC patients who were treated with capecitabine monotherapy had a significantly lower incidence of toxic effects in comparison to patients treated with 5FU/LV[106]. Moreover, since the enzymatic activity of TP is essential to obtain an adequate level of concentration of an active form of capecitabine, it may be a useful marker for predicting the effectiveness of chemotherapy using this drug[98].

Soong *et al*[107] published a study on the relationship between the expression level of TP (determined by microarrays and immunohistochemistry) and survival time of 945 CRC patients treated with 5-FU. The results of this study suggest that the low level of TP expression may be associated with improved treatment outcomes observed, and so that it may be a good predictive marker for response to 5-FU chemotherapy[107]. Also, the results presented by Salonga *et al*[17] confirm the link between low TP expression and a positive response to 5-FU. However, results different from the above were obtained Meropol *et al*[98]. Patients with metastatic CRC treated with combination therapy using CPT-11 plus capecitabine (CAPIRI) and were subjected an assessment for TP protein expression in primary tumour tissues and metastases. Positive results of TP expression confirmed by IHC technique were associated with a statistically significantly longer time to progression (TTP) in comparison with those cases in which a low level of TP expression was found (8.7 mo *vs* 6.0 mo). Conversely, neither TS nor DPD, both enzymes that have been previously shown to correlate with resistance to 5-FU, were able to predict response to CAPIRI[98,108]. Presumably, the cells with higher expression of TP may exhibit an increased sensitivity to 5-FU, due to the increase in FdUMP concentration, which is the result of increased 5-FU activation. On the other hand, low TS expression may lead to serious DNA damages. Since cancer cells are characterized by a higher degree of proliferation compared to normal cells, a low TS expression in tumour tissue may lead to a decrease of the dUMP substrate necessary for DNA synthesis, which would inhibit its replication and proliferation. Therefore, the low level of TS expression in tumour cells is associated with less aggressive course of the disease and a more favourable prognosis for a patient. Concluding, low level of TS expression may indicate a prognostic factor rather than a predictor of fluoropyrimidines effectiveness[108,109]. However, the prognostic value of TS expression was not observed in one of the largest retrospective studies[110], what may rise questions whether further retrospective analysis can provide useful data to confirm the clinical significance of this marker. As highlighted in the meta-analysis by Popat *et al*[20], large methodological differences of individual primary studies make it difficult to place decisive conclusions. The results of this analysis showed that patients in whose tumour tissue a high level of expression of TS was observed have worse OS compared the group of patients with low level of expression. However, as emphasized by the authors of the meta-analysis, the heterogeneity of the studies and a possible publication bias to not allow a straightforward conclusion[20].

***Uridine monophosphate synthetase***

In mammalian cells, the last step of pyrimidine nucleotide synthesis involves the conversion of orotate to uridine monophosphate (UMP) and is catalysed by UMP synthase (UMPS). This bifunctional enzyme has 2 sequential activities, orotate phosphoribosyltransferase (OPRT) and orotidine-5-monophosphate decarboxylase (ODC)[111]. Protein product of *UMPS* gene isOPRT enzyme, which catalyses the conversion of 5-FU into FUMP, a common substrate for the production of 5-fluorouridine triphosphate and dUTP, two cytotoxic metabolites that target RNA and DNA, respectively. Muhal *et al*[112] showed that in the anabolic pathway of 5-FU, *UMPS* is the only gene that rounds out a manifestation of the phenotype of resistance to 5-FU. Furthermore, the high OPRT enzyme activity or increased expression of mRNA for *UMPS* gene is associated with longer survival times, suggesting that the *UMPS* may be a clinically useful marker for predicting the effectiveness of treatment with 5-FU[113-121]. In clinical *in vitro* studies carried out by Isshi *et al*[122], in which OPRT and DPD enzymatic activity was determined by radioassay in tumour tissues taken from patients diagnosed with CRC (*n* = 62) where fluorescein diacetate assay (FDA) or histoculture drug response assay (HDRA) were used to determine the chemosensitivity in relation to 5-FU. The chemosensitivity test proved positive in 60% of the specimens with ORPT activity of 0.413 (nmol/min per mg protein) or above and 50% of those with DPD activity of 30 (pmol/min per mg protein) or below. Of the patient specimens showing OPRT activity of 0.413 or above and DPD activity of 30 or below, 88.9% were positive for 5-FU sensitivity, suggesting the possibility that the combination of these two levels may be predictive of 5-FU positive sensitivity[122]. Tokunaga *et al*[116] indicated that high OPRT (IHC) expression marked in patients in the II-IV stage of CRC is associated with a longer OS what has not been confirmed in a study using RT-PCR technique in a smaller study group[37]. A prognostic value of *UMPS*/OPRT expression in both tumour and stromal cells but each with an opposite effect on outcome was an unexpected finding in a retrospective analysis of a large trial[110].

There are several described SNPs located in *UMPS*[123-126], among others: 286A>G (Arg96Gly), 1285G>C (Gly429Arg), 326T>G (Val109Gly), 638G>C (Gly213Ala). Kitajima *et al*[123] analysed the effects of several SNPs gene *UMPS* (638G>C, 1050T>A, 1336A>G) on the sensitivity to 5-FU in a group of 31 patients with CRC. They found no relationship between the effectiveness of treatment with 5-FU and frequency of any of the genetic variants among respondents[123]. In clinical *in vitro* trials it has been shown that functional polymorphisms, Gly213Ala (638G>C) substitution, contributes to an increase in enzymatic OPRT activity[127]. With reference to the above results, *in vivo* studies showed that patients with substitution of 213Ala in OPRT protein sequence, after exposure to 5-FU, experience much more severe symptoms of toxicity[124] such as grade 3 diarrhoea (*P* = 0.031) and grade 2-3 anorexia (*P* = 0.035)[125]. The probable mechanism of gastrointestinal toxicity is related to the incorporation of 5-FU into RNA (F-RNA), but not with inhibition of the biosynthesis of dTMP by conversion of 5-FU to FdUMP[128]. Therefore, when 5-FU/LV administration at a higher OPRT enzymatic activity (especially with the homozygous genotype 638CC) significantly increases the level of F-RNA in enterocytes, which may increase the likelihood of severe diarrhoea[125].

There are still many unknown factors that may participate along with SNPs gene *UMPS* in chemosensitivity or mechanisms of resistance to 5-FU, what makes it necessary to analyse other regions of the gene including the promoter and regulatory region. No confirmed reliable test data from *in vivo* studies on the correlation between expression of *UMPS*/OPRT and the effectiveness of treatment with 5-FU, makes it now impossible to determine the potential clinical value of this marker.

***Other potential factors***

Described a total of 20 polymorphic variants and 20 haplotype systems of *CYP2A6* gene,whichencode P-450 cytochrome isoenzyme involved in metabolic activation of tegafur (UFT). Based on the results obtained from genotype/haplotype-phenotype association tests, Wang *et al*[129] showed that the variant *CYP2A6\*4* is the main determinant contributing to the reduction of formed 5-FU with UFT, also presence of the allele is also affecting a level decrease of *CYP2A6* gene expression*.* A different correlation was observed in case of 14 haplotype (a novel *CYP2A6\*1B* alleles), which was associated with an increase in UTF microsomal activation to 5-FU, and the presence of the haplotype contributed to increased expression of *CYP2A6*. The authors speculate that the phenotype of increased metabolic activity of CYP2A6may be the result of the sum of three different variants (22C>T, 1620T>C and a gene conversion in the 3'-UTR) included in this haplotype. Wang *et al*[129] conclude that variants *CYP2A6\*4* and *CYP2A6\*1B* are major genetic factors responsible for inter-individual variation of UTF activation degree to 5-FU.

Microsatellite instability (MSI) is common in many types of tumours and is observed in 10%-14% of sporadic CRC. The MSI phenomenon is caused by mutations located in mismatch repair (MMR) genes, this group of genes are *hMSH2*, *hMLH1* and *hMSH6*. Protein products of these genes are responsible for the repair of DNA damage caused during the replication process. It is believed that the MMR deficiency operation is one of the possible causes of resistance to fluoropyrimidines[130]. Meyers *et al*[131] said that the restoration of a functional protein MLH1 in MMR-deficient human colon cancer cell line contributes to increased sensitivity to 5-FU, which suggests that MMR deficiency in cells may be associated with resistance to 5-FU. Probably, MMR deficiency in cancer cells contributes to increased tolerance for the presence of DNA damage occurring as a result of replication errors, instead of undergoing cell cycle arrest or death[132]. The results of several studies suggest that the presence of MMR deficit in tumour cells is associated with chemosensitivity to 5-FU based therapy[133]. Most of these studies concluded low sensitivity to 5-FU in the case of MMR deficiency, which was confirmed by a recent pooled reanalysis of randomized trials[134]. On the other hand, among patients with II and III stage of CRC, prolonged survival time in cases with high MSI was detected[133,135,136]. In addition, comparing the group of MSI patients with patients diagnosed with microsatellite stable it was found that MSI prolongs disease-free time but is not beneficial in 5-FU adjuvant chemotherapy[137]. Furthermore, it was found that in most of these cases, where the tumours showed positive results in the MSI, the expression was observed wild type p53[138] which is an important determinant of 5-FU sensitivity.

The tumour suppressor protein p53 plays a key role in the control of cell cycle progression and cell death[139]. It is estimated that in about 50% of cases of various types of tumours can be seen a number of mutations in *P53* gene which encodes the p53[140]. p53 is responsible for cell cycle arrest and directing cells to apoptotic pathway in a situation when there is a risk of sustaining integrity of the genome what should prevent the transfer of damaged DNA into daughter cells. Longley *et al*[41] have demonstrated that p53 and p53-target genes are activated in response to RNA-directed 5-FU cytotoxicity. Moreover, *in vitro* test results indicate that the loss of p53 functionality contributes to reducing chemosensitivity of cells to 5-FU[41,141]. Studies on expression have also shown that overexpression of p53 is correlated with resistance to 5-FU based chemotherapy[136,142,143] although there is no conformity with the results obtained by other researchers[35]. Impact of the presence of specific mutations of *P53* gene was also described, what may contribute to transformation and drug resistance[144]. Indeed, Pugacheva *et al*[145] suggested that certain p53 mutants may increase dUTPase expression, resulting in 5-FU resistance. So, 5-FU chemosensitivity may be dependent on the particular *TP53* genotype.

**IRINOTECAN**

7-ethyl-10-[4-(1-piperidino)-1-piperidino] carbonyloxycamptothecin (CPT-11) is a synthetic analogue of a naturally occurring alkaloid, camptothecin. CPT-11 was first approved for clinical use in Japan in 1994 for the treatment of small-cell lung cancer and hematologic malignancies, and then in 1995 in France in the treatment of advanced CRC. Finally, in 1996, CPT-11 has been approved by the US Food and Drug Administration (FDA) and approved for use in the treatment of CRC in 1998. Currently, CPT-11 is mainly used in CRC diagnosed patients with metastases, with recorded relapse or progression after application of standard 5-FU based therapy[146].

In preclinical screening tests using HST-1 human squamous carcinoma cell line, SN-38, which is an active CPT-11 metabolite, exhibited the ability to increase the antitumour effect of such cytostatics as cisplatin, mitomycin C, 5-FU, and etoposide[147]. In *vitro* tests using colon and hepatocellular carcinoma cell lines it was also observed that the SN-38 has a greater cytotoxic activity compared to cisplatin, mitomycin C, doxorubicin and 5-FU[148]. The *in vivo* tests showed that the positive response rate to CPT-11 monotherapy ranges from 17% to 27% of cases[149]. The effectiveness of CPT-11 based treatment is observed in both the group of patients for which this is the first application of the treatment as well as in case of patients for whom 5-FU therapy was found to be ineffective[150]. The clinical application of a combination of CPT-11 with 5-FU/LV (FOLFIRI) resulted in a significant percentage increase of positive responses and prolonged time to tumour progression and survival. Efficacy was demonstrated both in chemotherapy-naive patients and those who progressed after 5-FU-based chemotherapy when compared with 5-FU/LV alone[151].

Tumour-specific somatic mutations and abnormal gene expression as well as germline genetic variations have been reported to be associated with CPT-11 therapeutic efficacy and toxicity. However, the available studies do not provide unequivocal confirmation that somatic mutations have a significant impact on the outcome of CPT-11 treatment, what prevents their usage as predictive markers. Generally, the genetic variations may influence both the pharmacokinetics and pharmacodynamics of CPT-11[152-154]. Taking into account the results of previous preclinical and clinical tests, resistance phenotype to CPT-11 may be associated with three different mechanisms: (1) insufficient intra-tumour degree of SN-38 accumulation (determined by pharmacokinetic factors); (2) a change in TOPI activity that decreases levels of the SN-38-Topo I-DNA complex (pharmacodynamic factors); and (3) alterations in the events downstream from the ternary complex, for example, apoptosis, cell cycle regulation, checkpoints, and DNA repair (pharmacodynamic factors)[155,156].

***Carboxylesterase***

Hydrolysis of the bulky dipiperidino moiety of CPT-11 produces the active metabolite SN-38. The enzyme responsible of these reactions have been identified as human carboxylesterases CES1, CES2 (Figure 5) and recently described isoenzyme CES3. However, CES3 catalytic activity is low and therefore not likely to play a significant role in the metabolism of CPT-11. Several studies indicated that CES2 isoenzyme plays a major role in CPT-11 and SN-38 hydrolysis[157].

Resequencing of *CES1* and *CES2* allowed the identification of SNPs and haplotype structure of these genes[158-163]. Numerous SNPs and haplotypes have been described in several populations: Europeans, Africans, and Asian-Americans[163]. Charasson *et al*[158] studied 115 cases (Caucasian population) for sequence analysis of all 12 exons of *CES2* gene and 5 'and 3' untranslated regions, and identified 11 SNPs. One of these SNP located at position 830 of gene (830C>G) is associated with a decrease in *CES2* expression, what has been reported in 60 cases in the North American population[158]. CPT-11 intra-tumour activation process is partially explained as some authors provide experimental data indicating the level of CES2 activity may be a predictor of CPT-11 toxicity[164], while others failed to detect CES2 activity in cultured cells[165].

Kim *et al*[166] found 12 new SNPs located in *CES2* gene sequence including the nonsynonymous SNPs 100C>T (Arg34Trp) and the SNP at the splice acceptor site of intron 8 (IVS8-2A>G). *In vitro* test results regarding functional characterization of these SNPs, as well as additional nonsynonymous SNP 424G>A (Val142Met), suggest that the presence of 34Trp and 142Met variants is responsible for the loss of enzyme activity, and IVS8-2G allele associated with a significant reduction in metabolic activity of CES2[166]. Kim *et al*[161], studying Japanese population, based on linkage analysis of 21 polymorphisms of *CES2* gene, identified a panel comprising of a number of haplotypes and found that some rare in population haplotypes including nonsynonymous SNPs may contribute to the reduction of enzyme activity. Furthermore, Kim *et al*[161] found that patients who are carriers of nonsynonymous SNPs, 100C>T (Arg34Trp) or 1A>T (Met1Leu) have a significantly reduced ratio of (SN-38 + SN-38G)/CPT-11 AUC (area under the plasma concentration curve). *In vitro* test results regarding functional analysis of these SNPs allowed determining their impact on the efficiency of translation and transcription of *CES2* gene. It has been shown that the presence of 1A>T genetic variant does not affect the transcriptional activity of the gene, but it is important for the efficiency of translation course[161]. These observations are the starting point for further research into *CES2*/CES2 pharmacogenetics, the results of which can be used in future to individualize dosing of CPT-11 and other prodrugs activated by carboxylesterases.

Carboxylesterase hydrolyze CPT-11 to SN-38 primarily in the liver, but also in plasma and the gastrointestinal tract. It was found that *CES1* gene is highly expressed in a liver, which is the main organ responsible for the metabolic activation of CPT-11. It is likely that the genetic variants of *CES1* can affect the concentration of CPT-11 metabolites in plasma. However, the clinical relevance of genetic determinants *CES1* the pharmacokinetics/pharmacodynamics of CPT-11 is not fully understood. Functional human *CES1* genes include *CES1A1* and *CES1A2* are inversely located on chromosome 16q. In addition to structural variations of the *CES1* gene family, several SNPs and small deletion/insertion variants were found. The influence of -816C variant located in *CES1A2* promoter region on increased transcriptional activity of *CES1A2* gene was described. Furthermore, Tanimoto *et al*[167] showed that the mRNA expression level of *CES1A2* gene is related to the sensitivity of tumour cells to CPT-11. Besides, it was found that the polymorphism –816A>C is coupled to several other SNPs (–62T>C, –47G>C, –46G>T, –41C>G, –40A>G, –37G>C, –34del/G and –32G>T) located in the proximal promoter region, which is associated with increased transcription of *CES1A2,* because in this area are bound transcription factors such as Sp1. Results of Tanimoto *et al*[168] studies suggest that genetic variants *CES1A* may affect the dose-dependent antitumour activity of CPT-11.

In conclusion, there are certain conditions relating to the impact of polymorphisms located in *CES1/CES2* genes on metabolism of CPT-11, which, if they are confirmed in large clinical trials, in the future may allow setting of individual regimen of CPT-11 in patients with cancer (Table 3).

***UDP-glycosyltransferase 1 family***

SN-38 is glucuronidated, mainly in the liver, to SN-38 glucuronide (SN-38G) by the uridine diphosphate glucuronosyltransferase enzymes (UGTs), primarily the *UDP-*glycosyltransferase 1 family (UGT1As) isoenzyme. SN-38G metabolite is excreted into the bile and urine, where it can be removed from the body. However, rehydrolysis of SN-38G to SN-38, which can take place in digestive tract under the influence of bacterial β-glucuronidase, can cause acute diarrhoea observed during treatment with CPT-11[169].

UGTs are one of the most important classes of enzyme proteins participating in the coupling reaction II phase of xenobiotic metabolism. Currently there are described 17 human UGTs isoenzymes that have been assigned to one of two families identified as UGT1 and UGT2, which are further subdivided on the basis of similarity in amino acid sequence into UGT1A, UGT2A and UGT2B subfamilies. Members of the UGT1 family are encoded by the *UGT1A* locus on chromosome 2q37, which contains 13 first exons, each having its own promoter and enhancer regions, which are spliced to identical exons 2-5 (Figure 6). UGT1A1 isoenzyme is responsible in humans for bilirubin conjugation with glucuronic acid, and some genetic variants located in *UGT1A1* gene are associated with the development of hyperbilirubinemic syndromes. These diseases, including Gilbert's syndrome and Crigler-Najjar syndrome type I and II, are most often described in cases with no or low activity of UGT1A1 as a result of polymorphisms in the sequence of promoter or coding region[170-172]. Two other isoenzymes, namely the liver UGT1A9 and extrahepatic UGT1A7 are considered important in SN-38 enzymatic inactivation process. Several research groups have tested *in vitro* the impact of genetic variation *UGT1A1*, *UGT1A7* and *UGT1A9* on the level of SN-38 glucuronidation[173,174]. Among the frequently occurring genetic variants in *UGT1A* gene locus 100 SNPs were described, which are located both in the promoter region as well as the coding sequence of *UGT1A* gene, many of these polymorphisms remains in linkage disequilibrium to the other alleles[175]. Determining the possible clinical consequences of these functional changes is being studied, and has been fairly well documented for some of the identified alleles. A number of studies *in vivo* were aimed to determine the effect of different *UGT1A* genotypes on the pharmacokinetics and toxicity of CPT-11[176-183].

One of the best known *UGT1A1* polymorphisms is VNTR concerning number of repetitions of dinucleotide part of TA (A(TA)nTAA, *n* = 5-8), which is located in TATA sequence of promoter region. The wild-type allele contains six repeats (TA)6 (*UGT1A1\*1*), which are located between position -53 and -42 of the translational start codon. While the (TA)7 (*UGT1A1\*28*), often quoted variant in the Gilbert's syndrome[172], in the *in vitro* study is responsible for a 63% reduction in translational activity compared to wild-type alleles[184]. Other variations such as (TA)5 (*UGT1A1\*36*), and (TA)8 (*UGT1A1\*37*) respectively, contribute to the growth and reduction of transcriptional activity, as observed *in vitro* studies (Figure 6). Iyer *et al*[185] found that human hepatic tissue homozygous for the (TA)7/(TA)7 polymorphism and tissue heterozygous for the (TA)6/(TA)7 genotype had a significantly decreased rate of glucuronidation of SN-38 and bilirubin compared with tissue with the reference sequence allele ((TA)6/(TA)6). SN-38 glucuronidation decreased in the following manner: 6/6 > 6/7 > 7/7[185].

Also, Han *et al*[186] investigated the genetic variation of the *UGT1A* gene. They showed that two SNPs *UGT1A1\*6* (211G>A, Gly71Arg) and *UGT1A9\*22* are important factors influencing the metabolism of CPT-11 and the toxicity of the therapy[186]. Both studied polymorphisms affect the coupling efficiency of SN-38 with glucuronic acid what results in serious toxic effects[186]. *UGT1A1\*60* allele is related to the presence of SNP –3279T>G, and is located in the distal enhancer region (phenobarbital-responsive enhancer module (PBREM)), and is another of the genetic variants of *UGT1A1* which contributes to the reduction of gene transcription activity and an increase in bilirubin concentration in serum[187]. *UGT1A1\*27* (686C>A, Pro229Gln) is a rare nonsynonymous polymorphism in the population, *in vitro* studies have been shown its relation with a reduced level of glucuronidation SN-38, and it has been observed in patients with symptoms of the Gilbert's syndrome[174]. Another nonsynonymous variant is *UGT1A1\*7* (1456T>G, Tyr486Asp) recorded in Asian population and is associated with the Crigler-Najjar syndrome type II[170] for which also observed a decrease activity in enzyme deactivation pathway of SN-38[174].

Among the frequently occurring functional SNPs *UGT1A7* gene include: *UGT1A7\*2* (387T>G (Asn129Lys), 391C>A, (Arg131Lys)), *UGT1A7\*3* (387T>G (Asn129Lys), 391C>A, (Arg131Lys), 622C>T (Trp208Arg)), and *UGT1A7\*4* [622C>T (W208R)][188]. For these SNPs in clinical *in vitro* studies conditioned by *UGT1A7\*3* and *UGT1A7\*4*, the phenotype shows a reduced rate of glucuronic acid conjugation with SN-38[189]. In contrast to these genetic variants, a common VNTR polymorphism -118(T)9>10 (*UGT1A9\*22*), which is located in the promoter region of *UGT1A9* gene is associated with increased transcriptional activity, what has been confirmed *in vitro*[190].

First evidence from clinical trials on the role of *UGT1A1\*28* in the development of toxicity resulting from administration of CPT-11, published Ando *et al*[191]. They studied the relationship of genetic variants of *UGT1A1* with serious toxic effects (grade 4 leucopoenia and/or grade 3 or 4 diarrhoea) in the group of 118 Japanese patients undergoing CPT-11 therapy in a variety of regimens[191]. Also Innocenti *et al*[192] studying a group of 66 patients (including 50 Caucasians) treated with CPT-11 alone, demonstrated that *UGT1A1\*28* allele is an important factor in the development of grade 4 neutropenia. In this study, it was observed that the incidence of severe neutropenia are much more common in patients with genotype (TA)7/(TA)7 (50%) compared to heterozygous (TA)6/(TA)7 (12%) and homozygous (TA)6/(TA)6 (0%). Moreover, other genetic variant –3156G>A is in strong linkage with *UGT1A1\*28* and was a better predictor of toxicity than *UGT1A1\*28* polymorphism[192]. Also Marcuello *et al*[182] studied the effect of the *UGT1A1\*28* variant on the occurrence of severe toxic effects in a group of 95 cases with CRC (Caucasians) who were treated with CPT-11 containing regimens (5-FU or raltitrexed). Also in this study, the incidence of acute diarrhoea (grade 3 or 4) were significantly higher in patients who are carriers of *UGT1A1\*28* mutations (homozygous (50%) and heterozygous (33%)) in comparison to homozygotes of wild type (17%). Also, symptoms of neutropenia were more frequently noted in the homozygotes group with *UGT1A1\*28* allele, however this relationship was not statistically significant[182]. The first systematic analysis of clinical studies on the impact of *UGT1A1\*28* the effectiveness of CPT-11 therapy was published by Dias *et al*[193]. These results were generally supportive of the clinical utility of genotyping *UGT1A1\*28* prior to commencement of CPT-11 therapy in order to decrease the risk of severe neutropenia and diarrhoea through the pre-emptive dose reduction of CPT-11 for *UGT1A1\*28* homozygotes. The meta-analyses indicate that there is unlikely to be an important association between *UGT1A1* genotype and ORR with CPT-11, this does not provide direct evidence that a dose reduction for *UGT1A1\*28* homozygotes will not lead to an important reduction in ORR[193]. Hu *et al*[194] published a meta-analysis of the relationship between the presence of *UGT1A1\*28* and the incidence of neutropenia induced by CPT-11. It has been shown that the presence of *UGT1A1\*28* is associated with increased risk of developing neutropenia, not only in cases of medium or high CPT-11 dose applied, but also in patients treated with low doses of the drug. The dose-dependent manner of SN-38 glucuronidation explained why the association between *UGT1A1\*28* and neutropenia was dose dependent[194]. Also, Hu *et al*[195] published a meta-analysis of clinical studies on the relationship between the presence of the variant *UGT1A1\*28* and the risk of severe diarrhoea. Also in this case, patients who are carriers of one or two mutant alleles (genotypes (TA)7/(TA)7 or (TA)6/(TA)7) there has been an increased risk of severe diarrhoea induced by CPT-11. However, this increased risk is present only in the group of patients with high and medium drug dose[195]. All of these evidences support the assessment of *UGT1A1\*28* in routine clinical practice. FDA-approved diagnostic blood test (Invader®) is available specifically testing for the *UGT1A1\*1* (wild-type) and the *UGT1A1\*28* genotype. However, the proposed benefit of testing CRC patients for *UGT1A1* genotype is that the risk for adverse drug-related side effects (*e.g.*, severe neutropenia) among patients found to be homozygous for the *\*28* genotype can be reduced by lowering their initial and/or subsequent doses of CPT-11. The concomitant harm is that reduction in CPT-11 dosage may also reduce the effectiveness of chemotherapy in tumour suppression and long-term survival[133,196].

In recent years, several studies were published on the effects of *UGT1A* polymorphisms on the CPT-11 effectiveness in CRC cancer therapy. Marcuello *et al*[182] observed a trend to reduce the OS for patients with genotype (TA)7/(TA)7 or (TA)6/(TA)7 in a study of 95 (Caucasians) cases with metastatic CRC who underwent therapy based on CPT-11. The probable reason for poor response to the treatment, as conclude authors, was the need to reduce the dose of CPT-11 in these patients with symptoms of severe diarrhoea, and who were carriers of the mutant allele *UGT1A1\*28*. Toffoli *et al*[177] studying a group of 71 patients (Caucasian) with CRC and metastasis observed that in the homozygous group (TA)7/(TA)7 there is a higher percentage of positive responses to the treatment based on CPT-11 and longer survival time as compared to the homozygous group (TA)6/(TA)6. The authors suggested that toxicities in (TA)7/(TA)7 patients could be well-managed during the entire course of treatment without reduction of CPT-11 dosage[177]. Impact of genetic variants of *UGT1A7* was examined on the effectiveness of therapy with capecitabine/CPT-11[197]. Analysis of 66 cases of CRC (including 55 Caucasians) demonstrated that the homozygous groups *UGT1A7\*2/\*2* and *UGT1A7\*3/\*3* which show low enzymatic activity and record much less incidences of severe diarrhoea (*P* = 0.003), but also a higher percentage of positive responses to treatment (*P* = 0.013) compared with the other genotypes[197]. Also, considering the impact of another polymorphism located in the sequence *UGT1A9* (-118 (T)9>10,*UGT1A9\*22*), it was observed that the presence of genotype (T)9/(T)9 significantly reduces the toxicity (*P* = 0.002) and increases the degree of response to treatment (*P* = 0.047)[197]. These results suggest that the low activity phenotype of isoenzymes UGT1A7/1A9 conditioned by the presence of genetic variants is associated with a protective effect against the toxicity such as severe diarrhoea. The authors explain that this observation may be due to reduced excretion of SN-38G to the intestine, where it is under the influence bacterial β-glucuronidase hydrolysed to SN-38, responsible for the toxic effects such as severe diarrhoea[197,198]. This finding also raised a caution that higher intestinal levels of SN-38G can promote diarrhoea, while hepatic glucuronidation offers protection from neutropenia[197].

Cecchin *et al*[176] performed genotyping of (*UGT1A1\*28, UGT1A1\*60, UGT1A1\*93, UGT1A7\*3* and *UGT1A9\*22*) a large group of 250 CRC patients with metastatic treated with FOLFIRI regimen. In addition, the study determined the relationship of these genetic variants with an incidence frequency of severe hematologic and nonhematologic toxicity, the degree of response to therapy, and TTP and OS[176]. The results allowed to demonstrate that only the variant *UGT1A7\*3* may be a marker of severe hematologic toxicity after the application of first cycle of therapy (*P* = 0.04). In addition, *UGT1A1\*28* allele and II haplotype (all the variant alleles but no *UGT1A9\*22*) are associated with a response indicator of the therapy (*P* = 0.01), and *UGT1A1\*28* allele was also the only marker associated with TTP. The authors conclude that genetic variants near *UGT1A1\*28* may be predictors for CRC treatment patients treated with FOLFIRI[176]. Li *et al*[199] examined the impact of a polymorphic variant *UGT1A1\*28* for toxicity and the results of treatment in the group of 128 Chinese CRC patients with metastatic undergoing therapy and FOLFIRI. It was found that, although the need to reduce the dose of CPT-11 was significantly higher in patients with genotype (TA)6/(TA)6 (*P* < 0.01), it had no significant effect on the rate of response to CPT-11 therapy, PFS and OS[199].

The above reports make it difficult to draw clear conclusions weather reduced UGT1A activity conditioned by the presence of genetic variants in the gene sequence only intensifies the anti-cancer CPT-11, or gives a better response to treatment with the simultaneous frequency increase of severe toxic complications. It seems that the overall balance of the effectiveness/toxicity of the therapy depends primarily on the treatment regimen used. Moreover, the appearance of severe toxicities depends on the exposure levels of SN-38 in the tissues, but the antitumour responses can be influenced by additional factors related to properties of target tumours, such as the tumour stage, acquisition of resistant factors, and sensitivity to other chemotherapeutic agents when combined.

***CYP3A4 and CYP3A5***

CYP3A4, which is highly expressed in liver, is considered one of the major P-450 cytochrome isoenzyme involved in the metabolism of a large group of drugs. CYP3A4 and CYP3A5 responsible to CPT-11 oxidation to APC metabolite 7-ethyl-10 [4-*N*-(5-amino-pentanoicacid)-1-piperidino] carbonyloxycamptothecin and inactive NPC (7-ethyl-10(4-amino-1piperidino) carbonyloxycamptothecin) which, however, can be hydrolysed to an active form of SN-38 (Figure 5). Inter-individual variation of CYP3A4 activity may contribute to changes in the pharmacokinetics parameters of CPT-11[200-202].

Described several polymorphisms located in genes *CYP3A4* and *CYP3A5*[203-206]*.* There are different gene SNPs *CYP3A4* for which there are published frequency of genotypes and alleles occurrence in different populations. Relatively frequent SNPs are *CYP3A4\*2* (664T>C, Ser222Pro), *CYP3A4\*10* (520G>C, Asp174His), and *CYP3A4\*17* (566T>C, Phe189Ser) in Caucasians and Mexicans (2%–5%), *CYP3A4\*15* (485G>A, Arg162Gln) in African–Americans (2%–4%) and *CYP3A4\*16* (554C>G, Thr185Ser) and *CYP3A4\*18* (878T>C, Leu293Pro) in East Asians (1%–10%)[207]. Perhaps some of these genetic variants *CYP3A4* may have impact on the pharmacokinetics of CPT-11. Analysis of gene haplotypes *CYP3A4* conductedon the group of 416 cases from the Japanese population has allowed the identification of 25 haplotypes[208]. However, the influence of individual haplotypes on the pharmacokinetics parameters of CPT-11 was tested among 177 Japanese patients undergoing chemotherapy[209]. Haplotype *\*16B* which consists of polymorphisms 554C>G (Thr185Ser) and IVS10+12G>A was present only in male patients, and in this group was observed a significantly lower concentration ratio of APC/CPT-11 (*in vivo* tests activity parameter CYP3A4) than in other patients. However, no relationship was observed between the genotypes and total clearance of CPT-11, and frequency of the incidence of toxicity symptoms in the study group[209]. Despite significant individual variability[206] and occurrence of more polymorphisms within genes *CYP3A4* and *CYP3A5*, in the currently published studies there is no significant correlation between genotype CYP3A4/5 and pharmacokinetics CPT-11 or toxicity[210,211]. No significant correlation between genotypes *CYP3A4/5* and the pharmacokinetic parameters of CPT-11 may be associated with a low frequency of alleles in most described genetic variants *CYP3A* in Caucasian population (*e.g.*, *CYP3A4\*17, CYP3A4\*18, and CYP3A5\*1*), or the presence of these variants do not provide *in vivo* measurable changes in enzyme activity (*e.g.,* *CYP3A4\*1B*)[157]. In conclusion, the current research findings do not support the clinical use of *CYP3A4/5* genotyping in order to differentiate individual dose of CPT-11.

***ABC and SLC transporters***

In addition to the importance of metabolism CPT-11 is undergoing, under the influence of described above enzymes on pharmacokinetics of the drug, its own influence can also demonstrate different transporters, especially from the group ABC (ATP-binding cassette transporter superfamily). ABC transporters play an important role in the pharmacology of CPT-11[157], and are one of the major causes of observed *in vitro* and *in vivo* cancer cell resistance[212]. There is described a number of polymorphic variants of genes encoding proteins of ABC transporters and their potential impact on the transcription/expression and changes of transport activity[213]. CPT-11, SN-38 and SN-38G are transported from cells to the extracellular environment *via* ABCB1 (MDR1, multidrug resistance), ABCC1 (MRP1, multidrug resistance protein 1), ABCC2 (MRP2, multidrug resistance protein 2), ABCG2 (BCRP, breast cancer resistance protein) and SLCO1B1 (OATP1B1, organic anion-transporting polypeptide 1B1) (Figure 7)[214]. Transport proteins that export CPT-11 and its metabolites to bile and urine were examined because of their potential impact on the effectiveness of anticancer therapy, and occurrence of adverse reactions[215,216].

Studies regarding the influence of encoding by gene *ABCB1/MDR1* transport protein P-glycoprotein on CPT-11 pharmacology, give ambiguous results. More than a dozen different polymorphisms have been identified in the sequence of the gene *ABCB1*. Research evaluating the impact of SNPs on pharmacokinetics of CPT-11 typically focus on three well-known polymorphisms 1236C>T, 2677G>T/A and 3435C>T, which are together in a strong linkage disequilibrium[157]. Some studies have shown that both single genetic variants and haplotypes *ABCB1* can increase the bioavailability of CPT-11 and SN-38[210,217], while other studies lead to the opposite conclusion[216,218]. Furthermore, Korean studies found an association between the presence of wild-type *ABCB1* and the occurrence of neutropenia[218], what has not been confirmed with results of American research[216]. Similarly, the lack of correlation with the occurrence of SNPs *ABCB1* and toxicity of CTP-11 therapy were not found in French studies[179]. On the other hand, studies of Glimeliuset *et al*[219] demonstrated that patients who are carriers of the mutated allele *ABCB1* are less responsive to treatment with CPT-11. Carriers of at least one TT genotype of *ABCB1* 1236C>T, 2677G>T/A or 3435C>T were less likely to respond to treatment (OR = 0.32). A *post hoc* analysis showed that fewer patients with at least one *ABCB1* 1236T-2677T-3435T haplotype responded to treatment compared with others (43% *vs* 67%, *P* = 0.027)[219]. Given the conflicting results obtained in earlier research on the impact of genetic variants *ABCB1* the effectiveness of the CPT-11 therapy[179,210,216-218], the conclusions presented by Glimeliuset *et al*[219] need to be confirmed *in vivo* studies on a larger population.

Several *in vitro* studies have showed that ABCC1/MRP1 is involved in transport of CPT-11 and SN-38. The ABCC1 transporter is responsible for the efflux of SN-38 from the hepatocyte into the interstitial space[220]. Polymorphisms 462C>T, 1684T>C, 4002G>A, 14008G>A, 34215C>G, IVS9+8A>G, IVS30+18A>G, IVS11-48C>T and IVS18-30C>G in the *ABCC1* gene have been identified[210,216]. Two SNPs *ABCC1* 1684T>C and IVS18-30C>G are responsible for differentiated pharmacokinetic phenotype of CPT-11 as measured by the AUC values for its metabolites: APC and SN-38G/SN-38. Polymorphism 1684T>C contributes to an increase of AUC value for SN-38, and SNP IVS11-48C>T causes a decrease in AUC for APC. The positive association between *ABCC1* 1684T>C and SN-38 AUC is consistent with increased transport of SN-38 from the hepatocyte into the plasma[216]. In comparison to the available data on the role of *ABCB1* in drug resistance and bioavailability of CPT-11, the clinical significance of genetic variation of *ABCC1* is not sufficiently documented, and therefore further functional studies should be carried out to confirm these preliminary observations[216]. There is several rare variants of ABCC1, which may potentially affect transport function but low frequency of occurrence of these allele hinders unequivocal conclusions about the clinical significance in pharmacotherapy of CPT-11[221-224]. Similarly, there is insufficient evidence regarding the effect of the polymorphisms in the gene expression *ABCC1* measured with mRNA levels in lymphocytes or duodenal enterocytes[225].

*In vivo* tests on animals, it was observed that the biliary excretion of CPT-11 carboxylate and SN-38 carboxylate, and both the lactone and carboxylate forms of SN-38G was lower in ABCC2-deficient rats[226]. Moreover, there is described impact of gene polymorphisms *ABCC2/MRP2* on the bioavailability of CPT-11. Innocenti *et al*[192,227] examining a group of 64 cancer patients showed that the silent polymorphic variant 3972T>C was associated with the AUC value of the CPT-11 (*P* = 0.02), for APC (*P* < 0.0001) and for APC/CPT-11 ratio (*P* < 0.0001). Kitigawa *et al*[228] also studied the effects of gene SNPs *ABCC2*, but for the toxicity of CPT-11 therapy. However, in the studied 120 Japanese group of patients, there was no association between genetic variants 1249G>A, or –24C>T gene *ABCC2* and the incidence of severe complications after treatment with CPT-11[228].

There are many studies confirming the important role of protein ABCG2/BCRP in transport of CPT-11 and its metabolites. Numerous scientific evidence support the proposition that overexpression of *ABCG2*/ABCG2 leads to the development of drug resistance of tumour cells against drugs that are derivatives of camptothecin such as topotecan[229], CPT-11 and SN-38[230-233]. Several possible mechanisms were described that may contribute to drug resistance conditioned by activity of gene *ABCG2*, such as: demethylation of CpG islets in the *ABCG2* promoter resulting in increased gene transcription[234], gene amplification[235], and truncation at the 3’UTR of the *ABCG2* mRNA, which is associated with a loss of the miRNA-159c binding site conferring higher mRNA stability[236]. Furthermore, it has recently been demonstrated that the *ABCG2* mRNA content of liver metastatic tumour cells from CRC patients treated with CPT-11 is higher than those from CPT-11-native patients[207]. Cha *et al*[237] suggested that the present of introning SNP in gene sequence *ABCG2* (rs2622604) may contribute to changes in transport protein activity what can effect in an increase of CPT-11 concentration in cells. This may lead to an increased risk of severe myelosuppression (grades 3 and 4) in patients with such genetic variant[237]. The same research team also identified another SNP (rs3109823), which like the previous one had a strong association with severe myelosuppression[237]. Following this study, the team of Poonkuzhali *et al*[238] showed that a polymorphic variant of rs2622604 is associated with decreased expression of the *ABCG2* measured by the level of mRNA. These results support the hypothesis that patients who are carriers of rs2622604 negative variant, in liver there is low level of excretion of SN-38 to the bile which leads to the growth of intracellular concentrations of SN-38 in hepatocytes. This, in turn, contributes to the accumulation of CPT-11/SN-38 in blood and an increased risk of severe myelosuppression. On the other hand, although described by Cha *et al*[237] other SNP rs3109823 showed a stronger association with myelosuppression than the variant rs2622604, a Poonkuzhali *et al*[238] has not proved it has an effect on gene expression level *ABCG2*.

The functional *in vitro* studies on the importance of amino acid substitution in the sequence of protein ABCG2 (Gln141Lys, 421C>A) have shown that it contributes to the reduction of transport activity substrates such as mitoxantrone, topotecan, SN-38[239,240], and therefore can contribute to an increase in cell chemosensitivity[241,242]. There were also published several *in vivo* studies on the effect of this polymorphism on the pharmacokinetics of CPT-11. De Jong *et al*[243] studied a group of 85 patients diagnosed with solid tumour and chemotherapy based on CPT-11. They reported greater accumulation of SN-38 and SN-38 glucuronide in one of two homozygous carriers of the 421 variant alleles. However, the AUC of CPT-11 (*P* = 0.72) and its active metabolite SN-38 (*P* = 0.67) did not differ significantly between patients carrying the wild-type sequence and patients carrying at least one variant allele[243]. Also, the results of research published by Jada *et al*[244] confirm these findings that there is no relationship between the presence of genetic variants 421C>A gene *ABCG2*, and the change of the pharmacokinetics for SN-38. Results available of the study suggest that the probable coexistence of SNPs other than 421C>A genetic variants [*e.g.,* 34G>A (Val12Met) and 1322G>T (Ser441Asn)] gene *ABCG2* may have some clinical implications for pharmacology of CPT-11. Furthermore, additional *in vitro* and *in vivo* studies are needed to better clarify the role of the 34G>A polymorphism because this SNP is prevalent in many populations and there are many conflicting reports regarding the functional effects of this polymorphism[245]. Also conducting systematic prospective studies of well-chosen and less heterogeneous group of patients can provide more reliable evidence on the role of gene polymorphisms *ABCG2* in pharmacokinetics of CPT-11.

Organic anion-transporting polypeptide 1B1 (OATP1B1, SLCO1B1), expressed on the basolateral membrane in hepatocytes, has been reported to contribute to the hepatic uptake of SN-38[246]. SLCO1B1 transports among other CPT-11, SN-38 and SN-38G from blood to liver cells. There are described several polymorphic variants of the gene *SLCO1B1*, among them *SLCO1B1\*1b* (388A>G) and *SLCO1B1\*5* (521T>C). *In vitro* research on the haplotype *SLCO1B1\*15*, which is a combination of the SNPs, showed that it is responsible for 50% reduction in the intracellular concentration of CPT-11, which may cause intra-individual variability in the toxicity of this drug therapy[246,247]. Another pharmacokinetic study reveals that CPT-11 clearance is 3-fold reduced and systemic exposure to CPT-11 is enhanced in patients with the *SLCO1B1\*15* haplotype[248]. The literature also describes the case of a patient with severe toxic complications after application of CPT-11 treatment and the presence of the haplotype *\*15*[249]. Effect of these SNPs and haplotype *\*15* onto induction of toxicity of CPT-11 should be confirmed in further *in vivo* studies. Other studies on the toxicity of CPT-11 and its effects on different genetic factors were carried by Takane *et al*[250]. By analysing three genetic variants of *UGT1A1\*6*, *UGT1A1\*28* and *SLCO1B1\*15* a strong correlation was found between the presence of these alleles and the excessive accumulation of SN-38, which resulted in severe toxic complications observed with the use of CPT-11.

In summary, it can be stated that frequent polymorphisms in genes encoding ABC and SLC transporters can have a significant impact on the change in the pharmacokinetics and pharmacodynamics of CPT-11. However, the practical application of previously published results will require additional study *in vivo* including CRC patients.

***Topoisomerase I, DNA repair genes and cell cycle regulation***

There is substantially less knowledge about the CPT-11 pharmacodynamics, including DNA damage repair or cell death pathways, following the formation of camptothecin-TOPI-DNA complexes[251]. SN-38 is an inhibitor of topoisomerase I (TOPI) an enzyme that prevents the unfolding of DNA during transcription and replication. Scientists studying cancer cells which exhibited resistance to CPT-11, have found that a possible cause of a low sensitivity to the drug may be associated with the presence of mutations or low *TOP1* gene expression [252,253]. The impact of the presence of different genetic variants of *TOP1* gene expression was described, which can be a cause of primary drug resistance[254]. Genetic variation in the drug target of SN-38, as well as in cellular effectors responsible for DNA repair and apoptosis, a potential source of clinically observed inter-individual variability in the efficacy and toxicity of treatment based on CPT-11[255]. Knowledge of the causes of drug resistance leading to CPT-11 treatment failure, gives the opportunity to better plan treatment and to predict the effects of therapy for an individual patient. Activity of numerous genes and proteins[155,255] and mutual network of connections between various intracellular pathways are responsible for the phenotype of sensitivity to CPT-11, among these molecular factors involved in CPT-11 pharmacodynamics may be mentioned: drug target-TOPI, and cell cycle division 45-like protein (CDC45L), nuclear factor-κB (p50 subunit; NFκB1), poly(ADP-ribose) polymerase I (PARP1), tyrosyl DNA phosphodiesterase (TDP1), and X-ray cross complementation factor (XRCC1)[256-260].

XRCC1 plays a key role in base excision repair by forming a complex with DNA repair proteins including PARP1 and DNA polymerase β[261]. Hoskins *et al*[251] studied a group of 107 (European) patients with advanced CRC, treated with CPT-11. They conducted an analysis of the impact of genetic variant 1196G>A (Arg399Gln) gene *XRCC1* on the efficiency of CPT-11 therapy. They found that patients who demonstrated a favourable response to treatment are more common genotype in 1196GG variant allele than in 1196T (genotypes GA or AA) (46% *vs* 26%, *P* = 0.10). Patients homozygous for an *XRCC1* haplotype (GGCC-G) were more likely to show an objective response to therapy than other patients (83% *vs* 30%, *P* = 0.02). This effect was also confirmed in a multivariate analysis (OR = 11.9, *P* = 0.04)[251]. A possible explanation for these findings is that the presence of the allele in 1196G gene sequence *XRCC1* conditioning the presence of arginine in the protein sequence XRCC1 (399ARG) leads to weaker DNA repair capacity, as compared with 1196A (399Gln). However, these findings deriving from *in vivo* studies have no confirmation in numerous *in vitro* studies which unanimously show that the presence of glutamine in codon 399 is associated with a reduced ability to repair DNA as assessed by the persistence of DNA adducts, elevated levels of sister chromatid exchanges, increased RBC glycophorin A, *TP53* mutations, and prolonged cell cycle delay[262]. Hoskins *et al*[251] also investigated the effect of the gene variant IVS4+61 *TOP1* on the frequency of severe neutropenia (grade 3/4). The cause of the observed *in vivo* differences in the toxicity of CPT-11 therapy, the frequency of different variants of *TOP1* gene, can be related to the stability of complexes SN-38-TOPI-DNA in cells of the bone marrow, which may lead to greater sensitivity and an increased toxicity for bone marrow. Furthermore, Hoskins *et al*[251] found that patients who are carriers of the homozygous CC gene haplotype *PARP1* (with SNPs combination 852T>C - IVS19-297C>T) often suffer toxic effects of CPT-11 treatment in comparison with patients with different arrangement of alleles in this haplotype. This observation suggests that the presence of the haplotype 852C - IVS19-297C is related with decreased DNA repair capacity by PARP1 protein, leading to increased loss of bone marrow cells and symptoms of neutropenia as a result the cytotoxic effect of CPT-11[251].

*In vitro* research using colon/colorectal carcinoma cell lines, showed that there is a link between the presence of aberration of functional p53 and hypersensitivity phenotype to camptothecins[263-266], whereby some of the experimental test models showed only a moderate cellular sensitivity[267]. Moreover, HT-29 cells colon carcinoma characterized by mutations in p53 had a much higher sensitivity to CPT-11, than control cells expressing wild-type p53[268]. Also, experiments with cell clones derived from tumour tissues with evidence of impaired activity of p53 showed that apoptosis induction path is an important determinant of sensitivity to camptothecins. On the other hand, p53 is required for targeting apoptotic proteins in sensitization of colon carcinoma to TNF-related apoptosis-inducing ligand (TRAIL) pathway therapy using CPT-11[269]. Most of experimental data shows that the initiation of apoptosis resulting from exposure to camptothecins is much weaker for cells with wild-type p53 compared with mutated p53. Tomicic and Cain[270] proposed that the phenotype conditioned by wild-type p53, forming in the presence of CPT-11 complex with DNA and TOPI is easier degraded, leading to reduced transcription/replication DNA effect of camptothecins and contributes to the development of drug resistance. In cells lacking functional p53 TOP1-cc (TOP1-cleaved DNA 3′-phosphotyrosyl intermediates are referred to as cleavable complexes) is not efficiently degraded upon transcription stalling, thus TOP1-linked single-strand breaks accumulate, which may interfere with DNA replication. p53 defective cells are, due to lack of p21 expression, only transiently arrested in G2, having no time for repair of excessive camptothecin-induced replication-dependent double-strand breaks (DSB), thus undergoing mitotic cell death accompanied by apoptosis[270].

Malfunction of DSB repair mechanisms is essential for the survival of cancer cells and is one of the major reasons for these cells to avoid cytotoxic effects of camptothecins derivatives. Therefore, it seems reasonable to state that cells with compromised DSB repair mechanism may have a greater susceptibility to therapy based on camptothecins. The main paths consisting DSB repair mechanisms include homologous recombination (HR) and non-homologous end-joining (NHEJ). Mutations in genes *RAD51*, *XRCC2*, *BRCA2*, *RAD54* and *MUS81* involved in HR contribute to the hypersensitivity of exposed cells to camptothecins because the protein products of these genes are essential for proper functioning of HR pathway in S and G2 phases of the cell cycle[270]. The results indicate that DSB induced in cells by derivatives of camptothecin are repaired either by NHEJ or HR[270-272]. As HR requires replication it might even be the predominant route of defence against the killing effects of camptothecins that require replication for eliciting cytotoxicity[270]. Concluding, the decisive role in the creation of drug resistance phenotype to CPT-11 has the status of p53, the degree of degradation of TOPI complex from DNA, DSB repair by HR on stalled replication forks, and downstream pro- and anti-apoptotic, while NHEJ pathway seems to be much less important[270].

**OX**

Within the last 40 years, a few thousands of platinum derivatives have been synthesised and tested with regards to its anti-cancer activities. Among these compounds, the most interesting ones seem to be those discovered in early 70s, derivatives of 1,2-diaminocyclohexane (DACH) carrier ligand that are non-cross-resistant with cisplatin. In the last two decades, many scientists searching for new and effective cytostatic medicines, directed their research efforts towards this platinum derivative group. The interest in DACH group compounds is associated with their beneficial properties in comparison with other platinum derivatives such as cisplatin or carboplatin. Not only DACH compounds present much nephrotoxicity (as opposed to cisplatin) and myelosuppression (as opposed to carboplatin), but also higher efficiency towards cancer that proved to be resistant to treatment with cisplatin. Research results of both cell lines and *in vivo* observations prove DACH compounds efficiency in comparison with cisplatin and carboplatin, which may have certain connection with breaking inner resistance to those cytostatics. Great cytostatic activity of OX was proven during tests of several human cancer cell lines and is believed to be the most important platinum derivative from DACH group[273,274].

Combined therapy of 5-FU/LV plus OX (FOLFOX) is currently a standard in treating gastric cancer and CRC with 40% positive response ratio during the first relapse therapy[275]. Despite the efficiency of combined therapy, a high percentage of patients shows drug resistance to a higher or lower degree, which points to the fact that therapeutic efficiency of FOLFOX is characterised by a high variability. Since the approval of clinical application of OX in treatment of patients with advanced CRC in 1999 in Europe and then in 2004 in the United States, access to data concerning OX pharmacology grew significantly. In preclinical studies OX presented activity towards colon cancer cell lines characterised by primary and acquired resistance to cisplatin[132]. Also in many other experimental models with phenotype of resistance to cisplatin it was show that sensitivity/drug resistance profiles of both platinum derivatives are different[276].

Resistance to platinum compounds, as is the case with other cytotoxic compounds, is of multi-factor character and individual platinum derivatives present cross-resistance to a different degree. Generally, in majority of tests of experimental cancers, carboplatin presents cross-resistance with cisplatin, but not with OX. On the basis of numerous studies, six major cell drug resistance mechanisms towards platinum derivatives, have been identified[277,278]. Processes connected with transporting to and from cells could be listed here, as they condition lowering intracellular drug concentration. Also, the increase of drug detoxication may be of importance (*e.g.,* increase concentration sulphydril-containing molecules or activity of metabolic enzymes) or an increase in the quenching of DNA monoadducts. Lastly, in the cells presenting resistance to platinum compounds, a system of recognition and/or DNA damage repair may malfunction[279].

***Intracellular drug accumulation***

Membrane transporters and channels, collectively known as the transporters, are some of the best known factors determining chemosensitivity and drug resistance and the history of research into their significance in anticancer therapy dates back to the beginnings of the scientists’ interest in the causes of chemotherapy failure[280]. Only a small group of the known transporters have been recognised as relevant for intracellular accumulation of platinum derivatives. There is a broad review concerning membrane transporters and channels that can be found in the publications of Choi and Kim[281], Hall *et al*[282] and Liu *et al*[283].

Potential platinum uptake or influx transporters include copper transporter (CTR) proteins[284], organic cation transporters (OCTs) belonging to the SLC22 family[285] and an undefined cis-configuration specific platinum influx transporter[286]. In addition, some outward-directed drug transporters facilitating the active efflux of platinum compounds have been linked to decreased accumulation of platinum compounds and include adenosine triphosphate (ATP) binding cassette (ABC) multidrug transporters[287], copper-transporting P-type adenosine triphosphatases (ATPases) (Figure 8). Insufficient intra-tumour concentration of platinum compounds is a critical factor determining both primary and secondary resistance. Lowered inflow and/or increased activity of outward-directed cellular transport is a frequent phenomenon in the clones of chemoresistant cancer cells[280] expose to the activity of cisplatin, OX[288] and carboplatin. However, currently, it is not quite clear whether and to what degree transporters help maintain therapeutic concentration of platinum concentration in the cancer cells, thus playing a crucial (clinically relevant) role in sensitivity and cell resistance to platinum derivatives[283]. During the last 15 years, a series of clinical studies designed to establish the connection between efficiency of chemotherapy based on OX and the level of expression of membrane transporters marked both cancer cells and in healthy tissue. These studies of transporters including ATP7A, ATP7B, ABCC2, ABCG2, ABCB1, OCT2 and CTR1 are detailed below and summarized in Table 4.

First clinical studies concerning dependencies between the results of treatment with platinum compounds in cancer chemotherapy and the expression of transporter concerned the P-type copper transporting ATPases ATP7A and ATP7B. In the study of 50 patients in an advanced stage of CRC and treated with 5-FU/LV/OX (FOLFOX) a correlation was observed between resistance and the level of expression of these transporters[289]. ATP7A and ATP7B involved in the sequestration and extrusion of copper from a compartment localized within the trans-Golgi network to the plasma membrane, have also been implicated in the efflux of platinum compounds[290]. While examining their CRC patients, Martinez-Balibrea *et al*[289] showed that low expression of *ATP7B* gene measured with the level of mRNA is linked with the significantly longer TTP (*P* = 0.0009) as opposed to the group of patients with the higher level of mRNA (12.14 mo *vs* 6.43 mo) who additionally presented a greater risk of disease progression (HR = 3.56, *P* = 0.002). Furthermore, patients with both low level of mRNA and ATP7B protein noted, obtained the longest TTP and benefitted from FOLFOX therapy to the fullest, as opposed to patients with high level of mRNA and protein (14.64 *vs* 4.63 mo, respectively, *P* = 0.01)[289].

Various multidrug resistance-associated proteins (MRPs) belonging to the ABCC subfamily of ABC efflux transporters have been implicated to mediate resistance to platinum compounds[291]. Cancer cells resistant to platinum compounds are able to remove OX metabolites that are coupled with glutathione (GSH) into intracellular environment *via* ATP transport dependent on hydrolysis through biological membranes[292]. On the basis of the above mechanism, it may be assumed that GHS accessibility and effectiveness of conjunction with GHS are the key factors for the development of such resistance towards OX. Beretta *et al*[293] stated that some of the superfamily ABC transporters (ABCC1/MRP1 and ABCC4/MRP4) present a significant expression in ovarian cancer cells with secondary OX resistance. Overexpression of ABCC1 or ABCC4 in cancer cell lines derived from ovarian cancer cells was connected with resistance to cisplatin and OX. The above results prove that the development of OX resistance is induced by the activity of MRPs proteins, which may be conducive to use in patients with relapsing cancer treated previously with OX, cytostatics other than platinum derivatives that are not substrates ABCC1 or ABCC4[293]. Furthermore, in other research it was observed that administering 5-FU inhibits the expression of *ATP7B* and human organic cation transporter 2 (*OCT2*) with a simultaneous 5.8-fold increase in the level of mRNA for *ABCC2* gene(*MRP2*) coding another transporter from ABCC[294]. Theile *et al*[294] proposed as one mechanism for FOLFOX synergism the 5-FU mediated suppression of *ATP7B*, the overexpression of glutathione exporters such as *MRP2* and the decrease of glutathione levels by OX metabolite oxalate.

In the studies over another transporter from the superfamily of ABC – ABCG2/BCRP it was fund that overexpression may be a negative marker of OX therapy effectiveness[294]. Lin *et al*[295] tested the level of expression of protein ABCG2 measured with IHC method in a group of patients with CRC both in the primary and metastatic cancer tissue. They observed that the lower expression of ABCG2 is noted more frequently in a group of patients with better response to FOLFOX therapy as opposed to the group of patients with higher protein expression (63.6% *vs* 9.5%, respectively). Moreover, it was fund that in majority of cases the level of ABCG2 expression was higher in tissue derived from metastatic tissue than from primary cancerous tumours[295]. Therefore, Lin *et al*[295] conclude that ABCG2 expression is related to the response to therapy based on a combination of FOLFOX among patients with metastatic CRC and that ABCG2 may be a selective marker in predicting the effectiveness of FOLFOX.

Wu *et al*[296] evaluated the influence of SNPs of *ABCB1/MDR1* gene (1236C>T, 2677G>T/A and 3435C>T) on the results of treatment in CRC patients treated with OX-based therapy. Carriers of 1236C>T variation of *ABCB1* gene presented longer OS after the post-operation OX therapy. Additionally, carriers of 1236TT–2677TT–3435TT genotype combination presented worse PFS (*P* = 0.043) and recurrence-free survival (*P* = 0.006)[296]. On the other hand, Yue *et al*[297] showed that SNPs of *ABCB1* gene are not pharmacogenetic factors which determine prognostics for chemosensitivity towards OX-based therapy in CRC patients.

SLC22 family of transporters includes several subgroups of proteins classified on the basis of position and transporting mechanisms. The subgroup of organic cation transporters (OCTs) consists of only three members: SLC22A1 (OCT1), SLC22A2 (OCT2) and SLC22A3 (OCT3)[285]. Currently, we have a limited range of accessible data concerning the connection between genetic variations and the level of *OCT1* or *OCT2* expression in tumour tissue and the results of treatment after administering therapy based on platinum derivatives. It is, however, postulated that these transporters may be of potential clinical importance as predictive markers. In an experimental model with the use of transfected cells it was noted that the expression of *OCT1* gene significantly increases intracellular OX accumulation[298]. On the other hand, research results show that OX is an excellent substrate for *OCT2*[298,299]. Zhang *et al*[298] showed that in transfected HEK293-hOCT2 cells, amount of collected OX was 23.9-fold greater than when compared with the cells of control. Whereas in the presence of cimetidine which is an OCT2 inhibitor, amount of collected OX was significantly lowered. They also stated that in the transfected cells, the cytotoxic effect significantly increases when caused by OX as opposed to the control group[298]. It is supposed that OCT2 expression may be the factor modulating sensitivity of CRC cells to OX. It is also postulated that the level of OCT2 expression may condition drug resistance in CRC patients treated with therapy based on a scheme including platinum[298]. However, the results of the above studies are not fully fund credible as while testing OCT2 expression in tissue, it was noted that the positive result was obtained in 11 out of 20 cases of tissue samples from patients with colon cancer, while the negative effect was obtained in 4 cases of healthy tissue[300]. In contrast, all colon cancer cell lines investigated for transporter gene expression were found to lack *OCT2* mRNA expression[298,300]. Therefore it is worth stressing that if in pre-clinical studies a significant role of OCT2 was proven in mediating platinum derivatives transport[298], the results of clinical studies do not confirm this observation.

The role and significance of copper influx and transporters efflux (CTRs) in cell accumulation of platinum compounds was widely discussed in literature[284,301,302]. CTR1 is an important transporting protein that is responsible for regulating copper concentrations, ensuring biological balance of this metal’s ions concentration. Too low copper concentration leads to deactivation of enzymatic systems dependent on copper ions, whereas too high concentration is toxic for a cell[303]. Holzer *et al*[304] put forward a thesis that CTR1 plays an important role in OX accumulation only turning exposition to relatively low concentration (2 μM) and it does not have any relevance in higher OX concentrations. Furthermore, it is postulated that intracellular OX concentration is less dependent on transporting activity of CTR1 than in cases of other platinum derivatives, *e.g.,* cisplatin and carboplatin. Additionally, it was showed that similarly to CTR1, also CTR2 may have analogical properties as a cisplatin and carbonplatin concentration regulator and OX most probably as well[305]. Further *in vivo* research confirming the above hypotheses is necessary.

Clinical studies concerning transporters for drugs that are platinum derivatives concentrate on the evaluation of connection between intratumour expression of certain transporters and the results of treatment after the administered chemotherapy based on platinum derivatives. The results of these studies are not completely certain due to many limitations. One of these limitations is lack of functional research into transporting activity because accessible data concern only research into gene or protein expression using methods such as RT-PCR or IHC respectively. Generally, correlations observed in the research were not supported by any analysis of pharmacokinetic variables in relation to accumulation of platinum derivatives in the tumour tissue, also the size of individual groups was also small. Furthermore, it is necessary to conduct *in vivo* research into the meaning of genetic variability of membrane transporters and channels for gene expression and its influence on pharmacokinetic and effectiveness of OX-based therapy.

***Glutathione S-transferases***

Phenotype of resistance to compounds that are platinum derivatives may be dependent on the variable activity of detoxification channels. In cytoplasm, platinating agents become acquated, which then enables them to react with thiol-containing molecules, including GSH and metallothioneins (Figure 8). In the cell, GSH play the role of antioxidant that helps maintain reductive intracellular environment by coupling oxidated particles with sulphydryl groups. It is assumed that high GSH concentration and/or metallothionein may cause deactivation of platinum compounds before they have a chance to interact with DNA in the nucleus (it is estimated that only 1% of a dosage that entered the cell stands a chance to bond with nucleus DNA[306]) to quench Pt-DNA monoadducts before conversion to more lethal diadducts, or efflux of the Pt-glutathione conjugates[307,308]. Numerous evidence point out that glutathione S-transferers (GSTs) belonging to superfamily of dimeric enzymes of the second metabolism phase are responsible for a differential sensitivity profile towards anticancer drugs, including platinum derivatives[309]. GSTs are coded by genes belonging to at least five main groups: α (*GSTA1*), μ (*GSTM1*), π (*GSTP1*), σ (*GSTS1*) and θ (*GSTT1*). Many of these genes present genetic polymorphism that influences their transcription and/or enzymatic activity of proteins coded by[310]. One of the isoenzyme from GSTs family – GSTP1, undergoes high expression in CRC tissues and partakes in detoxication processes of platinum derivatives, therefore it may be a source of drug resistance in some patients treated with therapy based on cytostatics that are platinum analogues. The published research suggests a connection of some of polymorphic variables of *GSTP1* gene with the increase of effectiveness of anticancer therapy[51].

Two major polymorphisms in GSTP1 – 313A>G (Ile105Val) and 341C>T (Ala114Val) – induce amino acid changes in the electrophile-binding active site of the enzyme[311]. SNP 313A>G responsible for substitution of isoluecine through valine in codon 105 (Ile105Val) causes lowering in the enzymatic activity of GSTP1[312]. There are a few clinical studies accessible that refer to the influence of this polymorphism on the frequency of occurrence of toxic effects of FOLFOX or IROX therapy (CPT-11/OX) in patients with metastatic CRC[180,313,314]. McLeod *et al*[180] stated that in case of a group of patients treated with FOLFOX, which were homozygous for the 105Val variation, it was more frequent for treatment discontinuation to take place due to the symptoms of neurotoxicity (*P* = 0.01). However, the necessity to discontinue therapy was not dependent on the frequency of occurrence of individual genotypes in groups treated with other combinations (IROX or capecitabine/OX). Most probably, presence of 313GG genotype is connected more with a significant lowering of catabolic activity of GSTP1 than it is the case of allele 313A carriers (genotypes 313AG or 313AA), this leads to increased OX accumulation and thus causes greater risk of occurrence of neurotoxicity of the 3rd degree[313,314]. On the other hand, Inada *et al*[315] while examining their CRC patients, stated that genotype 313AA carriers are more exposed to the development of early OX-induced grade 1 peripheral neurotoxicity than patients with 313G alleles (313AG or 313GG), but they did not observe a connection between the frequency of occurrence of these genetic variations and the risk of neurotoxicity ≥ 2. Also the results of some other research did not conform the existence of dependence SNP 313A>G and neurotoxicity of OX therapy[316-321].

Since replacing isoluecine with valine (Ile105Val) leads to lowering the cell’s ability to protect itself against cytotoxic factors, this polymorphism may contribute to the increase of chemosensitivity towards OX[312]. A few clinical research it was observed that patients with 313GG genotype benefitted more from the combined therapy including OX in its scheme of treatment than patients with 313A allele[51,322-324]. However, three recently published studies concerning the efficiency of treatment with FOLFOX scheme in patients with advanced CRC on the basis of genotyping *GSTP1* gene for SNP 313A>G presented no connection with the presence of allele and PFS[313,321,325]. Ye *et al*[326] publisher a systematic analysis of five clinical studies[314,325,327-329] on a group of 415 CRC patients, treated with OX. Also in this case, no dependence between 313A>G polymorphism and the level of response to the OX-based therapy (*P* = 0.13) was confirmed[326]. Yet in order to put forward any definite conclusions concerning predictive significance of SNP 313A>G, it is necessary to carry out clinical research on a large group of patients.

Among the accessible clinical data, one may also find studies concerning copy number variations (CNV) of *GSTT1* and its potential influence on toxicity of OX-based therapy. While investigating CNV of *GSTT1,* Goekkurt *et al*[330] found no statistically relevant dependencies between genetic variables of this gene and the frequency of occurrence of toxic effects of therapy in patients gastric cancer, although there was a trend showing that patients with the null variant were less likely to develop hematologic toxicity. Two other clinical studies of patients with metastatic CRC treated with OX did not confirm the hypothesis of potential influence of CNV of *GSTT1* on the therapy toxicity[316,317]. It is necessary to conduct further research that would allow to clearly resolving the role of genetic GSTs variable in the development of toxicity in CRC patients who undergo treatment with therapy including OX in the scheme of treatment.

***Nucleotide excision repair pathway (ERCC1, ERCC2, XRCC1)***

Blocking the process of DNA replication by the platinum derivatives through creating adducts with nuclear nucleic acid leads to the induction of apoptosis and the death of cancer cell[331,332]. The observed inter-individual variability in the ability to recognise and repair such DNA damage through the nucleotide excision repair (NER) pathway is one of the factors that may influence the success of OX-based therapy. DNA strands are separated and a DNA residue containing the adducts is removed (Figure 9). Mechanism of recognition and repair of the damaged DNA fragments itself is dependent on several factors. Lowered efficiency of DNA repair system may, in consequence, lead to the increased sensitivity of cancer cells to therapy that includes platinum compounds[333]. ERCC1 (excision repair cross-complementation group 1) and ERCC2 protein (otherwise known as XPD, xeroderma pigmentosum group D) are the two main compounds of NER group that play a crucial role in the regulation of activity of other elements that are part of NER pathway. Together with XPF protein (xeroderma pigmentosum group F), ERCC1 is responsible for recognising these places in the DNA strand where adducts are located, whereas ERCC2 is a subunit of human transcriptional initiation factor TFIIH with ATP-dependent helicase activity[334]. Considering the above dependencies, it may be assumed that functional SNPs in *ERCC1* and *ERCC2* genes may directly contribute to the sensitivity phenotype to platinum compounds, such as OX, through conditioning congenital suboptimal activity of the NER pathway. For genes *ERCC1* and *ERCC2*, there were several frequent and probably functional SNPs described, among them are 354C>T and 8092C>A in *ERCC1* gene there is also a contribution of the changes in activity measured by the level mRNA[335] and in *ERCC2* SNPs 312G>A gene (Asp312Asn) and 2251T>G (Lys751Gln) are recognised as determinants of suboptimal activity of the DNA repair system[336,337]. Hitherto study results point out that ERCC1 is a potential predictive marker of a response to the therapy based on platinum compounds due to the fact that low ERCC1 expression is connected with the cancer cells’ sensitivity to chemotherapy with those drugs[34,338-340].

Shirota *et al*[34] were the first research group that studied the influence of *ERCC1* gene expression on the results of treatment of 50 CRC patients in their advanced stage and the phenotype of resistance of those treated with 5-FU/OX. They stated that patients with high intra-tumour *ERCC1* expression measured by the mRNA level present shorter survival time than patients from the group with the lower level of expression (*P* = 0.008)[34]. Also Uchida *et al*[341], while examining 91 patients treated with a combination of capecitabine /OX stated that a high mRNA level for *ERCC1* gene was connected with the shorter time of treatment failure as opposed to the group of patients with lower expression (*P* = 0.046). In another study, low expression of *ERCC1* gene was also connected with better response to both primary (*P* = 0.047) and secondary chemotherapy, although in the latter case this dependence was on the verge of statistical relevance (*P* = 0.054). Furthermore, high expression of *ERCC1* gene was connected with shorter OS in primary therapy (*P* = 0.014)[342]. The above results of clinical studies support the hypothesis put forward at the beginning about the influence of *ERCC1* gene expression on the results of treatment with platinum derivatives, whereas a high level of mRNA may be the cause of clinical resistance towards OX.

Literature also describes polymorphisms located in the *ERCC1* gene sequence, one of them being a silent SNP 354C>T (Arg118Arg). Although the mechanism through which this SNP influences the change of ERCC1 activity is not fully known, it is postulated that AAC codon exchange on a rarely occurring AAT influences the effectiveness of the translation process, however, for 354T allele, there is a decrease in protein expression of about 50%[343]. In two clinical studies in which participated patients with advanced CRC it was observed that carriers of 354TT genotype present higher response rates to OX treatment[344] and longer PFS[345]. However, in five other studies, the survival time of patients with CRC was longer in case of genotype 354CC carriers[51,313,314,339,346]. While examining 168 patients, Chang *et al*[346] showed that in a group with genotypes which included allele 354T (354CT or 354TT), worse treatment results were noted in comparison with patients with genotype 354CC (in terms of response (*P* = 0.01), PFS (*P* = 0.01) and OS (*P* = 0.01)). Additionally, while testing the dependence between genetic variants 354C>T and protein expression determined by IHC, they stated that a higher level of expression is connected with the presence of allele 354T[346]. Also the group of Chen *et al*[314], while examining 166 patients, pointed out that carriers of genotypes with at least one allele 354T are characterised by poor response (*P* = 0.01) and shorter OS (*P* = 0.01). Park *et al*[339] also found a significant correlation between polymorphic variants in codon 118 and the results of treatment among 106 patients with advanced refractory CRC receiving 5-FU/OX. For patients with genotype 354CC , survival time median was 15.3 mo, while in a group of carriers of allele 354T (354CT and 354TT genotypes) it was only 11.1 mo.

Partly different from fluoropyrimidines genes previously described, the frequency of these polymorphisms varies with race and may account for reduced response rates in black patients when compared with white patients, as expressed by Goldberg *et al*[347] and confirmed in more recent studies, as in the subgroup of patients of CAIRO study[110]. It is postulated that the differences in the observed dependencies and the strength of correlation may be connected with inter-population differences in the frequency of occurrence of allele and genotype. For instance, the frequency of occurrence of SNP 354C>T (Arg118Arg) in the population of Easter Asia is much lower than in other ethnic[340].

The presence of allele 354T in *ERCC1* gene is connecter with the change in the expression of gene/protein[339], while allele 2251G which is a variation of *ERCC2* gene was described as having influence on a low number of X-ray induced chromatic aberrations[336]. Carriers of genotype 2251TT present a 7-fold greater risk of suboptimal ability to repair DNA damages as opposed to the group of carriers of allele 2251G (genotypes 2251GG or 2251GT)[336]. It is postulated that patients who have both allele, 354T (*ERCC1*) and 2251G (*ERCC2*) that are connected with a high efficiency of detection system and DNA damage repair, may present certain resistance towards OX, thus contributing to a worse prognosis. However, results of clinical studies do not confirm the above hypothesis. 2251T>G (Lys751Gln) polymorphism did not show any connection with the time length of survival as opposed to the frequency of genotype dispersion both in the group of patients with gastro-oesophageal cancer[348,349] and CRC[350,351] who underwent a therapy based on various platinum derivatives. Whereas studies of synonymous SNP Arg156Arg (C>A) *ERCC2* gene that were carried out on a group of patients with gastric cancer and treated with OX allowed to observe that carriers of A allele (genotypes CA or AA) were characterised by a higher response rate and longer TTP in comparison with patients with genotype CC[352]. A similar trend was observed in the studies of Park *et al*[353], who examined patients with metastatic CRC, noted that the presence of A allele contributed to a better response to treatment and longer median of survival rate as opposed to patients with different variant of *ERCC2* gene. Functional studies confirm the SNPs influence of *ERCC1* (354C>T) and *ERCC2* (2251T>G) genes on the phenotype of NER pathway efficiency[335,354,355]. In the studies of 73 patients treated with 5-FU/OX it was observed that in the group with genotype 2251TT (751Lys/Lys) time median of survival rate was 17.4 mo while for the carriers of genotypes with 2251G allele it was 12.8 (751Lys/Gln) and 3.3 mo (751Gln/Gln)(*P* = 0.02)[353]. Influence on genetic variants of genes *ERCC1* and *ERCC2* was also studied in a group of 166 patients metastatic CRC who were treated with a drug combination of 5-FU/LV/OX (FOLFOX4)[356]. In the analysis of dependencies between SNPs and the results of treatment it was shown that occurrence of each genotype *ERCC1*-354TT, *ERCC2*-2251AC and *ERCC2*-2251CC, independent of each other, is connected with a shorter PFS. The median PFS was 11.2 mo for patients without any of the 3 genotypes, 9.8 mo for those with 1 of the high-risk genotypes, and 8 mo for those with both the *ERCC1*-354TT and either *ERCC2*-2251AC or -2251CC genotypes (*P* = 0.002)[356]. In the meta-analysis published by Yin *et al*[357] it was shown that SNPs354C>T (*ERCC1*) and 2251T>G(*ERCC2*) may be clinically useful factors in evaluation of treatment results of patients with gastric and CRC who were subject to treatment which included OX (FOLFOX or XELOX). However, as the authors of this analysis emphasise, it is necessary to carry out wide and well-planned prospective clinical studies that would allow to clearly present the utility of these markers in clinical practise[357].

Apart from studies that focused on the analysis of individual determinants of therapy efficiency such as SNPs, also a joined analysis of a few potential predictive factors in forecasting the effects of chemotherapy of CRC patients was carried through. Kim *et al*[358] assessed the expression of proteins ERCC1, TS and GSTP1 using IHC technique for their potential application in predicting the effects of therapy in 70 patients in advanced stage of CRC who underwent treatment with 5-FU/OX. They observed in their study that a positive result of expression occurs in 55.7% (ERCC1), 68.6% (TS) and 71.4% (GSTP1) of the analysed cases. It was confirmed that a low level of TS expression is connected with better results of chemotherapy (*P* = 0.009), however in case of ERCC1 and GSTP1 proteins there was no statistically relevant dependence between the level of expression and efficiency of treatment (*P* = 0.768, *P* = 0.589, respectively). Yet OS median was significantly longer in patients with a negative result in assessment of ERCC1 protein expression (*P* = 0.0474). Additionally, patients in whom a positive result of expression was noted, both in ERCC1 and TS expression, had poor OS (*P* = 0.0017). Also, multi-variant analysis confirmed that a positive result of ERCC1 and TS expression significantly influences OS (HR = 1.72; *P* = 0.023), which justifies simultaneous clinical application of the two markers in predicting efficiency of 5-FU/OX therapy[358].

Apart from NER pathway, also the base pair excision repair pathway (BER) may have influence on the efficiency of therapy based on compounds that are platinum derivatives. XRCC1 plays a key role in BER pathway it has been demonstrated that the Arg399Gln (1196A>G) substitution in the *XRCC1* gene is associated with the increased levels of DNA damage markers[359]. This relatively frequently occurring polymorphism probably contributes to the change in XRCC1 protein conformation in the domain binding other elements of BER complex, which may lead to the decrease in the efficiency of DNA repair system. Deficiency in DNA repair pathways has been shown to confer to resistance to several drugs, including platinum compounds[360]. It was shown that the presence of allele 399Arg (1196A) is connected with the better time of survival in patients with gastric[349] and lung cancer[361] undergoing chemotherapy with platinum derivatives. Also, Suh *et al*[362] observed that better results of therapy in patients with metastatic CRC treated with FOLFOX occur in the cases where the presence of allele 399Arg (1196A) is noted. However, the results of other clinical studies published so far in a group of patients with advanced CRC and gastric cancer treated with OX, do not confirm the above observations[51,313,350]. Liang *et al*[363] attempted to analyse the influence of both polymorphisms for genes engaged in DNA repair processes: *ERCC1* (354C>T) and *XRCC1* (1196A>G). They studied a group of 113 patients diagnosed with metastatic CRC who underwent chemotherapy that included OX. The analysis of influence of individual SNPs showed no significant influence on prediction disease control rates (DCR) or OS (*P* = 0.662 and 0.631, respectively). However, while evaluating the influence of combination in both SNPs, it was shown that there is a significant correlation between genetic variations of *ERCC1* (354C>T) and *XRCC1* (1196A>G), and DCR (*P* = 0.01) and OS (*P* = 0.001), independently. This was the first prove of clinical application of genetic determinants located in *ERCC1* and *XRCC1* genesin selection of patients with metastatic CRC for whom the greatest benefits from OX-based therapy are expected[363]. Also later results obtained by Stoehlmacher *et al*[364], who studied the influence of Arg399Gln (1196A>G) polymorphism on the efficiency of treatment in 61 patients with metastatic CRC who underwent treatment with 5-FU/OX, confirmed the significance of this SNP as a predictive marker. Seventy-three per cent of patients with the favourable 399Arg/Arg (1196AA) genotype responded to treatment, and patients who possessed at least one 399Gln (1196A) allelic polymorphism in XRCC1 were 5.2-fold more likely to fail 5-FU/OX chemotherapy[364].

Among the accessible data, one clinical study concerns multivariate analysis of a few predictive factors described above in the therapy of patients with refractory CRC who underwent treatment with 5-FU/OX combination. Analysis of multiple gene polymorphisms proves that the efficiency of such a therapy may be dependent on the presence of two or more unfavourable variants for genes *ERCC1*, *ERCC2*, *TYMS* and *GSTP1* because the carriers of these SNPs are characterised by a significantly shorter OS[51]. Summarising, it may be stated that is we wish to successfully predict the effectiveness of a therapy, we need to apply a combination of a few predictive markers, which concerns cases in which several cytostatic drugs are used in a combination therapy.

***The MMR and apoptosis regulation***

Cytotoxic effect caused by OX is stronger than in the case of cisplatin because it is the result of a stronger DNA damage reduction[365]. Resistance to cytostatic compounds that are platinum derivatives is probably a result of variable functionality of proteins responsible for recognising damages that occurred as a result of Pt-DNA adducts[366]. MMR is a highly conserved, strand-specific repair pathway which is a multi-stage process initiated on the way of recognising DNA damaged places by specific proteins[367]. In many types of cancer, various defects of activity are noted in those proteins, which particularly concerns three of them MSH2, MSH6 and MLH1[368]. In a situation when MMR present a deficit of activity, it results in accumulation of numerous DNA damages in the genome, which leads to MSI[369]. Accessible experimental data prove that MMR deficit is connected with resistance to cytotoxic activity of alkylating agents[370]. Studies of DNA repair mechanisms after exposure to cisplatin showed that created Pt-DNA adducts are recognised by the complex of MMR proteins[371]. MMR pathway is one of the factors influencing the power of cisplatin activity, which was proved by pre-clinical studies where cells with deficiency of activity of proteins MLH1, MSH2 and MSH6 had the phenotype of moderate resistance towards cisplatin, yet they remained sensitive to cytotoxic activity of OX[276,372]. Interestingly, Pt-DNA adducts are recognised by MSH1 protein only in a situation when damages occurred after the exposure of these cells to cisplatin, but not in case of those that are created under the influence of OX[371,372]. Therefore, even though MMR pathway is a key element in the mechanism of DNA repair, this system seems not to recognise Pt-DNA adducts which are created after the exposure to OX. Generally, it is assumed that if attempts to repair Pt-induced DNA damage fail, this eventually leads to initiation of the process of apoptosis[373,374]. Adducts induced by OX do not activate JNK (JNK-c-Jun NH2-terminal kinase, also known as stress activated protein kinase) and c-Abl (a nuclear protein)[375], which allows OX to maintain its cytotoxic activity in both MMR-proficient and -deficient cells[372,375]. Cisplatin depends on an intact MMR system for its maximal cytotoxicity for signalling apoptosis *via* the JNK-mediated pathway[371,375,376]. The binding of the MMR complex to Pt–DNA adducts appears to increase the cytotoxicity of the adducts[377], either by activating downstream signalling pathways that lead to apoptosis[375] or by causing “futile cycling” during translation synthesis past Pt–DNA adducts[372]. Therefore, between cisplatin and OX there is a different ability to activate signal paths inducing apoptosis in response to creating Pt-DNA adducts, which may be the basis of the observed differences in the profile of drug resistance of both platinum derivatives[378].

Protein p53 mediates a transduction of a signal induced by DNA damage after the exposure to cisplatin[379]. p53 interacts with several significant elements that are part of NER pathway, such as xeroderma pigmentosum, complementation group C (XPC), transcription factor IIH (TFIIH) and replication protein A (RPA), which points out to its role in supervising the DNA repair process[380]. While testing 60 different cell lines, Vekris *et al*[381] showed that expression of p53 is positively correlated with cell sensitivity to four different platinum derivatives: cisplatin, carboplatin, OX and tetraplatin. Since p53 partakes in apoptosis induction and participates in the process of removing Pt-DNA adducts created as a result of activities of platinum derivatives, this protein may contribute to both chemosensitivity and also drug resistance[382]. Systematic analysis of cellular sensitivity to OX in relation to p53 status in pairs of cisplatin-sensitive and -resistant cells shows that OX is less potent than cisplatin on the cisplatin-sensitive cell lines, whereas it was capable of overcoming cisplatin resistance in majority of the sublines. Cell sensitivity towards OX seems to also dependent on the occurrence of genetic variants in gene *TP53*. While studying cell line A431 that is characterised by the occurrence of mutation in codon 273 of p53, it was observed that it presents high resistance to the activity of OX[276].

Clinical application of the above *in vitro* studies that allowed to test various panel of factors influencing the phenotype of chemosensitivity or drug resistance with require a series of *in vivo* studies with participation of well selected groups of patients. Currently accessible data from pre-clinical studies point out to potential significance of some molecular factors connected with the DNA repair processes and those participating in the control of cell cycle and apoptosis, which could serve as predictive markers in forecasting the efficiency of OX therapy in CRC patients.

**FUTURE PERSPECTIVE PERSONALIZED MEDICINE IN TREATMENT OF COLORECTAL CANCER**

Latest decades brought huge progress in understanding complex processes regulating growth and development of tumours. However, a major challenge for basic and clinical research still remains a difficult to solve problem of primary and secondary drug resistance, which in many cases significantly reduces the antitumour efficacy of the therapy. Early research on the development of new chemotherapeutic agents with significant antitumour potency, led to the introduction in oncology practice of few effective drugs, including currently used in the treatment of CRC. Although they strongly induce apoptosis in intensively dividing cells, their strongest drawback is the same effect on both cancer cells and healthy tissue. Therefore, to maintain the effectiveness of cancer treatment, it is necessary to use a maximum dose that provides a strong cytotoxic effect against tumour tissue while minimizing toxicity to a patient. On the other hand, the intensive development of molecular tests in last two decades started the development of "targeted" drugs and new treatment strategies such as targeted therapy. These new capabilities have given hope of achieving substantial benefits for patients for whom using cytostatics in chemotherapy proved not to be very effective. The main advantage of targeted therapy is the ability to avoid toxic effects of the drug and its small impact on healthy cells in a body. However, soon after the first targeted therapy research reports on its high potential for clinical applications, it turned out that the problem of drug resistance remains also an obstacle in 'smart drugs' category. Similarly to conventional cytostatics, the resistance to a new class of drugs is an important issue in oncology[383]. It should be noted that drug resistance remains the most critical factor in the success of therapy. Currently, the main problem for researchers working over the effectiveness of cancer treatment have to face is how to plan a rational treatment plan based on the classic cytostatic drugs and targeted drugs. Overcoming the resistance in many cases it is only possible through selection of an appropriate drug combination and optimal dosing in a treatment cycle. Due to the fact that many of the drug-resistance mechanisms are determined by individual patient's characteristics, the key to the therapy success can be personalized cancer medicine. However, in recent years most scientists conducting research in the field of molecular mechanisms of drug resistance focused on individual processes associated with metabolism, biodistribution, and anticancer drug mechanisms. Such reductionist research approach does not include a wider context and interpenetration of different processes in a body that constitutes the effectiveness of a therapeutic strategy[384].

In the currently accepted by scientists paradigm, it is considered that individual differences in response are results of individual patient features that can be identified at a molecular level. These features are subject to genetic variation and environment pattern of which is specific for each patient. It can be assumed that understanding the molecular mechanisms of inter-individual differences in the effectiveness of cancer treatment will allow the optimization of cancer therapy. Therefore, in the past two decades so great research effort has been made in order to acquire the knowledge of mechanisms that are responsible for a greater or lesser effectiveness of a used treatment. The approach that underlies an individualized medicine is based on the assumption that by using molecular profiling and a set of biomarkers we can improve treatment efficacy of a particular patient, prolonging survival time and/or reduce the risk of serious complications [385].

It is possible to practical apply these concepts in an individualization of CRC patient treatment in a near future? In the previous chapters there are described a variety of prognostic and predictive markers which in recent years have been subject to various test procedures in order to determine their potential clinical value in the treatment of CRC. A technological breakthrough in molecular studies, as observed in recent years (single-nucleotide polymorphism arrays, complementary DNA microarrays, DNA methylation and microRNA (miRNA) profiling as well as next-generation sequencing) also made it possible to create individual molecular profiling for patients and it is more profitable in economic terms. The data that can be obtained using these high-throughput methods give hope for practical application of various biomarkers to predict the effectiveness of treatment in a single patient with CRC.

Among main variables affecting the therapeutic efficacy of cytostatics there may be mentioned the level of DNA synthesis and/or the intensity of cell divisions, and in case of targeted drugs the expression level of molecules in a signalling pathway in which the drug is targeted. As in case of cytostatic drugs the predominant mechanism of drug resistance is a wide panel of pharmacokinetic factors, as for targeted therapy they are mainly processes related to pharmacodynamics (genetic alteration/mutation of the target itself, persistent activation of downstream signalling pathways, bypass mechanisms). Such a clear distinction, of course, does not describe the complexity of drug resistance mechanisms. Given the holistic nature of personalized medicine, it is necessary to develop and validate wider panel of biomarkers which would reflect the multifactor mechanisms of resistance. In addition, when using predictors in clinical practice, we must take into account different therapeutic objectives which are set for specific subgroups of patients. From the point of view of drug resistance in cancer therapy, at least two main objectives to be met in personalized medicine should be considered: (1) risk minimalization of inducing resistance; and (2) breaking the existing primary or secondary resistance. Finding the optimum combination of drugs and dosage regimen can in many cases lead to better efficiency in first-line treatment, and prevent cancer relapse. Furthermore, an equally important problem is the selection of resistant clones during the first treatment cycle, what in the case of relapse can significantly reduce therapeutically effective new combination of drugs. Usage of dynamic-response markers in clinical practice that could allow monitoring of the course of treatment is a promising trend of research in personalized medicine. Changing the level of expression of marker genes or activity of posttranslational protein modification in the course of used therapy was already a subject of several studies. Analysis of molecular changes taking place during treatment may provide information about development of resistance resulting from exposure to a drug, which is particularly important in the context of existence of secondary drug resistance mechanisms. In such cases, the change of treatment regimen may be important for a future of a patient.

There are several main obstacles that currently prevent the full application in clinical practice of personalized medicine, despite significant progress in the study of causes of drug resistance occurrence in the treatment of CRC. Inter-individual differences in the response to treatment in patients with CRC may be subject to genetic and epigenetic features that can be classified as genomic aberrations (*e.g.,* microsatellite instability (MSI)[386,387], chromosomal instability (CIN)[388,389] and CpG island methylator phenotype (CIMP)[390-393]) as well as polymorphic variation (*e.g.,* SNP or VNTR). This multifactor substrate conditioning efficacy of CRC makes it difficult to plan reliable research on predicting markers. In addition, the available clinical data indicate that CRCs are molecularly heterogeneous group of neoplasms, that is why it is important to plan future studies taking into account this heterogeneity. Only such an approach can provide a link between specific molecular features and effectiveness of the treatment. Another of the existing barriers for development of personalized medicine, is the need of invasive biological sampling from a patient. Large part of the results of clinical trials on the CRC drug resistance is based on an analysis of biological material derived from tumour biopsy. The possibility of using for this purpose a blood serum is one of ideas to solve this problem[394]. Yet another barrier that prevents a truly individualized treatment of patients with CRC is small amount of research system data that could connect mutation analysis and gene expression in the course of translation and activity of specific marker proteins. Main research stream basing on a transcriptome analysis does not provide information about protein expression, and mRNA level does not allow to determine the activity of proteins. It was not until recent years when the methods of proteome analysis (proteomics) has been developed, including as important as protein-protein interactions. Development of this research area has led to development of a number of new drugs for targeted therapy, such as inhibitors of kinases and their substrates. The analysis of activity of individual proteins involved in intracellar signal transduction is a very important aspect research on tumour biology and as shown Pierobon *et al*[395], the level of protein expression and the level of protein activation (*e.g.,* phosphorylation) do not always correlate, suggesting that the latter could represent a better predictive biomarker for patient stratification. Concluding, due to the heterogeneity of CRCs and complexity of drug resistance phenomenon, prediction of the effectiveness of treatment in individual patients should be based on usage of prediction biomarkers derived from genome and proteome. Analysis of multiple markers is also justified by the fact that most modern standards of CRC treatment use a combination of several anticancer drugs. Combination therapy is based on the inhibition of tumour cells on several molecular levels. In order to rationally combine different therapies that would presumably be more effective than monotherapy, it is therefore necessary to use an integrated approach for analysis of multiple pathways simultaneously. In this way, it will be possible to highlight pathway alterations that can be targeted by different agents.

The most recent data in the field of biomarker research allow making an important conclusion that only the interdisciplinary research approach, with combined analysis of genome and proteome makes it possible to recognise prognostic and predictive factors which will help select patients in terms of relevant clinical features for an individualized therapy[396]. Among a number of potential predictive markers described in the preceding sections of this review, only their small part was found to be clinically useful. In many cases, the analysis of the same marker provided contradictory data sometimes leading to opposing conclusions. There may be several reasons for these discrepancies, among them are (1) methodological differences (prevalence of retrospective studies on a more reliable prospective); (2) usage of different and non-standardized research techniques; (3) usage of statistical analysis inappropriate for a given type of data; and (4) diverse and/or insufficiently large group of patients[385]. Therefore, to increase the credibility of preclinical and clinical prediction, it is necessary when planning a research to take into account all variables that can affect the outcome of the analysis. Adoption of uniform research standards in the form of guidelines, such as reporting recommendations for tumour MARKer prognostic studies[397], provides an opportunity to obtain reliable data. Moreover, the prevailing current retrospective analysis, results of which suggest a correlation should be used only as a source of hypotheses to be verified in the course of the later well-designed studies.

In summary, from a clinical point of view, there is a need for innovative patient stratification methods which basing on validated biomarkers will help clinicians to make correct therapeutic decisions. The effectiveness of anticancer drugs from both classical cytostatics group as well as targeted drugs should be carefully reviewed in properly selected groups of patients whose common molecular profile features determine susceptibility or resistance to used treatment[398]. The implementation of new technologies is leading to the accumulation of huge amounts of genomic and proteomic data and the identification and validation of predictive biomarkers for existing and new targeted therapies, and will likely improve patient outcomes in the future[399]. Although the initial costs for cancer management and personalized medicine may be high[400], in more distant time perspective they should bring large benefits from both a clinical and economical perspective.

**REFERENCES**

1 **Porteous M**. Insights from next generation sequencing of the cancer genome. *J R Coll Physicians Edinb* 2011; **41**: 323 [PMID: 22184570 DOI: 10.4997/jrcpe.2011.408]

2 **Russell C**, Rahman A, Mohammed AR. Application of genomics, proteomics and metabolomics in drug discovery, development and clinic. *Ther Deliv* 2013; **4**: 395-413 [PMID: 23442083 DOI: 10.4155/tde.13.4]

3 **Gonzalez de Castro D**, Clarke PA, Al-Lazikani B, Workman P. Personalized cancer medicine: molecular diagnostics, predictive biomarkers, and drug resistance. *Clin Pharmacol Ther* 2013; **93**: 252-259 [PMID: 23361103 DOI: 10.1038/clpt.2012.237]

4 **Cascorbi I**, Bruhn O, Werk AN. Challenges in pharmacogenetics. *Eur J Clin Pharmacol* 2013; **69 Suppl 1**: 17-23 [PMID: 23640184 DOI: 10.1007/s00228-013-1492-x]

5 **Abrahams E**, Silver M. The case for personalized medicine. *J Diabetes Sci Technol* 2009; **3**: 680-684 [PMID: 20144313]

6 **Spławiński J**, Kuźniar J. Clinical trials: active control vs placebo--what is ethical? *Sci Eng Ethics* 2004; **10**: 73-79 [PMID: 14986774]

7 **Lenz HJ**, Hayashi K, Salonga D, Danenberg KD, Danenberg PV, Metzger R, Banerjee D, Bertino JR, Groshen S, Leichman LP, Leichman CG. p53 point mutations and thymidylate synthase messenger RNA levels in disseminated colorectal cancer: an analysis of response and survival. *Clin Cancer Res* 1998; **4**: 1243-1250 [PMID: 9607583]

8 **Loupakis F**, Schirripa M, Zhang W, Falcone A, Lenz H-J. Pharmacogenetic Concerns in Metastatic Colorectal Cancer Therapy. *Current Colorectal Cancer Reports* 2012; **8**: 263-271 [DOI: 10.1007/s11888-012-0137-2]

9 **Stoehlmacher J**. Prediction of efficacy and side effects of chemotherapy in colorectal cancer. *Recent Results Cancer Res* 2007; **176**: 81-88 [PMID: 17607918]

10 **Heidelberger C**, Chaudhuri NK, Danneberg P, Mooren D, Griesbach L, Duschinsky R, Schnitzer RJ, Pleven E, Scheiner J. Fluorinated pyrimidines, a new class of tumour-inhibitory compounds. *Nature* 1957; **179**: 663-666 [PMID: 13418758]

11 **Chaudhuri NK**, Montag BJ, Heidelberger C. Studies on fluorinated pyrimidines. III. The metabolism of 5-fluorouracil-2-C14 and 5-fluoroorotic-2-C14 acid in vivo. *Cancer Res* 1958; **18**: 318-328 [PMID: 13523598]

12 **Cassidy J**, Saltz L, Twelves C, Van Cutsem E, Hoff P, Kang Y, Saini JP, Gilberg F, Cunningham D. Efficacy of capecitabine versus 5-fluorouracil in colorectal and gastric cancers: a meta-analysis of individual data from 6171 patients. *Ann Oncol* 2011; **22**: 2604-2609 [PMID: 21415237 DOI: 10.1093/annonc/mdr031]

13 **Grogan L**, Sotos GA, Allegra CJ. Leucovorin modulation of fluorouracil. *Oncology (Williston Park)* 1993; **7**: 63-72; discussion 75-6 [PMID: 8398636]

14 **Thirion P**, Michiels S, Pignon JP, Buyse M, Braud AC, Carlson RW, O'Connell M, Sargent P, Piedbois P. Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: an updated meta-analysis. *J Clin Oncol* 2004; **22**: 3766-3775 [PMID: 15365073 DOI: 10.1200/JCO.2004.03.104]

15 **Zhou JY**, Shi R, Yu HL, Zeng Y, Zheng WL, Ma WL. The association between two polymorphisms in the TS gene and risk of cancer: a systematic review and pooled analysis. *Int J Cancer* 2012; **131**: 2103-2116 [PMID: 22307944 DOI: 10.1002/ijc.27465]

16 **Berger SH**, Jenh CH, Johnson LF, Berger FG. Thymidylate synthase overproduction and gene amplification in fluorodeoxyuridine-resistant human cells. *Mol Pharmacol* 1985; **28**: 461-467 [PMID: 2932632]

17 **Salonga D**, Danenberg KD, Johnson M, Metzger R, Groshen S, Tsao-Wei DD, Lenz HJ, Leichman CG, Leichman L, Diasio RB, Danenberg PV. Colorectal tumors responding to 5-fluorouracil have low gene expression levels of dihydropyrimidine dehydrogenase, thymidylate synthase, and thymidine phosphorylase. *Clin Cancer Res* 2000; **6**: 1322-1327 [PMID: 10778957]

18 **Leichman L**, Lenz HJ, Leichman CG, Groshen S, Danenberg K, Baranda J, Spears CP, Boswell W, Silberman H, Ortega A. Quantitation of intratumoral thymidylate synthase expression predicts for resistance to protracted infusion of 5-fluorouracil and weekly leucovorin in disseminated colorectal cancers: preliminary report from an ongoing trial. *Eur J Cancer* 1995; **31A**: 1306-1310 [PMID: 7577041]

19 **Leichman CG**, Lenz HJ, Leichman L, Danenberg K, Baranda J, Groshen S, Boswell W, Metzger R, Tan M, Danenberg PV. Quantitation of intratumoral thymidylate synthase expression predicts for disseminated colorectal cancer response and resistance to protracted-infusion fluorouracil and weekly leucovorin. *J Clin Oncol* 1997; **15**: 3223-3229 [PMID: 9336359]

20 **Popat S**, Matakidou A, Houlston RS. Thymidylate synthase expression and prognosis in colorectal cancer: a systematic review and meta-analysis. *J Clin Oncol* 2004; **22**: 529-536 [PMID: 14752076 DOI: 10.1200/jco.2004.05.064]

21 **Qiu LX**, Tang QY, Bai JL, Qian XP, Li RT, Liu BR, Zheng MH. Predictive value of thymidylate synthase expression in advanced colorectal cancer patients receiving fluoropyrimidine-based chemotherapy: evidence from 24 studies. *Int J Cancer* 2008; **123**: 2384-2389 [PMID: 18729195 DOI: 10.1002/ijc.23822]

22 **Marsh S**, McKay JA, Curran S, Murray GI, Cassidy J, McLeod HL. Primary colorectal tumour is not an accurate predictor of thymidylate synthase in lymph node metastasis. *Oncol Rep* 2002; **9**: 231-234 [PMID: 11836585]

23 **Aschele C**, Debernardis D, Tunesi G, Maley F, Sobrero A. Thymidylate synthase protein expression in primary colorectal cancer compared with the corresponding distant metastases and relationship with the clinical response to 5-fluorouracil. *Clin Cancer Res* 2000; **6**: 4797-4802 [PMID: 11156237]

24 **Iyevleva AG**, Buslov KG, Togo AV, Matsko DE, Filimonenko VP, Moiseyenko VM, Imyanitov EN. Measurement of DPD and TS transcripts aimed to predict clinical benefit from fluoropyrimidines: confirmation of the trend in Russian colorectal cancer series and caution regarding the gene referees. *Onkologie* 2007; **30**: 295-300 [PMID: 17551252 DOI: 10.1159/0000102046]

25 **Ishida H**, Shirakawa K, Ohsawa T, Sobajima J, Hayashi Y, Nakada H, Yokoyama M, Hashimoto D. [Expression of mRNA levels of thymidylate synthase, dihydropyrimidine dehydrogenase, and orotate phosphoribosyltransferase of colorectal cancer--relationships among mRNA levels in association with response to 5-FU based treatment]. *Gan To Kagaku Ryoho* 2005; **32**: 1929-1934 [PMID: 16282729]

26 **Hosokawa A**, Yamada Y, Shimada Y, Muro K, Hamaguchi T, Morita H, Araake M, Orita H, Shirao K. Prognostic significance of thymidylate synthase in patients with metastatic colorectal cancer who receive protracted venous infusions of 5-fluorouracil. *Int J Clin Oncol* 2004; **9**: 388-392 [PMID: 15549590 DOI: 10.1007/s10147-004-0425-1]

27 **Ciaparrone M**, Quirino M, Schinzari G, Zannoni G, Corsi DC, Vecchio FM, Cassano A, La Torre G, Barone C. Predictive role of thymidylate synthase, dihydropyrimidine dehydrogenase and thymidine phosphorylase expression in colorectal cancer patients receiving adjuvant 5-fluorouracil. *Oncology* 2006; **70**: 366-377 [PMID: 17179731 DOI: 10.1159/000098110]

28 **Nakajima TE**, Yamada Y, Shimoda T, Matsubara J, Kato K, Hamaguchi T, Shimada Y, Okayama Y, Oka T, Shirao K. Combination of O6-methylguanine-DNA methyltransferase and thymidylate synthase for the prediction of fluoropyrimidine efficacy. *Eur J Cancer* 2008; **44**: 400-407 [PMID: 18068349 DOI: 10.1016/j.ejca.2007.11.010]

29 **Kornmann M**, Schwabe W, Sander S, Kron M, Sträter J, Polat S, Kettner E, Weiser HF, Baumann W, Schramm H, Häusler P, Ott K, Behnke D, Staib L, Beger HG, Link KH. Thymidylate synthase and dihydropyrimidine dehydrogenase mRNA expression levels: predictors for survival in colorectal cancer patients receiving adjuvant 5-fluorouracil. *Clin Cancer Res* 2003; **9**: 4116-4124 [PMID: 14519634]

30 **Link KH**, Kornmann M, Butzer U, Leder G, Sunelaitis E, Pillasch J, Salonga D, Danenberg KD, Danenberg PV, Beger HG. Thymidylate synthase quantitation and in vitro chemosensitivity testing predicts responses and survival of patients with isolated nonresectable liver tumors receiving hepatic arterial infusion chemotherapy. *Cancer* 2000; **89**: 288-296 [PMID: 10918158]

31 **Davies MM**, Johnston PG, Kaur S, Allen-Mersh TG. Colorectal liver metastasis thymidylate synthase staining correlates with response to hepatic arterial floxuridine. *Clin Cancer Res* 1999; **5**: 325-328 [PMID: 10037181]

32 **Kornmann M**, Link KH, Lenz HJ, Pillasch J, Metzger R, Butzer U, Leder GH, Weindel M, Safi F, Danenberg KD, Beger HG, Danenberg PV. Thymidylate synthase is a predictor for response and resistance in hepatic artery infusion chemotherapy. *Cancer Lett* 1997; **118**: 29-35 [PMID: 9310257]

33 **Etienne MC**, Chazal M, Laurent-Puig P, Magné N, Rosty C, Formento JL, Francoual M, Formento P, Renée N, Chamorey E, Bourgeon A, Seitz JF, Delpero JR, Letoublon C, Pezet D, Milano G. Prognostic value of tumoral thymidylate synthase and p53 in metastatic colorectal cancer patients receiving fluorouracil-based chemotherapy: phenotypic and genotypic analyses. *J Clin Oncol* 2002; **20**: 2832-2843 [PMID: 12065560]

34 **Shirota Y**, Stoehlmacher J, Brabender J, Xiong YP, Uetake H, Danenberg KD, Groshen S, Tsao-Wei DD, Danenberg PV, Lenz HJ. ERCC1 and thymidylate synthase mRNA levels predict survival for colorectal cancer patients receiving combination oxaliplatin and fluorouracil chemotherapy. *J Clin Oncol* 2001; **19**: 4298-4304 [PMID: 11731512]

35 **Paradiso A**, Simone G, Petroni S, Leone B, Vallejo C, Lacava J, Romero A, Machiavelli M, De Lena M, Allegra CJ, Johnston PG. Thymidilate synthase and p53 primary tumour expression as predictive factors for advanced colorectal cancer patients. *Br J Cancer* 2000; **82**: 560-567 [PMID: 10682666 DOI: 10.1054/bjoc.1999.0964]

36 **Aschele C**, Debernardis D, Bandelloni R, Cascinu S, Catalano V, Giordani P, Barni S, Turci D, Drudi G, Lonardi S, Gallo L, Maley F, Monfardini S. Thymidylate synthase protein expression in colorectal cancer metastases predicts for clinical outcome to leucovorin-modulated bolus or infusional 5-fluorouracil but not methotrexate-modulated bolus 5-fluorouracil. *Ann Oncol* 2002; **13**: 1882-1892 [PMID: 12453856]

37 **Yanagisawa Y**, Maruta F, Iinuma N, Ishizone S, Koide N, Nakayama J, Miyagawa S. Modified Irinotecan/5FU/Leucovorin therapy in advanced colorectal cancer and predicting therapeutic efficacy by expression of tumor-related enzymes. *Scand J Gastroenterol* 2007; **42**: 477-484 [PMID: 17454858 DOI: 10.1080/00365520600994418]

38 **Bendardaf R**, Lamlum H, Elzagheid A, Ristamäki R, Pyrhönen S. Thymidylate synthase expression levels: a prognostic and predictive role in advanced colorectal cancer. *Oncol Rep* 2005; **14**: 657-662 [PMID: 16077970]

39 **Ichikawa W**, Uetake H, Shirota Y, Yamada H, Nishi N, Nihei Z, Sugihara K, Hirayama R. Combination of dihydropyrimidine dehydrogenase and thymidylate synthase gene expressions in primary tumors as predictive parameters for the efficacy of fluoropyrimidine-based chemotherapy for metastatic colorectal cancer. *Clin Cancer Res* 2003; **9**: 786-791 [PMID: 12576451]

40 **Chu E**, Koeller DM, Johnston PG, Zinn S, Allegra CJ. Regulation of thymidylate synthase in human colon cancer cells treated with 5-fluorouracil and interferon-gamma. *Mol Pharmacol* 1993; **43**: 527-533 [PMID: 8474431]

41 **Longley DB**, Boyer J, Allen WL, Latif T, Ferguson PR, Maxwell PJ, McDermott U, Lynch M, Harkin DP, Johnston PG. The role of thymidylate synthase induction in modulating p53-regulated gene expression in response to 5-fluorouracil and antifolates. *Cancer Res* 2002; **62**: 2644-2649 [PMID: 11980662]

42 **Chu E**, Voeller DM, Jones KL, Takechi T, Maley GF, Maley F, Segal S, Allegra CJ. Identification of a thymidylate synthase ribonucleoprotein complex in human colon cancer cells. *Mol Cell Biol* 1994; **14**: 207-213 [PMID: 8264588]

43 **Suh KW**, Kim JH, Kim YB, Kim J, Jeong S. Thymidylate synthase gene polymorphism as a prognostic factor for colon cancer. *J Gastrointest Surg* 2005; **9**: 336-342 [PMID: 15749593 DOI: 10.1016/j.gassur.2004.09.030]

44 **Gosens MJ**, Moerland E, Lemmens VP, Rutten HT, Tan-Go I, van den Brule AJ. Thymidylate synthase genotyping is more predictive for therapy response than immunohistochemistry in patients with colon cancer. *Int J Cancer* 2008; **123**: 1941-1949 [PMID: 18661526 DOI: 10.1002/ijc.23740]

45 **Fernández-Contreras ME**, Sánchez-Prudencio S, Sánchez-Hernández JJ, García de Paredes ML, Gisbert JP, Roda-Navarro P, Gamallo C. Thymidylate synthase expression pattern, expression level and single nucleotide polymorphism are predictors for disease-free survival in patients of colorectal cancer treated with 5-fluorouracil. *Int J Oncol* 2006; **28**: 1303-1310 [PMID: 16596248]

46 **Gusella M**, Frigo AC, Bolzonella C, Marinelli R, Barile C, Bononi A, Crepaldi G, Menon D, Stievano L, Toso S, Pasini F, Ferrazzi E, Padrini R. Predictors of survival and toxicity in patients on adjuvant therapy with 5-fluorouracil for colorectal cancer. *Br J Cancer* 2009; **100**: 1549-1557 [PMID: 19384296 DOI: 10.1038/sj.bjc.6605052]

47 **Páez D**, Paré L, Altés A, Sancho-Poch FJ, Petriz L, Garriga J, Monill JM, Salazar J, del Rio E, Barnadas A, Marcuello E, Baiget M. Thymidylate synthase germline polymorphisms in rectal cancer patients treated with neoadjuvant chemoradiotherapy based on 5-fluorouracil. *J Cancer Res Clin Oncol* 2010; **136**: 1681-1689 [PMID: 20165956 DOI: 10.1007/s00432-010-0826-7]

48 **Villafranca E**, Okruzhnov Y, Dominguez MA, García-Foncillas J, Azinovic I, Martínez E, Illarramendi JJ, Arias F, Martínez Monge R, Salgado E, Angeletti S, Brugarolas A. Polymorphisms of the repeated sequences in the enhancer region of the thymidylate synthase gene promoter may predict downstaging after preoperative chemoradiation in rectal cancer. *J Clin Oncol* 2001; **19**: 1779-1786 [PMID: 11251009]

49 **Graziano F**, Ruzzo A, Loupakis F, Santini D, Catalano V, Canestrari E, Maltese P, Bisonni R, Fornaro L, Baldi G, Masi G, Falcone A, Tonini G, Giordani P, Alessandroni P, Giustini L, Vincenzi B, Magnani M. Liver-only metastatic colorectal cancer patients and thymidylate synthase polymorphisms for predicting response to 5-fluorouracil-based chemotherapy. *Br J Cancer* 2008; **99**: 716-721 [PMID: 18728661 DOI: 10.1038/sj.bjc.6604555]

50 **Marcuello E**, Altés A, del Rio E, César A, Menoyo A, Baiget M. Single nucleotide polymorphism in the 5' tandem repeat sequences of thymidylate synthase gene predicts for response to fluorouracil-based chemotherapy in advanced colorectal cancer patients. *Int J Cancer* 2004; **112**: 733-737 [PMID: 15386371 DOI: 10.1002/ijc.20487]

51 **Stoehlmacher J**, Park DJ, Zhang W, Yang D, Groshen S, Zahedy S, Lenz HJ. A multivariate analysis of genomic polymorphisms: prediction of clinical outcome to 5-FU/oxaliplatin combination chemotherapy in refractory colorectal cancer. *Br J Cancer* 2004; **91**: 344-354 [PMID: 15213713 DOI: 10.1038/sj.bjc.6601975]

52 **Lurje G**, Manegold PC, Ning Y, Pohl A, Zhang W, Lenz HJ. Thymidylate synthase gene variations: predictive and prognostic markers. *Mol Cancer Ther* 2009; **8**: 1000-1007 [PMID: 19383851 DOI: 10.1158/1535-7163.MCT-08-0219]

53 **Horie N**, Aiba H, Oguro K, Hojo H, Takeishi K. Functional analysis and DNA polymorphism of the tandemly repeated sequences in the 5'-terminal regulatory region of the human gene for thymidylate synthase. *Cell Struct Funct* 1995; **20**: 191-197 [PMID: 7586009]

54 **Kawakami K**, Watanabe G. Identification and functional analysis of single nucleotide polymorphism in the tandem repeat sequence of thymidylate synthase gene. *Cancer Res* 2003; **63**: 6004-6007 [PMID: 14522928]

55 **Pullarkat ST**, Stoehlmacher J, Ghaderi V, Xiong YP, Ingles SA, Sherrod A, Warren R, Tsao-Wei D, Groshen S, Lenz HJ. Thymidylate synthase gene polymorphism determines response and toxicity of 5-FU chemotherapy. *Pharmacogenomics J* 2001; **1**: 65-70 [PMID: 11913730]

56 **Mandola MV**, Stoehlmacher J, Muller-Weeks S, Cesarone G, Yu MC, Lenz HJ, Ladner RD. A novel single nucleotide polymorphism within the 5' tandem repeat polymorphism of the thymidylate synthase gene abolishes USF-1 binding and alters transcriptional activity. *Cancer Res* 2003; **63**: 2898-2904 [PMID: 12782596]

57 **Mandola MV**, Stoehlmacher J, Zhang W, Groshen S, Yu MC, Iqbal S, Lenz HJ, Ladner RD. A 6 bp polymorphism in the thymidylate synthase gene causes message instability and is associated with decreased intratumoral TS mRNA levels. *Pharmacogenetics* 2004; **14**: 319-327 [PMID: 15115918]

58 **Ulrich CM**, Bigler J, Velicer CM, Greene EA, Farin FM, Potter JD. Searching expressed sequence tag databases: discovery and confirmation of a common polymorphism in the thymidylate synthase gene. *Cancer Epidemiol Biomarkers Prev* 2000; **9**: 1381-1385 [PMID: 11142426]

59 **Schaaf MJ**, Cidlowski JA. AUUUA motifs in the 3'UTR of human glucocorticoid receptor alpha and beta mRNA destabilize mRNA and decrease receptor protein expression. *Steroids* 2002; **67**: 627-636 [PMID: 11996936]

60 **Lu JW**, Gao CM, Wu JZ, Cao HX, Tajima K, Feng JF. Polymorphism in the 3'-untranslated region of the thymidylate synthase gene and sensitivity of stomach cancer to fluoropyrimidine-based chemotherapy. *J Hum Genet* 2006; **51**: 155-160 [PMID: 16424979 DOI: 10.1007/s10038-005-0339-4]

61 **Pinedo HM**, Peters GF. Fluorouracil: biochemistry and pharmacology. *J Clin Oncol* 1988; **6**: 1653-1664 [PMID: 3049954]

62 **Frosst P**, Blom HJ, Milos R, Goyette P, Sheppard CA, Matthews RG, Boers GJ, den Heijer M, Kluijtmans LA, van den Heuvel LP. A candidate genetic risk factor for vascular disease: a common mutation in methylenetetrahydrofolate reductase. *Nat Genet* 1995; **10**: 111-113 [PMID: 7647779 DOI: 10.1038/ng0595-111]

63 **Bagley PJ**, Selhub J. A common mutation in the methylenetetrahydrofolate reductase gene is associated with an accumulation of formylated tetrahydrofolates in red blood cells. *Proc Natl Acad Sci U S A* 1998; **95**: 13217-13220 [PMID: 9789068]

64 **Eisenberg-Lerner A**, Bialik S, Simon HU, Kimchi A. Life and death partners: apoptosis, autophagy and the cross-talk between them. *Cell Death Differ* 2009; **16**: 966-975 [PMID: 19325568 DOI: 10.1038/cdd.2009.33]

65 **Sohn KJ**, Croxford R, Yates Z, Lucock M, Kim YI. Effect of the methylenetetrahydrofolate reductase C677T polymorphism on chemosensitivity of colon and breast cancer cells to 5-fluorouracil and methotrexate. *J Natl Cancer Inst* 2004; **96**: 134-144 [PMID: 14734703]

66 **Cohen V**, Panet-Raymond V, Sabbaghian N, Morin I, Batist G, Rozen R. Methylenetetrahydrofolate reductase polymorphism in advanced colorectal cancer: a novel genomic predictor of clinical response to fluoropyrimidine-based chemotherapy. *Clin Cancer Res* 2003; **9**: 1611-1615 [PMID: 12738713]

67 **Etienne MC**, Formento JL, Chazal M, Francoual M, Magné N, Formento P, Bourgeon A, Seitz JF, Delpero JR, Letoublon C, Pezet D, Milano G. Methylenetetrahydrofolate reductase gene polymorphisms and response to fluorouracil-based treatment in advanced colorectal cancer patients. *Pharmacogenetics* 2004; **14**: 785-792 [PMID: 15608557]

68 **Jakobsen A**, Nielsen JN, Gyldenkerne N, Lindeberg J. Thymidylate synthase and methylenetetrahydrofolate reductase gene polymorphism in normal tissue as predictors of fluorouracil sensitivity. *J Clin Oncol* 2005; **23**: 1365-1369 [PMID: 15735113 DOI: 10.1200/JCO.2005.06.219]

69 **Marcuello E**, Altés A, Menoyo A, Rio ED, Baiget M. Methylenetetrahydrofolate reductase gene polymorphisms: genomic predictors of clinical response to fluoropyrimidine-based chemotherapy? *Cancer Chemother Pharmacol* 2006; **57**: 835-840 [PMID: 16187112 DOI: 10.1007/s00280-005-0089-1]

70 **van der Put NM**, Gabreëls F, Stevens EM, Smeitink JA, Trijbels FJ, Eskes TK, van den Heuvel LP, Blom HJ. A second common mutation in the methylenetetrahydrofolate reductase gene: an additional risk factor for neural-tube defects? *Am J Hum Genet* 1998; **62**: 1044-1051 [PMID: 9545395 DOI: 10.1086/301825]

71 **Weisberg I**, Tran P, Christensen B, Sibani S, Rozen R. A second genetic polymorphism in methylenetetrahydrofolate reductase (MTHFR) associated with decreased enzyme activity. *Mol Genet Metab* 1998; **64**: 169-172 [PMID: 9719624 DOI: 10.1006/mgme.1998.2714]

72 **Sharma R**, Hoskins JM, Rivory LP, Zucknick M, London R, Liddle C, Clarke SJ. Thymidylate synthase and methylenetetrahydrofolate reductase gene polymorphisms and toxicity to capecitabine in advanced colorectal cancer patients. *Clin Cancer Res* 2008; **14**: 817-825 [PMID: 18245544 DOI: 10.1158/1078-0432.CCR-07-0425]

73 **Zhang W**, Press OA, Haiman CA, Yang DY, Gordon MA, Fazzone W, El-Khoueiry A, Iqbal S, Sherrod AE, Lurje G, Lenz HJ. Association of methylenetetrahydrofolate reductase gene polymorphisms and sex-specific survival in patients with metastatic colon cancer. *J Clin Oncol* 2007; **25**: 3726-3731 [PMID: 17704422 DOI: 10.1200/JCO.2007.11.4710]

74 **Zintzaras E**, Ziogas DC, Kitsios GD, Papathanasiou AA, Lau J, Raman G. MTHFR gene polymorphisms and response to chemotherapy in colorectal cancer: a meta-analysis. *Pharmacogenomics* 2009; **10**: 1285-1294 [PMID: 19663673 DOI: 10.2217/pgs.09.59]

75 **Afzal S**, Gusella M, Vainer B, Vogel UB, Andersen JT, Broedbaek K, Petersen M, Jimenez-Solem E, Bertolaso L, Barile C, Padrini R, Pasini F, Jensen SA, Poulsen HE. Combinations of polymorphisms in genes involved in the 5-Fluorouracil metabolism pathway are associated with gastrointestinal toxicity in chemotherapy-treated colorectal cancer patients. *Clin Cancer Res* 2011; **17**: 3822-3829 [PMID: 21471424 DOI: 10.1158/1078-0432.CCR-11-0304]

76 **Diasio RB**, Harris BE. Clinical pharmacology of 5-fluorouracil. *Clin Pharmacokinet* 1989; **16**: 215-237 [PMID: 2656050]

77 **Ezzeldin H**, Diasio R. Dihydropyrimidine dehydrogenase deficiency, a pharmacogenetic syndrome associated with potentially life-threatening toxicity following 5-fluorouracil administration. *Clin Colorectal Cancer* 2004; **4**: 181-189 [PMID: 15377401]

78 **Mattison LK**, Soong R, Diasio RB. Implications of dihydropyrimidine dehydrogenase on 5-fluorouracil pharmacogenetics and pharmacogenomics. *Pharmacogenomics* 2002; **3**: 485-492 [PMID: 12164772 DOI: 10.1517/14622416.3.4.485]

79 **Etienne MC**, Lagrange JL, Dassonville O, Fleming R, Thyss A, Renée N, Schneider M, Demard F, Milano G. Population study of dihydropyrimidine dehydrogenase in cancer patients. *J Clin Oncol* 1994; **12**: 2248-2253 [PMID: 7964939]

80 **Ridge SA**, Sludden J, Brown O, Robertson L, Wei X, Sapone A, Fernandez-Salguero PM, Gonzalez FJ, Vreken P, van Kuilenburg AB, van Gennip AH, McLeod HL. Dihydropyrimidine dehydrogenase pharmacogenetics in Caucasian subjects. *Br J Clin Pharmacol* 1998; **46**: 151-156 [PMID: 9723824]

81 **Ofverholm A**, Arkblad E, Skrtic S, Albertsson P, Shubbar E, Enerbäck C. Two cases of 5-fluorouracil toxicity linked with gene variants in the DPYD gene. *Clin Biochem* 2010; **43**: 331-334 [PMID: 19822137 DOI: 10.1016/j.clinbiochem.2009.09.024]

82 **Johnson MR**, Wang K, Tillmanns S, Albin N, Diasio RB. Structural organization of the human dihydropyrimidine dehydrogenase gene. *Cancer Res* 1997; **57**: 1660-1663 [PMID: 9135003]

83 **Yu J**, McLeod HL, Ezzeldin HH, Diasio RB. Methylation of the DPYD promoter and dihydropyrimidine dehydrogenase deficiency. *Clin Cancer Res* 2006; **12**: 3864; author reply 3864 [PMID: 16778115 DOI: 10.1158/1078-0432.ccr-06-0549]

84 **Bakkeren JA**, De Abreu RA, Sengers RC, Gabreëls FJ, Maas JM, Renier WO. Elevated urine, blood and cerebrospinal fluid levels of uracil and thymine in a child with dihydrothymine dehydrogenase deficiency. *Clin Chim Acta* 1984; **140**: 247-256 [PMID: 6467612]

85 **Van Kuilenburg AB**, Vreken P, Abeling NG, Bakker HD, Meinsma R, Van Lenthe H, De Abreu RA, Smeitink JA, Kayserili H, Apak MY, Christensen E, Holopainen I, Pulkki K, Riva D, Botteon G, Holme E, Tulinius M, Kleijer WJ, Beemer FA, Duran M, Niezen-Koning KE, Smit GP, Jakobs C, Smit LM, Van Gennip AH. Genotype and phenotype in patients with dihydropyrimidine dehydrogenase deficiency. *Hum Genet* 1999; **104**: 1-9 [PMID: 10071185]

86 **van Kuilenburg AB**, Muller EW, Haasjes J, Meinsma R, Zoetekouw L, Waterham HR, Baas F, Richel DJ, van Gennip AH. Lethal outcome of a patient with a complete dihydropyrimidine dehydrogenase (DPD) deficiency after administration of 5-fluorouracil: frequency of the common IVS14+1G& gt; A mutation causing DPD deficiency. *Clin Cancer Res* 2001; **7**: 1149-1153 [PMID: 11350878]

87 **Van Kuilenburg AB**, Meinsma R, Zoetekouw L, Van Gennip AH. High prevalence of the IVS14 + 1G& gt; A mutation in the dihydropyrimidine dehydrogenase gene of patients with severe 5-fluorouracil-associated toxicity. *Pharmacogenetics* 2002; **12**: 555-558 [PMID: 12360106]

88 **Ciccolini J**, Mercier C, Evrard A, Dahan L, Boyer JC, Duffaud F, Richard K, Blanquicett C, Milano G, Blesius A, Durand A, Seitz JF, Favre R, Lacarelle B. A rapid and inexpensive method for anticipating severe toxicity to fluorouracil and fluorouracil-based chemotherapy. *Ther Drug Monit* 2006; **28**: 678-685 [PMID: 17038885 DOI: 10.1097/01.ftd.0000245771.82720.c7]

89 **Meinsma R**, Fernandez-Salguero P, Van Kuilenburg AB, Van Gennip AH, Gonzalez FJ. Human polymorphism in drug metabolism: mutation in the dihydropyrimidine dehydrogenase gene results in exon skipping and thymine uracilurea. *DNA Cell Biol* 1995; **14**: 1-6 [PMID: 7832988]

90 **Wei X**, McLeod HL, McMurrough J, Gonzalez FJ, Fernandez-Salguero P. Molecular basis of the human dihydropyrimidine dehydrogenase deficiency and 5-fluorouracil toxicity. *J Clin Invest* 1996; **98**: 610-615 [PMID: 8698850 DOI: 10.1172/JCI118830]

91 **van Kuilenburg AB**, Haasjes J, Richel DJ, Zoetekouw L, Van Lenthe H, De Abreu RA, Maring JG, Vreken P, van Gennip AH. Clinical implications of dihydropyrimidine dehydrogenase (DPD) deficiency in patients with severe 5-fluorouracil-associated toxicity: identification of new mutations in the DPD gene. *Clin Cancer Res* 2000; **6**: 4705-4712 [PMID: 11156223]

92 **Amstutz U**, Farese S, Aebi S, Largiadèr CR. Dihydropyrimidine dehydrogenase gene variation and severe 5-fluorouracil toxicity: a haplotype assessment. *Pharmacogenomics* 2009; **10**: 931-944 [PMID: 19530960 DOI: 10.2217/pgs.09.28]

93 **Amstutz U**, Farese S, Aebi S, Largiadèr CR. Hypermethylation of the DPYD promoter region is not a major predictor of severe toxicity in 5-fluorouracil based chemotherapy. *J Exp Clin Cancer Res* 2008; **27**: 54 [PMID: 18937829 DOI: 10.1186/1756-9966-27-54]

94 **Scartozzi M**, Maccaroni E, Giampieri R, Pistelli M, Bittoni A, Del Prete M, Berardi R, Cascinu S. 5-Fluorouracil pharmacogenomics: still rocking after all these years? *Pharmacogenomics* 2011; **12**: 251-265 [PMID: 21332317 DOI: 10.2217/pgs.10.167]

95 **van Kuilenburg AB**, Meinsma R, Zonnenberg BA, Zoetekouw L, Baas F, Matsuda K, Tamaki N, van Gennip AH. Dihydropyrimidinase deficiency and severe 5-fluorouracil toxicity. *Clin Cancer Res* 2003; **9**: 4363-4367 [PMID: 14555507]

96 **Thomas HR**, Ezzeldin HH, Guarcello V, Mattison LK, Fridley BL, Diasio RB. Genetic regulation of beta-ureidopropionase and its possible implication in altered uracil catabolism. *Pharmacogenet Genomics* 2008; **18**: 25-35 [PMID: 18216719 DOI: 10.1097/FPC.0b013e3282f2f134]

97 **Vallböhmer D**, Yang DY, Kuramochi H, Shimizu D, Danenberg KD, Lindebjerg J, Nielsen JN, Jakobsen A, Danenberg PV. DPD is a molecular determinant of capecitabine efficacy in colorectal cancer. *Int J Oncol* 2007; **31**: 413-418 [PMID: 17611699]

98 **Meropol NJ**, Gold PJ, Diasio RB, Andria M, Dhami M, Godfrey T, Kovatich AJ, Lund KA, Mitchell E, Schwarting R. Thymidine phosphorylase expression is associated with response to capecitabine plus irinotecan in patients with metastatic colorectal cancer. *J Clin Oncol* 2006; **24**: 4069-4077 [PMID: 16943524 DOI: 10.1200/JCO.2005.05.2084]

99 **Vallböhmer D**, Kuramochi H, Shimizu D, Danenberg KD, Lindebjerg J, Nielsen JN, Jakobsen A, Danenberg PV. Molecular factors of 5-fluorouracil metabolism in colorectal cancer: analysis of primary tumor and lymph node metastasis. *Int J Oncol* 2006; **28**: 527-533 [PMID: 16391809]

100 **Bronckaers A**, Gago F, Balzarini J, Liekens S. The dual role of thymidine phosphorylase in cancer development and chemotherapy. *Med Res Rev* 2009; **29**: 903-953 [PMID: 19434693 DOI: 10.1002/med.20159]

101 **Miyadera K**, Sumizawa T, Haraguchi M, Yoshida H, Konstanty W, Yamada Y, Akiyama S. Role of thymidine phosphorylase activity in the angiogenic effect of platelet derived endothelial cell growth factor/thymidine phosphorylase. *Cancer Res* 1995; **55**: 1687-1690 [PMID: 7536129]

102 **Takebayashi Y**, Yamada K, Miyadera K, Sumizawa T, Furukawa T, Kinoshita F, Aoki D, Okumura H, Yamada Y, Akiyama S, Aikou T. The activity and expression of thymidine phosphorylase in human solid tumours. *Eur J Cancer* 1996; **32A**: 1227-1232 [PMID: 8758258]

103 **Walko CM**, Lindley C. Capecitabine: a review. *Clin Ther* 2005; **27**: 23-44 [PMID: 15763604 DOI: 10.1016/j.clinthera.2005.01.005]

104 **Temmink OH**, de Bruin M, Turksma AW, Cricca S, Laan AC, Peters GJ. Activity and substrate specificity of pyrimidine phosphorylases and their role in fluoropyrimidine sensitivity in colon cancer cell lines. *Int J Biochem Cell Biol* 2007; **39**: 565-575 [PMID: 17098463 DOI: 10.1016/j.biocel.2006.10.009]

105 **Schüller J**, Cassidy J, Dumont E, Roos B, Durston S, Banken L, Utoh M, Mori K, Weidekamm E, Reigner B. Preferential activation of capecitabine in tumor following oral administration to colorectal cancer patients. *Cancer Chemother Pharmacol* 2000; **45**: 291-297 [PMID: 10755317]

106 **Lamberti C**, Sauerbruch T, Glasmacher A. Adjuvant capecitabine is at least as effective as fluorouracil plus leucovorin for survival in people with resected stage III colon cancer. *Cancer Treat Rev* 2005; **31**: 648-652 [PMID: 16289340 DOI: 10.1016/j.ctrv.2005.09.009]

107 **Soong R**, Shah N, Salto-Tellez M, Tai BC, Soo RA, Han HC, Ng SS, Tan WL, Zeps N, Joseph D, Diasio RB, Iacopetta B. Prognostic significance of thymidylate synthase, dihydropyrimidine dehydrogenase and thymidine phosphorylase protein expression in colorectal cancer patients treated with or without 5-fluorouracil-based chemotherapy. *Ann Oncol* 2008; **19**: 915-919 [PMID: 18245778 DOI: 10.1093/annonc/mdm599]

108 **Aprile G**, Mazzer M, Moroso S, Puglisi F. Pharmacology and therapeutic efficacy of capecitabine: focus on breast and colorectal cancer. *Anticancer Drugs* 2009; **20**: 217-229 [PMID: 19247178 DOI: 10.1097/CAD.0b013e3283293fd4]

109 **Allegra CJ**, Paik S, Colangelo LH, Parr AL, Kirsch I, Kim G, Klein P, Johnston PG, Wolmark N, Wieand HS. Prognostic value of thymidylate synthase, Ki-67, and p53 in patients with Dukes' B and C colon cancer: a National Cancer Institute-National Surgical Adjuvant Breast and Bowel Project collaborative study. *J Clin Oncol* 2003; **21**: 241-250 [PMID: 12525515]

110 **Koopman M**, Venderbosch S, van Tinteren H, Ligtenberg MJ, Nagtegaal I, Van Krieken JH, Punt CJ. Predictive and prognostic markers for the outcome of chemotherapy in advanced colorectal cancer, a retrospective analysis of the phase III randomised CAIRO study. *Eur J Cancer* 2009; **45**: 1999-2006 [PMID: 19457654 DOI: 10.1016/j.ejca.2009.04.017]

111 **Evans DR**, Guy HI. Mammalian pyrimidine biosynthesis: fresh insights into an ancient pathway. *J Biol Chem* 2004; **279**: 33035-33038 [PMID: 15096496 DOI: 10.1074/jbc.R400007200]

112 **Muhale FA**, Wetmore BA, Thomas RS, McLeod HL. Systems pharmacology assessment of the 5-fluorouracil pathway. *Pharmacogenomics* 2011; **12**: 341-350 [PMID: 21449674 DOI: 10.2217/pgs.10.188]

113 **Matsuyama R**, Togo S, Shimizu D, Momiyama N, Ishikawa T, Ichikawa Y, Endo I, Kunisaki C, Suzuki H, Hayasizaki Y, Shimada H. Predicting 5-fluorouracil chemosensitivity of liver metastases from colorectal cancer using primary tumor specimens: three-gene expression model predicts clinical response. *Int J Cancer* 2006; **119**: 406-413 [PMID: 16477629 DOI: 10.1002/ijc.21843]

114 **Ishikawa M**, Miyauchi T, Kashiwagi Y. Clinical implications of thymidylate synthetase, dihydropyrimidine dehydrogenase and orotate phosphoribosyl transferase activity levels in colorectal carcinoma following radical resection and administration of adjuvant 5-FU chemotherapy. *BMC Cancer* 2008; **8**: 188 [PMID: 18597678 DOI: 10.1186/1471-2407-8-188]

115 **Ochiai T**, Nishimura K, Noguchi H, Kitajima M, Tsuruoka Y, Takahashi Y, Tsukada A, Watanabe E, Nagaoka I, Futagawa S. Prognostic impact of orotate phosphoribosyl transferase activity in resectable colorectal cancers treated by 5-fluorouracil-based adjuvant chemotherapy. *J Surg Oncol* 2006; **94**: 45-50 [PMID: 16788943 DOI: 10.1002/jso.20553]

116 **Tokunaga Y**, Sasaki H, Saito T. Clinical role of orotate phosphoribosyl transferase and dihydropyrimidine dehydrogenase in colorectal cancer treated with postoperative fluoropyrimidine. *Surgery* 2007; **141**: 346-353 [PMID: 17349846 DOI: 10.1016/j.surg.2006.06.025]

117 **Tokunaga Y**, Ohnishi T, Sasaki H. [Investigation of chemotherapy based on enzyme expression and drug sensitivity test in colorectal cancer]. *Gan To Kagaku Ryoho* 2011; **38**: 69-73 [PMID: 21368461]

118 **Ichikawa W**, Uetake H, Shirota Y, Yamada H, Takahashi T, Nihei Z, Sugihara K, Sasaki Y, Hirayama R. Both gene expression for orotate phosphoribosyltransferase and its ratio to dihydropyrimidine dehydrogenase influence outcome following fluoropyrimidine-based chemotherapy for metastatic colorectal cancer. *Br J Cancer* 2003; **89**: 1486-1492 [PMID: 14562021 DOI: 10.1038/sj.bjc.6601335]

119 **Yamada H**, Iinuma H, Watanabe T. Prognostic value of 5-fluorouracil metabolic enzyme genes in Dukes' stage B and C colorectal cancer patients treated with oral 5-fluorouracil-based adjuvant chemotherapy. *Oncol Rep* 2008; **19**: 729-735 [PMID: 18288408]

120 **Fujii R**, Seshimo A, Kameoka S. Relationships between the expression of thymidylate synthase, dihydropyrimidine dehydrogenase, and orotate phosphoribosyltransferase and cell proliferative activity and 5-fluorouracil sensitivity in colorectal carcinoma. *Int J Clin Oncol* 2003; **8**: 72-78 [PMID: 12720098 DOI: 10.1007/s101470300013]

121 **Ochiai T**, Nishimura K, Noguchi H, Kitajima M, Tsukada A, Watanabe E, Nagaoka I, Futagawa S. Prognostic impact of orotate phosphoribosyl transferase among 5-fluorouracil metabolic enzymes in resectable colorectal cancers treated by oral 5-fluorouracil-based adjuvant chemotherapy. *Int J Cancer* 2006; **118**: 3084-3088 [PMID: 16425285 DOI: 10.1002/ijc.21779]

122 **Isshi K**, Sakuyama T, Gen T, Nakamura Y, Kuroda T, Katuyama T, Maekawa Y. Predicting 5-FU sensitivity using human colorectal cancer specimens: comparison of tumor dihydropyrimidine dehydrogenase and orotate phosphoribosyl transferase activities with in vitro chemosensitivity to 5-FU. *Int J Clin Oncol* 2002; **7**: 335-342 [PMID: 12494248 DOI: 10.1007/s101470200051]

123 **Kitajima M**, Takita N, Hata M, Maeda T, Sakamoto K, Kamano T, Ochiai T. The relationship between 5-fluorouracil sensitivity and single nucleotide polymorphisms of the orotate phosphoribosyl transferase gene in colorectal cancer. *Oncol Rep* 2006; **15**: 161-165 [PMID: 16328050]

124 **Ichikawa W**, Takahashi T, Suto K, Sasaki Y, Hirayama R. Orotate phosphoribosyltransferase gene polymorphism predicts toxicity in patients treated with bolus 5-fluorouracil regimen. *Clin Cancer Res* 2006; **12**: 3928-3934 [PMID: 16818689 DOI: 10.1158/1078-0432.CCR-05-2665]

125 **Tsunoda A**, Nakao K, Watanabe M, Matsui N, Ooyama A, Kusano M. Associations of various gene polymorphisms with toxicity in colorectal cancer patients receiving oral uracil and tegafur plus leucovorin: a prospective study. *Ann Oncol* 2011; **22**: 355-361 [PMID: 20647221 DOI: 10.1093/annonc/mdq358]

126 **Gusella M**, Bertolaso L, Bolzonella C, Pasini F, Padrini R. Frequency of uridine monophosphate synthase Gly(213)Ala polymorphism in Caucasian gastrointestinal cancer patients and healthy subjects, investigated by means of new, rapid genotyping assays. *Genet Test Mol Biomarkers* 2011; **15**: 691-695 [PMID: 21631301 DOI: 10.1089/gtmb.2011.0021]

127 **Suchi M**, Mizuno H, Kawai Y, Tsuboi T, Sumi S, Okajima K, Hodgson ME, Ogawa H, Wada Y. Molecular cloning of the human UMP synthase gene and characterization of point mutations in two hereditary orotic aciduria families. *Am J Hum Genet* 1997; **60**: 525-539 [PMID: 9042911]

128 **Houghton JA**, Houghton PJ, Wooten RS. Mechanism of induction of gastrointestinal toxicity in the mouse by 5-fluorouracil, 5-fluorouridine, and 5-fluoro-2'-deoxyuridine. *Cancer Res* 1979; **39**: 2406-2413 [PMID: 156065]

129 **Wang H**, Bian T, Liu D, Jin T, Chen Y, Lin A, Chen C. Association analysis of CYP2A6 genotypes and haplotypes with 5-fluorouracil formation from tegafur in human liver microsomes. *Pharmacogenomics* 2011; **12**: 481-492 [PMID: 21521021 DOI: 10.2217/pgs.10.202]

130 **Carethers JM**, Chauhan DP, Fink D, Nebel S, Bresalier RS, Howell SB, Boland CR. Mismatch repair proficiency and in vitro response to 5-fluorouracil. *Gastroenterology* 1999; **117**: 123-131 [PMID: 10381918]

131 **Meyers M**, Wagner MW, Hwang HS, Kinsella TJ, Boothman DA. Role of the hMLH1 DNA mismatch repair protein in fluoropyrimidine-mediated cell death and cell cycle responses. *Cancer Res* 2001; **61**: 5193-5201 [PMID: 11431359]

132 **Raymond E**, Chaney SG, Taamma A, Cvitkovic E. Oxaliplatin: a review of preclinical and clinical studies. *Ann Oncol* 1998; **9**: 1053-1071 [PMID: 9834817]

133 **Popat S**, Hubner R, Houlston RS. Systematic review of microsatellite instability and colorectal cancer prognosis. *J Clin Oncol* 2005; **23**: 609-618 [PMID: 15659508 DOI: 10.1200/JCO.2005.01.086]

134 **Sargent DJ**, Marsoni S, Thibodeau SN, Labianca R, Hamilton SR, Torri V, Monges G, Ribic C, Grothey A, Gallinger S. Confirmation of deficient mismatch repair (dMMR) as a predictive marker for lack of benefit from 5-FU based chemotherapy in stage II and III colon cancer (CC): A pooled molecular reanalysis of randomized chemotherapy trials. *J Clin Oncol* 2008; **26**: 4008

135 **Gryfe R**, Kim H, Hsieh ET, Aronson MD, Holowaty EJ, Bull SB, Redston M, Gallinger S. Tumor microsatellite instability and clinical outcome in young patients with colorectal cancer. *N Engl J Med* 2000; **342**: 69-77 [PMID: 10631274 DOI: 10.1056/NEJM200001133420201]

136 **Elsaleh H**, Powell B, McCaul K, Grieu F, Grant R, Joseph D, Iacopetta B. P53 alteration and microsatellite instability have predictive value for survival benefit from chemotherapy in stage III colorectal carcinoma. *Clin Cancer Res* 2001; **7**: 1343-1349 [PMID: 11350904]

137 **Lim SB**, Jeong SY, Lee MR, Ku JL, Shin YK, Kim WH, Park JG. Prognostic significance of microsatellite instability in sporadic colorectal cancer. *Int J Colorectal Dis* 2004; **19**: 533-537 [PMID: 15175889 DOI: 10.1007/s00384-004-0596-2]

138 **Mori S**, Ogata Y, Shirouzu K. Biological features of sporadic colorectal carcinoma with high-frequency microsatellite instability: special reference to tumor proliferation and apoptosis. *Int J Clin Oncol* 2004; **9**: 322-329 [PMID: 15375710 DOI: 10.1007/s10147-004-0406-4]

139 **Vogelstein B**, Lane D, Levine AJ. Surfing the p53 network. *Nature* 2000; **408**: 307-310 [PMID: 11099028 DOI: 10.1038/35042675]

140 **Levine AJ**. p53, the cellular gatekeeper for growth and division. *Cell* 1997; **88**: 323-331 [PMID: 9039259]

141 **Bunz F**, Hwang PM, Torrance C, Waldman T, Zhang Y, Dillehay L, Williams J, Lengauer C, Kinzler KW, Vogelstein B. Disruption of p53 in human cancer cells alters the responses to therapeutic agents. *J Clin Invest* 1999; **104**: 263-269 [PMID: 10430607 DOI: 10.1172/JCI6863]

142 **Liang JT**, Huang KC, Cheng YM, Hsu HC, Cheng AL, Hsu CH, Yeh KH, Wang SM, Chang KJ. P53 overexpression predicts poor chemosensitivity to high-dose 5-fluorouracil plus leucovorin chemotherapy for stage IV colorectal cancers after palliative bowel resection. *Int J Cancer* 2002; **97**: 451-457 [PMID: 11802206]

143 **Garrity MM**, Burgart LJ, Mahoney MR, Windschitl HE, Salim M, Wiesenfeld M, Krook JE, Michalak JC, Goldberg RM, O'Connell MJ, Furth AF, Sargent DJ, Murphy LM, Hill E, Riehle DL, Meyers CH, Witzig TE. Prognostic value of proliferation, apoptosis, defective DNA mismatch repair, and p53 overexpression in patients with resected Dukes' B2 or C colon cancer: a North Central Cancer Treatment Group Study. *J Clin Oncol* 2004; **22**: 1572-1582 [PMID: 15117979 DOI: 10.1200/JCO.2004.10.042]

144 **van Oijen MG**, Slootweg PJ. Gain-of-function mutations in the tumor suppressor gene p53. *Clin Cancer Res* 2000; **6**: 2138-2145 [PMID: 10873062]

145 **Pugacheva EN**, Ivanov AV, Kravchenko JE, Kopnin BP, Levine AJ, Chumakov PM. Novel gain of function activity of p53 mutants: activation of the dUTPase gene expression leading to resistance to 5-fluorouracil. *Oncogene* 2002; **21**: 4595-4600 [PMID: 12096336 DOI: 10.1038/sj.onc.1205704]

146 **Wu AHB**, Yeo KTJ. Pharmacogenomic testing in current clinical practice: implementation in the clinical laboratory. New York: Humana Press, 2011

147 **Masumoto N**, Nakano S, Esaki T, Tatsumoto T, Fujishima H, Baba E, Nakamura M, Niho Y. Sequence-dependent modulation of anticancer drug activities by 7-ethyl-10-hydroxycamptothecin in an HST-1 human squamous carcinoma cell line. *Anticancer Res* 1995; **15**: 405-409 [PMID: 7763013]

148 **Matsuoka H**, Yano K, Seo Y, Saito T, Tomoda H, Takiguchi S, Kono A. Cytotoxicity of CPT-11 for gastrointestinal cancer cells cultured on fixed-contact-sensitive plates. *Anticancer Drugs* 1995; **6**: 413-418 [PMID: 7670139]

149 **Shimada Y**, Rougier P, Pitot H. Efficacy of CPT-11 (irinotecan) as a single agent in metastatic colorectal cancer. *Eur J Cancer* 1996; **32A** Suppl 3: S13-S17 [PMID: 8943660]

150 **Rougier P**, Bugat R, Douillard JY, Culine S, Suc E, Brunet P, Becouarn Y, Ychou M, Marty M, Extra JM, Bonneterre J, Adenis A, Seitz JF, Ganem G, Namer M, Conroy T, Negrier S, Merrouche Y, Burki F, Mousseau M, Herait P, Mahjoubi M. Phase II study of irinotecan in the treatment of advanced colorectal cancer in chemotherapy-naive patients and patients pretreated with fluorouracil-based chemotherapy. *J Clin Oncol* 1997; **15**: 251-260 [PMID: 8996150]

151 **Clarke SJ**, Yip S, Brown C, van Hazel GA, Ransom DT, Goldstein D, Jeffrey GM, Tebbutt NC, Buck M, Lowenthal RM, Boland A, Gebski V, Zalcberg J, Simes RJ. Single-agent irinotecan or FOLFIRI as second-line chemotherapy for advanced colorectal cancer; results of a randomised phase II study (DaVINCI) and meta-analysis [corrected]. *Eur J Cancer* 2011; **47**: 1826-1836 [PMID: 21665462 DOI: 10.1016/j.ejca.2011.04.024]

152 **Cortejoso L**, López-Fernández LA. Pharmacogenetic markers of toxicity for chemotherapy in colorectal cancer patients. *Pharmacogenomics* 2012; **13**: 1173-1191 [PMID: 22909207 DOI: 10.2217/pgs.12.95]

153 **Freyer G**, Duret A, Milano G, Chatelut E, Rebischung C, Delord JP, Merrouche Y, Lledo G, Etienne MC, Falandry C. Pharmacogenetic tailoring of irinotecan-based first-line chemotherapy in metastatic colorectal cancer: results of a pilot study. *Anticancer Res* 2011; **31**: 359-366 [PMID: 21273624]

154 **Shimoyama S**. Pharmacogenetics of irinotecan: An ethnicity-based prediction of irinotecan adverse events. *World J Gastrointest Surg* 2010; **2**: 14-21 [PMID: 21160829 DOI: 10.4240/wjgs.v2.i1.14]

155 **Rasheed ZA**, Rubin EH. Mechanisms of resistance to topoisomerase I-targeting drugs. *Oncogene* 2003; **22**: 7296-7304 [PMID: 14576839 DOI: 10.1038/sj.onc.1206935]

156 **Pommier Y**, Pourquier P, Urasaki Y, Wu J, Laco GS. Topoisomerase I inhibitors: selectivity and cellular resistance. *Drug Resist Updat* 1999; **2**: 307-318 [PMID: 11504505 DOI: 10.1054/drup.1999.0102]

157 **Smith NF**, Figg WD, Sparreboom A. Pharmacogenetics of irinotecan metabolism and transport: an update. *Toxicol In Vitro* 2006; **20**: 163-175 [PMID: 16271446 DOI: 10.1016/j.tiv.2005.06.045]

158 **Charasson V**, Bellott R, Meynard D, Longy M, Gorry P, Robert J. Pharmacogenetics of human carboxylesterase 2, an enzyme involved in the activation of irinotecan into SN-38. *Clin Pharmacol Ther* 2004; **76**: 528-535 [PMID: 15592324 DOI: 10.1016/j.clpt.2004.08.007]

159 **Bellott R**, Le Morvan V, Charasson V, Laurand A, Colotte M, Zanger UM, Klein K, Smith D, Bonnet J, Robert J. Functional study of the 830C& gt; G polymorphism of the human carboxylesterase 2 gene. *Cancer Chemother Pharmacol* 2008; **61**: 481-488 [PMID: 17483951 DOI: 10.1007/s00280-007-0493-9]

160 **Wu MH**, Chen P, Wu X, Liu W, Strom S, Das S, Cook EH, Rosner GL, Dolan ME. Determination and analysis of single nucleotide polymorphisms and haplotype structure of the human carboxylesterase 2 gene. *Pharmacogenetics* 2004; **14**: 595-605 [PMID: 15475733]

161 **Kim SR**, Sai K, Tanaka-Kagawa T, Jinno H, Ozawa S, Kaniwa N, Saito Y, Akasawa A, Matsumoto K, Saito H, Kamatani N, Shirao K, Yamamoto N, Yoshida T, Minami H, Ohtsu A, Saijo N, Sawada J. Haplotypes and a novel defective allele of CES2 found in a Japanese population. *Drug Metab Dispos* 2007; **35**: 1865-1872 [PMID: 17640957 DOI: 10.1124/dmd.107.015339]

162 **Sanghani SP**, Sanghani PC, Schiel MA, Bosron WF. Human carboxylesterases: an update on CES1, CES2 and CES3. *Protein Pept Lett* 2009; **16**: 1207-1214 [PMID: 19508181]

163 **Marsh S**, Xiao M, Yu J, Ahluwalia R, Minton M, Freimuth RR, Kwok PY, McLeod HL. Pharmacogenomic assessment of carboxylesterases 1 and 2. *Genomics* 2004; **84**: 661-668 [PMID: 15475243 DOI: 10.1016/j.ygeno.2004.07.008]

164 **van Ark-Otte J**, Kedde MA, van der Vijgh WJ, Dingemans AM, Jansen WJ, Pinedo HM, Boven E, Giaccone G. Determinants of CPT-11 and SN-38 activities in human lung cancer cells. *Br J Cancer* 1998; **77**: 2171-2176 [PMID: 9649129]

165 **Pavillard V**, Agostini C, Richard S, Charasson V, Montaudon D, Robert J. Determinants of the cytotoxicity of irinotecan in two human colorectal tumor cell lines. *Cancer Chemother Pharmacol* 2002; **49**: 329-335 [PMID: 11914913 DOI: 10.1007/s00280-001-0416-0]

166 **Kubo T**, Kim SR, Sai K, Saito Y, Nakajima T, Matsumoto K, Saito H, Shirao K, Yamamoto N, Minami H, Ohtsu A, Yoshida T, Saijo N, Ohno Y, Ozawa S, Sawada J. Functional characterization of three naturally occurring single nucleotide polymorphisms in the CES2 gene encoding carboxylesterase 2 (HCE-2). *Drug Metab Dispos* 2005; **33**: 1482-1487 [PMID: 16033949 DOI: 10.1124/dmd.105.005587]

167 **Tanimoto K**, Kaneyasu M, Shimokuni T, Hiyama K, Nishiyama M. Human carboxylesterase 1A2 expressed from carboxylesterase 1A1 and 1A2 genes is a potent predictor of CPT-11 cytotoxicity in vitro. *Pharmacogenet Genomics* 2007; **17**: 1-10 [PMID: 17264798 DOI: 10.1097/01.fpc.0000230110.18957.50]

168 **Yoshimura M**, Kimura T, Ishii M, Ishii K, Matsuura T, Geshi E, Hosokawa M, Muramatsu M. Functional polymorphisms in carboxylesterase1A2 (CES1A2) gene involves specific protein 1 (Sp1) binding sites. *Biochem Biophys Res Commun* 2008; **369**: 939-942 [PMID: 18328811 DOI: 10.1016/j.bbrc.2008.02.120]

169 **Ando Y**, Hasegawa Y. Clinical pharmacogenetics of irinotecan (CPT-11). *Drug Metab Rev* 2005; **37**: 565-574 [PMID: 16257834 DOI: 10.1080/03602530500316254]

170 **Aono S**, Yamada Y, Keino H, Hanada N, Nakagawa T, Sasaoka Y, Yazawa T, Sato H, Koiwai O. Identification of defect in the genes for bilirubin UDP-glucuronosyl-transferase in a patient with Crigler-Najjar syndrome type II. *Biochem Biophys Res Commun* 1993; **197**: 1239-1244 [PMID: 8280139 DOI: 10.1006/bbrc.1993.2610]

171 **Aono S**, Yamada Y, Keino H, Sasaoka Y, Nakagawa T, Onishi S, Mimura S, Koiwai O, Sato H. A new type of defect in the gene for bilirubin uridine 5'-diphosphate-glucuronosyltransferase in a patient with Crigler-Najjar syndrome type I. *Pediatr Res* 1994; **35**: 629-632 [PMID: 7936809 DOI: 10.1203/00006450-199406000-00002]

172 **Aono S**, Adachi Y, Uyama E, Yamada Y, Keino H, Nanno T, Koiwai O, Sato H. Analysis of genes for bilirubin UDP-glucuronosyltransferase in Gilbert's syndrome. *Lancet* 1995; **345**: 958-959 [PMID: 7715297]

173 **Villeneuve L**, Girard H, Fortier LC, Gagné JF, Guillemette C. Novel functional polymorphisms in the UGT1A7 and UGT1A9 glucuronidating enzymes in Caucasian and African-American subjects and their impact on the metabolism of 7-ethyl-10-hydroxycamptothecin and flavopiridol anticancer drugs. *J Pharmacol Exp Ther* 2003; **307**: 117-128 [PMID: 12944498 DOI: 10.1124/jpet.103.054072]

174 **Jinno H**, Tanaka-Kagawa T, Hanioka N, Saeki M, Ishida S, Nishimura T, Ando M, Saito Y, Ozawa S, Sawada J. Glucuronidation of 7-ethyl-10-hydroxycamptothecin (SN-38), an active metabolite of irinotecan (CPT-11), by human UGT1A1 variants, G71R, P229Q, and Y486D. *Drug Metab Dispos* 2003; **31**: 108-113 [PMID: 12485959]

175 **Strassburg CP**, Kalthoff S, Ehmer U. Variability and function of family 1 uridine-5'-diphosphate glucuronosyltransferases (UGT1A). *Crit Rev Clin Lab Sci* 2008; **45**: 485-530 [PMID: 19003600 DOI: 10.1080/10408360802374624]

176 **Cecchin E**, Innocenti F, D'Andrea M, Corona G, De Mattia E, Biason P, Buonadonna A, Toffoli G. Predictive role of the UGT1A1, UGT1A7, and UGT1A9 genetic variants and their haplotypes on the outcome of metastatic colorectal cancer patients treated with fluorouracil, leucovorin, and irinotecan. *J Clin Oncol* 2009; **27**: 2457-2465 [PMID: 19364970 DOI: 10.1200/JCO.2008.19.0314]

177 **Toffoli G**, Cecchin E, Corona G, Russo A, Buonadonna A, D'Andrea M, Pasetto LM, Pessa S, Errante D, De Pangher V, Giusto M, Medici M, Gaion F, Sandri P, Galligioni E, Bonura S, Boccalon M, Biason P, Frustaci S. The role of UGT1A1\*28 polymorphism in the pharmacodynamics and pharmacokinetics of irinotecan in patients with metastatic colorectal cancer. *J Clin Oncol* 2006; **24**: 3061-3068 [PMID: 16809730 DOI: 10.1200/JCO.2005.05.5400]

178 **Rouits E**, Charasson V, Pétain A, Boisdron-Celle M, Delord JP, Fonck M, Laurand A, Poirier AL, Morel A, Chatelut E, Robert J, Gamelin E. Pharmacokinetic and pharmacogenetic determinants of the activity and toxicity of irinotecan in metastatic colorectal cancer patients. *Br J Cancer* 2008; **99**: 1239-1245 [PMID: 18797458 DOI: 10.1038/sj.bjc.6604673]

179 **Côté JF**, Kirzin S, Kramar A, Mosnier JF, Diebold MD, Soubeyran I, Thirouard AS, Selves J, Laurent-Puig P, Ychou M. UGT1A1 polymorphism can predict hematologic toxicity in patients treated with irinotecan. *Clin Cancer Res* 2007; **13**: 3269-3275 [PMID: 17510208 DOI: 10.1158/1078-0432.CCR-06-2290]

180 **McLeod HL**, Sargent DJ, Marsh S, Green EM, King CR, Fuchs CS, Ramanathan RK, Williamson SK, Findlay BP, Thibodeau SN, Grothey A, Morton RF, Goldberg RM. Pharmacogenetic predictors of adverse events and response to chemotherapy in metastatic colorectal cancer: results from North American Gastrointestinal Intergroup Trial N9741. *J Clin Oncol* 2010; **28**: 3227-3233 [PMID: 20530282 DOI: 10.1200/jco.2009.21.7943]

181 **Massacesi C**, Terrazzino S, Marcucci F, Rocchi MB, Lippe P, Bisonni R, Lombardo M, Pilone A, Mattioli R, Leon A. Uridine diphosphate glucuronosyl transferase 1A1 promoter polymorphism predicts the risk of gastrointestinal toxicity and fatigue induced by irinotecan-based chemotherapy. *Cancer* 2006; **106**: 1007-1016 [PMID: 16456808 DOI: 10.1002/cncr.21722]

182 **Marcuello E**, Altés A, Menoyo A, Del Rio E, Gómez-Pardo M, Baiget M. UGT1A1 gene variations and irinotecan treatment in patients with metastatic colorectal cancer. *Br J Cancer* 2004; **91**: 678-682 [PMID: 15280927 DOI: 10.1038/sj.bjc.6602042]

183 **Rouits E**, Boisdron-Celle M, Dumont A, Guérin O, Morel A, Gamelin E. Relevance of different UGT1A1 polymorphisms in irinotecan-induced toxicity: a molecular and clinical study of 75 patients. *Clin Cancer Res* 2004; **10**: 5151-5159 [PMID: 15297419 DOI: 10.1158/1078-0432.CCR-03-0548]

184 **Beutler E**, Gelbart T, Demina A. Racial variability in the UDP-glucuronosyltransferase 1 (UGT1A1) promoter: a balanced polymorphism for regulation of bilirubin metabolism? *Proc Natl Acad Sci U S A* 1998; **95**: 8170-8174 [PMID: 9653159]

185 **Iyer L**, Hall D, Das S, Mortell MA, Ramírez J, Kim S, Di Rienzo A, Ratain MJ. Phenotype-genotype correlation of in vitro SN-38 (active metabolite of irinotecan) and bilirubin glucuronidation in human liver tissue with UGT1A1 promoter polymorphism. *Clin Pharmacol Ther* 1999; **65**: 576-582 [PMID: 10340924 DOI: 10.1016/S0009-9236(99)70078-0]

186 **Han JY**, Lim HS, Shin ES, Yoo YK, Park YH, Lee JE, Jang IJ, Lee DH, Lee JS. Comprehensive analysis of UGT1A polymorphisms predictive for pharmacokinetics and treatment outcome in patients with non-small-cell lung cancer treated with irinotecan and cisplatin. *J Clin Oncol* 2006; **24**: 2237-2244 [PMID: 16636344 DOI: 10.1200/JCO.2005.03.0239]

187 **Sugatani J**, Yamakawa K, Yoshinari K, Machida T, Takagi H, Mori M, Kakizaki S, Sueyoshi T, Negishi M, Miwa M. Identification of a defect in the UGT1A1 gene promoter and its association with hyperbilirubinemia. *Biochem Biophys Res Commun* 2002; **292**: 492-497 [PMID: 11906189 DOI: 10.1006/bbrc.2002.6683]

188 **Guillemette C**, Ritter JK, Auyeung DJ, Kessler FK, Housman DE. Structural heterogeneity at the UDP-glucuronosyltransferase 1 locus: functional consequences of three novel missense mutations in the human UGT1A7 gene. *Pharmacogenetics* 2000; **10**: 629-644 [PMID: 11037804]

189 **Gagné JF**, Montminy V, Belanger P, Journault K, Gaucher G, Guillemette C. Common human UGT1A polymorphisms and the altered metabolism of irinotecan active metabolite 7-ethyl-10-hydroxycamptothecin (SN-38). *Mol Pharmacol* 2002; **62**: 608-617 [PMID: 12181437]

190 **Yamanaka H**, Nakajima M, Katoh M, Hara Y, Tachibana O, Yamashita J, McLeod HL, Yokoi T. A novel polymorphism in the promoter region of human UGT1A9 gene (UGT1A9\*22) and its effects on the transcriptional activity. *Pharmacogenetics* 2004; **14**: 329-332 [PMID: 15115919]

191 **Ando Y**, Saka H, Ando M, Sawa T, Muro K, Ueoka H, Yokoyama A, Saitoh S, Shimokata K, Hasegawa Y. Polymorphisms of UDP-glucuronosyltransferase gene and irinotecan toxicity: a pharmacogenetic analysis. *Cancer Res* 2000; **60**: 6921-6926 [PMID: 11156391]

192 **Innocenti F**, Undevia SD, Iyer L, Chen PX, Das S, Kocherginsky M, Karrison T, Janisch L, Ramírez J, Rudin CM, Vokes EE, Ratain MJ. Genetic variants in the UDP-glucuronosyltransferase 1A1 gene predict the risk of severe neutropenia of irinotecan. *J Clin Oncol* 2004; **22**: 1382-1388 [PMID: 15007088 DOI: 10.1200/JCO.2004.07.173]

193 **Dias MM**, McKinnon RA, Sorich MJ. Impact of the UGT1A1\*28 allele on response to irinotecan: a systematic review and meta-analysis. *Pharmacogenomics* 2012; **13**: 889-899 [PMID: 22676194 DOI: 10.2217/pgs.12.68]

194 **Hu ZY**, Yu Q, Pei Q, Guo C. Dose-dependent association between UGT1A1\*28 genotype and irinotecan-induced neutropenia: low doses also increase risk. *Clin Cancer Res* 2010; **16**: 3832-3842 [PMID: 20562211 DOI: 10.1158/1078-0432.CCR-10-1122]

195 **Hu ZY**, Yu Q, Zhao YS. Dose-dependent association between UGT1A1\*28 polymorphism and irinotecan-induced diarrhoea: a meta-analysis. *Eur J Cancer* 2010; **46**: 1856-1865 [PMID: 20335017 DOI: 10.1016/j.ejca.2010.02.049]

196 **Winder T**, Lenz HJ. Molecular predictive and prognostic markers in colon cancer. *Cancer Treat Rev* 2010; **36**: 550-556 [PMID: 20363564 DOI: 10.1016/j.ctrv.2010.03.005]

197 **Carlini LE**, Meropol NJ, Bever J, Andria ML, Hill T, Gold P, Rogatko A, Wang H, Blanchard RL. UGT1A7 and UGT1A9 polymorphisms predict response and toxicity in colorectal cancer patients treated with capecitabine/irinotecan. *Clin Cancer Res* 2005; **11**: 1226-1236 [PMID: 15709193]

198 **Brandi G**, de Rosa F, Biasco G. Irinotecan toxicity: genes or intestinal microflora? *Br J Cancer* 2009; **100**: 1017 [PMID: 19293816 DOI: 10.1038/sj.bjc.6604957]

199 **Liu CY**, Chen PM, Chiou TJ, Liu JH, Lin JK, Lin TC, Chen WS, Jiang JK, Wang HS, Wang WS. UGT1A1\*28 polymorphism predicts irinotecan-induced severe toxicities without affecting treatment outcome and survival in patients with metastatic colorectal carcinoma. *Cancer* 2008; **112**: 1932-1940 [PMID: 18300238 DOI: 10.1002/cncr.23370]

200 **Rivory LP**, Haaz MC, Canal P, Lokiec F, Armand JP, Robert J. Pharmacokinetic interrelationships of irinotecan (CPT-11) and its three major plasma metabolites in patients enrolled in phase I/II trials. *Clin Cancer Res* 1997; **3**: 1261-1266 [PMID: 9815808]

201 **Haaz MC**, Riché C, Rivory LP, Robert J. Biosynthesis of an aminopiperidino metabolite of irinotecan [7-ethyl-10-[4-(1-piperidino)-1-piperidino]carbonyloxycamptothecine] by human hepatic microsomes. *Drug Metab Dispos* 1998; **26**: 769-774 [PMID: 9698291]

202 **Haaz MC**, Rivory L, Riché C, Vernillet L, Robert J. Metabolism of irinotecan (CPT-11) by human hepatic microsomes: participation of cytochrome P-450 3A and drug interactions. *Cancer Res* 1998; **58**: 468-472 [PMID: 9458091]

203 **Rebbeck TR**, Jaffe JM, Walker AH, Wein AJ, Malkowicz SB. Modification of clinical presentation of prostate tumors by a novel genetic variant in CYP3A4. *J Natl Cancer Inst* 1998; **90**: 1225-1229 [PMID: 9719084]

204 **Agundez JA**. Cytochrome P450 gene polymorphism and cancer. *Curr Drug Metab* 2004; **5**: 211-224 [PMID: 15180491]

205 **Bozina N**, Bradamante V, Lovrić M. Genetic polymorphism of metabolic enzymes P450 (CYP) as a susceptibility factor for drug response, toxicity, and cancer risk. *Arh Hig Rada Toksikol* 2009; **60**: 217-242 [PMID: 19581216 DOI: 10.2478/10004-1254-60-2009-1885]

206 **Xie HG**, Wood AJ, Kim RB, Stein CM, Wilkinson GR. Genetic variability in CYP3A5 and its possible consequences. *Pharmacogenomics* 2004; **5**: 243-272 [PMID: 15102541 DOI: 10.1517/phgs.5.3.243.29833]

207 **Fujiwara Y**, Minami H. An overview of the recent progress in irinotecan pharmacogenetics. *Pharmacogenomics* 2010; **11**: 391-406 [PMID: 20235794 DOI: 10.2217/pgs.10.19]

208 **Fukushima-Uesaka H**, Saito Y, Watanabe H, Shiseki K, Saeki M, Nakamura T, Kurose K, Sai K, Komamura K, Ueno K, Kamakura S, Kitakaze M, Hanai S, Nakajima T, Matsumoto K, Saito H, Goto Y, Kimura H, Katoh M, Sugai K, Minami N, Shirao K, Tamura T, Yamamoto N, Minami H, Ohtsu A, Yoshida T, Saijo N, Kitamura Y, Kamatani N, Ozawa S, Sawada J. Haplotypes of CYP3A4 and their close linkage with CYP3A5 haplotypes in a Japanese population. *Hum Mutat* 2004; **23**: 100 [PMID: 14695543 DOI: 10.1002/humu.9210]

209 **Sai K**, Saito Y, Fukushima-Uesaka H, Kurose K, Kaniwa N, Kamatani N, Shirao K, Yamamoto N, Hamaguchi T, Kunitoh H, Ohe Y, Tamura T, Yamada Y, Minami H, Ohtsu A, Yoshida T, Saijo N, Sawada J. Impact of CYP3A4 haplotypes on irinotecan pharmacokinetics in Japanese cancer patients. *Cancer Chemother Pharmacol* 2008; **62**: 529-537 [PMID: 17992531 DOI: 10.1007/s00280-007-0634-1]

210 **Mathijssen RH**, Marsh S, Karlsson MO, Xie R, Baker SD, Verweij J, Sparreboom A, McLeod HL. Irinotecan pathway genotype analysis to predict pharmacokinetics. *Clin Cancer Res* 2003; **9**: 3246-3253 [PMID: 12960109]

211 **Mathijssen RH**, de Jong FA, van Schaik RH, Lepper ER, Friberg LE, Rietveld T, de Bruijn P, Graveland WJ, Figg WD, Verweij J, Sparreboom A. Prediction of irinotecan pharmacokinetics by use of cytochrome P450 3A4 phenotyping probes. *J Natl Cancer Inst* 2004; **96**: 1585-1592 [PMID: 15523087 DOI: 10.1093/jnci/djh298]

212 **Sodani K**, Patel A, Kathawala RJ, Chen ZS. Multidrug resistance associated proteins in multidrug resistance. *Chin J Cancer* 2012; **31**: 58-72 [PMID: 22098952 DOI: 10.5732/cjc.011.10329]

213 **Fromm MF**, Kim RB. Drug transporters. Heidelberg: Springer, 2011

214 **Ishikawa T**, Kim RB, König Jr. Pharmacogenomics of human drug transporters: clinical impacts. Hoboken, NJ: John Wiley & Sons, 2013

215 **Kim TW**, Innocenti F. Insights, challenges, and future directions in irinogenetics. *Ther Drug Monit* 2007; **29**: 265-270 [PMID: 17529881 DOI: 10.1097/FTD.0b013e318068623b]

216 **Innocenti F**, Kroetz DL, Schuetz E, Dolan ME, Ramírez J, Relling M, Chen P, Das S, Rosner GL, Ratain MJ. Comprehensive pharmacogenetic analysis of irinotecan neutropenia and pharmacokinetics. *J Clin Oncol* 2009; **27**: 2604-2614 [PMID: 19349540 DOI: 10.1200/JCO.2008.20.6300]

217 **Sai K**, Kaniwa N, Itoda M, Saito Y, Hasegawa R, Komamura K, Ueno K, Kamakura S, Kitakaze M, Shirao K, Minami H, Ohtsu A, Yoshida T, Saijo N, Kitamura Y, Kamatani N, Ozawa S, Sawada J. Haplotype analysis of ABCB1/MDR1 blocks in a Japanese population reveals genotype-dependent renal clearance of irinotecan. *Pharmacogenetics* 2003; **13**: 741-757 [PMID: 14646693 DOI: 10.1097/01.fpc.0000054137.14659.f7]

218 **Han JY**, Lim HS, Yoo YK, Shin ES, Park YH, Lee SY, Lee JE, Lee DH, Kim HT, Lee JS. Associations of ABCB1, ABCC2, and ABCG2 polymorphisms with irinotecan-pharmacokinetics and clinical outcome in patients with advanced non-small cell lung cancer. *Cancer* 2007; **110**: 138-147 [PMID: 17534875 DOI: 10.1002/cncr.22760]

219 **Glimelius B**, Garmo H, Berglund A, Fredriksson LA, Berglund M, Kohnke H, Byström P, Sørbye H, Wadelius M. Prediction of irinotecan and 5-fluorouracil toxicity and response in patients with advanced colorectal cancer. *Pharmacogenomics J* 2011; **11**: 61-71 [PMID: 20177420 DOI: 10.1038/tpj.2010.10]

220 **Chen ZS**, Furukawa T, Sumizawa T, Ono K, Ueda K, Seto K, Akiyama SI. ATP-Dependent efflux of CPT-11 and SN-38 by the multidrug resistance protein (MRP) and its inhibition by PAK-104P. *Mol Pharmacol* 1999; **55**: 921-928 [PMID: 10220571]

221 **Conrad S**, Kauffmann HM, Ito K, Deeley RG, Cole SP, Schrenk D. Identification of human multidrug resistance protein 1 (MRP1) mutations and characterization of a G671V substitution. *J Hum Genet* 2001; **46**: 656-663 [PMID: 11721885 DOI: 10.1007/s100380170017]

222 **Conrad S**, Kauffmann HM, Ito K, Leslie EM, Deeley RG, Schrenk D, Cole SP. A naturally occurring mutation in MRP1 results in a selective decrease in organic anion transport and in increased doxorubicin resistance. *Pharmacogenetics* 2002; **12**: 321-330 [PMID: 12042670]

223 **Leslie EM**, Létourneau IJ, Deeley RG, Cole SP. Functional and structural consequences of cysteine substitutions in the NH2 proximal region of the human multidrug resistance protein 1 (MRP1/ABCC1). *Biochemistry* 2003; **42**: 5214-5224 [PMID: 12731862 DOI: 10.1021/bi027076n]

224 **Létourneau IJ**, Deeley RG, Cole SP. Functional characterization of non-synonymous single nucleotide polymorphisms in the gene encoding human multidrug resistance protein 1 (MRP1/ABCC1). *Pharmacogenet Genomics* 2005; **15**: 647-657 [PMID: 16041243]

225 **Moriya Y**, Nakamura T, Horinouchi M, Sakaeda T, Tamura T, Aoyama N, Shirakawa T, Gotoh A, Fujimoto S, Matsuo M, Kasuga M, Okumura K. Effects of polymorphisms of MDR1, MRP1, and MRP2 genes on their mRNA expression levels in duodenal enterocytes of healthy Japanese subjects. *Biol Pharm Bull* 2002; **25**: 1356-1359 [PMID: 12392094]

226 **Chu XY**, Kato Y, Niinuma K, Sudo KI, Hakusui H, Sugiyama Y. Multispecific organic anion transporter is responsible for the biliary excretion of the camptothecin derivative irinotecan and its metabolites in rats. *J Pharmacol Exp Ther* 1997; **281**: 304-314 [PMID: 9103511]

227 **Innocenti F**, Undevia SD, Chen PX, Das S, Ramirez J, Dolan ME, Relling MV, Kroetz DL, Ratain MJ. Pharmacogenetic analysis of interindividual irinotecan (CPT-11) pharmacokinetic (PK) variability: Evidence for a functional variant of ABCC2. *J Clin Oncol* 2004; **22**: 129S-129S [PMID: WOS: 000223512400510]

228 **Kitagawa C**, Ando M, Ando Y, Sekido Y, Usui M, Takahashi K, Shimokata K, Hasegawa Y. Genetic polymorphisms of the multidrug resistance-associated protein 2 gene (ABCC2) and Irinotecan toxicity. *J Clin Oncol* 2004; **22**: 129S-129S [PMID: WOS: 000223512400511]

229 **Maliepaard M**, van Gastelen MA, de Jong LA, Pluim D, van Waardenburg RC, Ruevekamp-Helmers MC, Floot BG, Schellens JH. Overexpression of the BCRP/MXR/ABCP gene in a topotecan-selected ovarian tumor cell line. *Cancer Res* 1999; **59**: 4559-4563 [PMID: 10493507]

230 **Schellens JH**, Maliepaard M, Scheper RJ, Scheffer GL, Jonker JW, Smit JW, Beijnen JH, Schinkel AH. Transport of topoisomerase I inhibitors by the breast cancer resistance protein. Potential clinical implications. *Ann N Y Acad Sci* 2000; **922**: 188-194 [PMID: 11193894]

231 **Kawabata S**, Oka M, Soda H, Shiozawa K, Nakatomi K, Tsurutani J, Nakamura Y, Doi S, Kitazaki T, Sugahara K, Yamada Y, Kamihira S, Kohno S. Expression and functional analyses of breast cancer resistance protein in lung cancer. *Clin Cancer Res* 2003; **9**: 3052-3057 [PMID: 12912956]

232 **Candeil L**, Gourdier I, Peyron D, Vezzio N, Copois V, Bibeau F, Orsetti B, Scheffer GL, Ychou M, Khan QA, Pommier Y, Pau B, Martineau P, Del Rio M. ABCG2 overexpression in colon cancer cells resistant to SN38 and in irinotecan-treated metastases. *Int J Cancer* 2004; **109**: 848-854 [PMID: 15027118 DOI: 10.1002/ijc.20032]

233 **Yoshikawa M**, Ikegami Y, Sano K, Yoshida H, Mitomo H, Sawada S, Ishikawa T. Transport of SN-38 by the wild type of human ABC transporter ABCG2 and its inhibition by quercetin, a natural flavonoid. *J Exp Ther Oncol* 2004; **4**: 25-35 [PMID: 15255290]

234 **Bram EE**, Stark M, Raz S, Assaraf YG. Chemotherapeutic drug-induced ABCG2 promoter demethylation as a novel mechanism of acquired multidrug resistance. *Neoplasia* 2009; **11**: 1359-1370 [PMID: 20019844]

235 **Bram EE**, Ifergan I, Grimberg M, Lemke K, Skladanowski A, Assaraf YG. C421 allele-specific ABCG2 gene amplification confers resistance to the antitumor triazoloacridone C-1305 in human lung cancer cells. *Biochem Pharmacol* 2007; **74**: 41-53 [PMID: 17481587 DOI: 10.1016/j.bcp.2007.03.028]

236 **To KK**, Robey RW, Knutsen T, Zhan Z, Ried T, Bates SE. Escape from hsa-miR-519c enables drug-resistant cells to maintain high expression of ABCG2. *Mol Cancer Ther* 2009; **8**: 2959-2968 [PMID: 19825807 DOI: 10.1158/1535-7163.MCT-09-0292]

237 **Cha PC**, Mushiroda T, Zembutsu H, Harada H, Shinoda N, Kawamoto S, Shimoyama R, Nishidate T, Furuhata T, Sasaki K, Hirata K, Nakamura Y. Single nucleotide polymorphism in ABCG2 is associated with irinotecan-induced severe myelosuppression. *J Hum Genet* 2009; **54**: 572-580 [PMID: 19696792 DOI: 10.1038/jhg.2009.80]

238 **Poonkuzhali B**, Lamba J, Strom S, Sparreboom A, Thummel K, Watkins P, Schuetz E. Association of breast cancer resistance protein/ABCG2 phenotypes and novel promoter and intron 1 single nucleotide polymorphisms. *Drug Metab Dispos* 2008; **36**: 780-795 [PMID: 18180275 DOI: 10.1124/dmd.107.018366]

239 **Morisaki K**, Robey RW, Ozvegy-Laczka C, Honjo Y, Polgar O, Steadman K, Sarkadi B, Bates SE. Single nucleotide polymorphisms modify the transporter activity of ABCG2. *Cancer Chemother Pharmacol* 2005; **56**: 161-172 [PMID: 15838659 DOI: 10.1007/s00280-004-0931-x]

240 **Sparreboom A**, Loos WJ, Burger H, Sissung TM, Verweij J, Figg WD, Nooter K, Gelderblom H. Effect of ABCG2 genotype on the oral bioavailability of topotecan. *Cancer Biol Ther* 2005; **4**: 650-658 [PMID: 15908806]

241 **Mizuarai S**, Aozasa N, Kotani H. Single nucleotide polymorphisms result in impaired membrane localization and reduced atpase activity in multidrug transporter ABCG2. *Int J Cancer* 2004; **109**: 238-246 [PMID: 14750175 DOI: 10.1002/ijc.11669]

242 **Tamura A**, Wakabayashi K, Onishi Y, Takeda M, Ikegami Y, Sawada S, Tsuji M, Matsuda Y, Ishikawa T. Re-evaluation and functional classification of non-synonymous single nucleotide polymorphisms of the human ATP-binding cassette transporter ABCG2. *Cancer Sci* 2007; **98**: 231-239 [PMID: 17297656]

243 **de Jong FA**, Marsh S, Mathijssen RH, King C, Verweij J, Sparreboom A, McLeod HL. ABCG2 pharmacogenetics: ethnic differences in allele frequency and assessment of influence on irinotecan disposition. *Clin Cancer Res* 2004; **10**: 5889-5894 [PMID: 15355921 DOI: 10.1158/1078-0432.ccr-04-0144]

244 **Jada SR**, Lim R, Wong CI, Shu X, Lee SC, Zhou Q, Goh BC, Chowbay B. Role of UGT1A1\*6, UGT1A1\*28 and ABCG2 c.421C& gt; A polymorphisms in irinotecan-induced neutropenia in Asian cancer patients. *Cancer Sci* 2007; **98**: 1461-1467 [PMID: 17627617 DOI: 10.1111/j.1349-7006.2007.00541.x]

245 **Gradhand U**, Kim RB. Pharmacogenomics of MRP transporters (ABCC1-5) and BCRP (ABCG2). *Drug Metab Rev* 2008; **40**: 317-354 [PMID: 18464048 DOI: 10.1080/03602530801952617]

246 **Nozawa T**, Minami H, Sugiura S, Tsuji A, Tamai I. Role of organic anion transporter OATP1B1 (OATP-C) in hepatic uptake of irinotecan and its active metabolite, 7-ethyl-10-hydroxycamptothecin: in vitro evidence and effect of single nucleotide polymorphisms. *Drug Metab Dispos* 2005; **33**: 434-439 [PMID: 15608127 DOI: 10.1124/dmd.104.001909]

247 **Han JY**, Lim HS, Shin ES, Yoo YK, Park YH, Lee JE, Kim HT, Lee JS. Influence of the organic anion-transporting polypeptide 1B1 (OATP1B1) polymorphisms on irinotecan-pharmacokinetics and clinical outcome of patients with advanced non-small cell lung cancer. *Lung Cancer* 2008; **59**: 69-75 [PMID: 17766002 DOI: 10.1016/j.lungcan.2007.07.019]

248 **Xiang X**, Jada SR, Li HH, Fan L, Tham LS, Wong CI, Lee SC, Lim R, Zhou QY, Goh BC, Tan EH, Chowbay B. Pharmacogenetics of SLCO1B1 gene and the impact of \*1b and \*15 haplotypes on irinotecan disposition in Asian cancer patients. *Pharmacogenet Genomics* 2006; **16**: 683-691 [PMID: 16906022 DOI: 10.1097/01.fpc.0000230420.05221.71]

249 **Takane H**, Miyata M, Burioka N, Kurai J, Fukuoka Y, Suyama H, Shigeoka Y, Otsubo K, Ieiri I, Shimizu E. Severe toxicities after irinotecan-based chemotherapy in a patient with lung cancer: a homozygote for the SLCO1B1\*15 allele. *Ther Drug Monit* 2007; **29**: 666-668 [PMID: 17898662 DOI: 10.1097/FTD.0b013e3181357364]

250 **Takane H**, Kawamoto K, Sasaki T, Moriki K, Moriki K, Kitano H, Higuchi S, Otsubo K, Ieiri I. Life-threatening toxicities in a patient with UGT1A1\*6/\*28 and SLCO1B1\*15/\*15 genotypes after irinotecan-based chemotherapy. *Cancer Chemother Pharmacol* 2009; **63**: 1165-1169 [PMID: 18998132 DOI: 10.1007/s00280-008-0864-x]

251 **Hoskins JM**, Marcuello E, Altes A, Marsh S, Maxwell T, Van Booven DJ, Paré L, Culverhouse R, McLeod HL, Baiget M. Irinotecan pharmacogenetics: influence of pharmacodynamic genes. *Clin Cancer Res* 2008; **14**: 1788-1796 [PMID: 18347181 DOI: 10.1158/1078-0432.CCR-07-1472]

252 **Takatani H**, Oka M, Fukuda M, Narasaki F, Nakano R, Ikeda K, Terashi K, Kinoshita A, Soda H, Kanda T, Schneider E, Kohno S. Gene mutation analysis and quantitation of DNA topoisomerase I in previously untreated non-small cell lung carcinomas. *Jpn J Cancer Res* 1997; **88**: 160-165 [PMID: 9119744]

253 **Tsurutani J**, Nitta T, Hirashima T, Komiya T, Uejima H, Tada H, Syunichi N, Tohda A, Fukuoka M, Nakagawa K. Point mutations in the topoisomerase I gene in patients with non-small cell lung cancer treated with irinotecan. *Lung Cancer* 2002; **35**: 299-304 [PMID: 11844605]

254 **McLeod HL**, Keith WN. Variation in topoisomerase I gene copy number as a mechanism for intrinsic drug sensitivity. *Br J Cancer* 1996; **74**: 508-512 [PMID: 8761363]

255 **Pommier Y**. Camptothecins and topoisomerase I: a foot in the door. Targeting the genome beyond topoisomerase I with camptothecins and novel anticancer drugs: importance of DNA replication, repair and cell cycle checkpoints. *Curr Med Chem Anticancer Agents* 2004; **4**: 429-434 [PMID: 15379698]

256 **Reid RJ**, Fiorani P, Sugawara M, Bjornsti MA. CDC45 and DPB11 are required for processive DNA replication and resistance to DNA topoisomerase I-mediated DNA damage. *Proc Natl Acad Sci U S A* 1999; **96**: 11440-11445 [PMID: 10500195]

257 **Malanga M**, Althaus FR. Poly(ADP-ribose) reactivates stalled DNA topoisomerase I and Induces DNA strand break resealing. *J Biol Chem* 2004; **279**: 5244-5248 [PMID: 14699148 DOI: 10.1074/jbc.C300437200]

258 **Barthelmes HU**, Habermeyer M, Christensen MO, Mielke C, Interthal H, Pouliot JJ, Boege F, Marko D. TDP1 overexpression in human cells counteracts DNA damage mediated by topoisomerases I and II. *J Biol Chem* 2004; **279**: 55618-55625 [PMID: 15494395 DOI: 10.1074/jbc.M405042200]

259 **Park SY**, Lam W, Cheng YC. X-ray repair cross-complementing gene I protein plays an important role in camptothecin resistance. *Cancer Res* 2002; **62**: 459-465 [PMID: 11809696]

260 **Cusack JC**, Liu R, Houston M, Abendroth K, Elliott PJ, Adams J, Baldwin AS. Enhanced chemosensitivity to CPT-11 with proteasome inhibitor PS-341: implications for systemic nuclear factor-kappaB inhibition. *Cancer Res* 2001; **61**: 3535-3540 [PMID: 11325813]

261 **El-Khamisy SF**, Masutani M, Suzuki H, Caldecott KW. A requirement for PARP-1 for the assembly or stability of XRCC1 nuclear foci at sites of oxidative DNA damage. *Nucleic Acids Res* 2003; **31**: 5526-5533 [PMID: 14500814]

262 **Hu Z**, Ma H, Chen F, Wei Q, Shen H. XRCC1 polymorphisms and cancer risk: a meta-analysis of 38 case-control studies. *Cancer Epidemiol Biomarkers Prev* 2005; **14**: 1810-1818 [PMID: 16030121 DOI: 10.1158/1055-9965.EPI-04-0793]

263 **Magrini R**, Bhonde MR, Hanski ML, Notter M, Scherübl H, Boland CR, Zeitz M, Hanski C. Cellular effects of CPT-11 on colon carcinoma cells: dependence on p53 and hMLH1 status. *Int J Cancer* 2002; **101**: 23-31 [PMID: 12209584 DOI: 10.1002/ijc.10565]

264 **Bhonde MR**, Hanski ML, Notter M, Gillissen BF, Daniel PT, Zeitz M, Hanski C. Equivalent effect of DNA damage-induced apoptotic cell death or long-term cell cycle arrest on colon carcinoma cell proliferation and tumour growth. *Oncogene* 2006; **25**: 165-175 [PMID: 16170360 DOI: 10.1038/sj.onc.1209017]

265 **Gupta M**, Fan S, Zhan Q, Kohn KW, O'Connor PM, Pommier Y. Inactivation of p53 increases the cytotoxicity of camptothecin in human colon HCT116 and breast MCF-7 cancer cells. *Clin Cancer Res* 1997; **3**: 1653-1660 [PMID: 9815856]

266 **te Poele RH**, Joel SP. Schedule-dependent cytotoxicity of SN-38 in p53 wild-type and mutant colon adenocarcinoma cell lines. *Br J Cancer* 1999; **81**: 1285-1293 [PMID: 10604724 DOI: 10.1038/sj.bjc.6694370]

267 **Goldwasser F**, Shimizu T, Jackman J, Hoki Y, O'Connor PM, Kohn KW, Pommier Y. Correlations between S and G2 arrest and the cytotoxicity of camptothecin in human colon carcinoma cells. *Cancer Res* 1996; **56**: 4430-4437 [PMID: 8813137]

268 **Abal M**, Bras-Goncalves R, Judde JG, Fsihi H, De Cremoux P, Louvard D, Magdelenat H, Robine S, Poupon MF. Enhanced sensitivity to irinotecan by Cdk1 inhibition in the p53-deficient HT29 human colon cancer cell line. *Oncogene* 2004; **23**: 1737-1744 [PMID: 15001986 DOI: 10.1038/sj.onc.1207299]

269 **Wang S**, El-Deiry WS. Requirement of p53 targets in chemosensitization of colonic carcinoma to death ligand therapy. *Proc Natl Acad Sci U S A* 2003; **100**: 15095-15100 [PMID: 14645705 DOI: 10.1073/pnas.2435285100]

270 **Tomicic MT**, Kaina B. Topoisomerase degradation, DSB repair, p53 and IAPs in cancer cell resistance to camptothecin-like topoisomerase I inhibitors. *Biochim Biophys Acta* 2013; **1835**: 11-27 [PMID: 23006513 DOI: 10.1016/j.bbcan.2012.09.002]

271 **Adachi N**, So S, Koyama H. Loss of nonhomologous end joining confers camptothecin resistance in DT40 cells. Implications for the repair of topoisomerase I-mediated DNA damage. *J Biol Chem* 2004; **279**: 37343-37348 [PMID: 15218034 DOI: 10.1074/jbc.M313910200]

272 **Otsuki M**, Seki M, Kawabe Y, Inoue E, Dong YP, Abe T, Kato G, Yoshimura A, Tada S, Enomoto T. WRN counteracts the NHEJ pathway upon camptothecin exposure. *Biochem Biophys Res Commun* 2007; **355**: 477-482 [PMID: 17303082 DOI: 10.1016/j.bbrc.2007.01.175]

273 **Tashiro T**, Kawada Y, Sakurai Y, Kidani Y. Antitumor activity of a new platinum complex, oxalato (trans-l-1,2-diaminocyclohexane)platinum (II): new experimental data. *Biomed Pharmacother* 1989; **43**: 251-260 [PMID: 2790145]

274 **Rixe O**, Ortuzar W, Alvarez M, Parker R, Reed E, Paull K, Fojo T. Oxaliplatin, tetraplatin, cisplatin, and carboplatin: spectrum of activity in drug-resistant cell lines and in the cell lines of the National Cancer Institute's Anticancer Drug Screen panel. *Biochem Pharmacol* 1996; **52**: 1855-1865 [PMID: 8951344]

275 **Tournigand C**, André T, Achille E, Lledo G, Flesh M, Mery-Mignard D, Quinaux E, Couteau C, Buyse M, Ganem G, Landi B, Colin P, Louvet C, de Gramont A. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *J Clin Oncol* 2004; **22**: 229-237 [PMID: 14657227 DOI: 10.1200/JCO.2004.05.113]

276 **Manic S**, Gatti L, Carenini N, Fumagalli G, Zunino F, Perego P. Mechanisms controlling sensitivity to platinum complexes: role of p53 and DNA mismatch repair. *Curr Cancer Drug Targets* 2003; **3**: 21-29 [PMID: 12570658]

277 **Gately DP**, Howell SB. Cellular accumulation of the anticancer agent cisplatin: a review. *Br J Cancer* 1993; **67**: 1171-1176 [PMID: 8512802]

278 **Perez RP**. Cellular and molecular determinants of cisplatin resistance. *Eur J Cancer* 1998; **34**: 1535-1542 [PMID: 9893624]

279 **Meijer C**, Mulder NH, Hospers GA, Uges DR, de Vries EG. The role of glutathione in resistance to cisplatin in a human small cell lung cancer cell line. *Br J Cancer* 1990; **62**: 72-77 [PMID: 2390486]

280 **Wernyj RP**, Morin PJ. Molecular mechanisms of platinum resistance: still searching for the Achilles' heel. *Drug Resist Updat* 2004; **7**: 227-232 [PMID: 15533760 DOI: 10.1016/j.drup.2004.08.002]

281 **Choi MK**, Kim DD. Platinum transporters and drug resistance. *Arch Pharm Res* 2006; **29**: 1067-1073 [PMID: 17225452]

282 **Hall MD**, Okabe M, Shen DW, Liang XJ, Gottesman MM. The role of cellular accumulation in determining sensitivity to platinum-based chemotherapy. *Annu Rev Pharmacol Toxicol* 2008; **48**: 495-535 [PMID: 17937596 DOI: 10.1146/annurev.pharmtox.48.080907.180426]

283 **Liu JJ**, Lu J, McKeage MJ. Membrane transporters as determinants of the pharmacology of platinum anticancer drugs. *Curr Cancer Drug Targets* 2012; **12**: 962-986 [PMID: 22794121]

284 **Howell SB**, Safaei R, Larson CA, Sailor MJ. Copper transporters and the cellular pharmacology of the platinum-containing cancer drugs. *Mol Pharmacol* 2010; **77**: 887-894 [PMID: 20159940 DOI: 10.1124/mol.109.063172]

285 **Koepsell H**, Endou H. The SLC22 drug transporter family. *Pflugers Arch* 2004; **447**: 666-676 [PMID: 12883891 DOI: 10.1007/s00424-003-1089-9]

286 **Helleman J**, Burger H, Hamelers IH, Boersma AW, de Kroon AI, Stoter G, Nooter K. Impaired cisplatin influx in an A2780 mutant cell line: evidence for a putative, cis-configuration-specific, platinum influx transporter. *Cancer Biol Ther* 2006; **5**: 943-949 [PMID: 16775422]

287 **Surowiak P**, Materna V, Kaplenko I, Spaczynski M, Dolinska-Krajewska B, Gebarowska E, Dietel M, Zabel M, Lage H. ABCC2 (MRP2, cMOAT) can be localized in the nuclear membrane of ovarian carcinomas and correlates with resistance to cisplatin and clinical outcome. *Clin Cancer Res* 2006; **12**: 7149-7158 [PMID: 17145840 DOI: 10.1158/1078-0432.CCR-06-0564]

288 **Hector S**, Bolanowska-Higdon W, Zdanowicz J, Hitt S, Pendyala L. In vitro studies on the mechanisms of oxaliplatin resistance. *Cancer Chemother Pharmacol* 2001; **48**: 398-406 [PMID: 11761458]

289 **Martinez-Balibrea E**, Martínez-Cardús A, Musulén E, Ginés A, Manzano JL, Aranda E, Plasencia C, Neamati N, Abad A. Increased levels of copper efflux transporter ATP7B are associated with poor outcome in colorectal cancer patients receiving oxaliplatin-based chemotherapy. *Int J Cancer* 2009; **124**: 2905-2910 [PMID: 19296535 DOI: 10.1002/ijc.24273]

290 **Samimi G**, Katano K, Holzer AK, Safaei R, Howell SB. Modulation of the cellular pharmacology of cisplatin and its analogs by the copper exporters ATP7A and ATP7B. *Mol Pharmacol* 2004; **66**: 25-32 [PMID: 15213293 DOI: 10.1124/mol.66.1.25]

291 **Zhou SF**, Wang LL, Di YM, Xue CC, Duan W, Li CG, Li Y. Substrates and inhibitors of human multidrug resistance associated proteins and the implications in drug development. *Curr Med Chem* 2008; **15**: 1981-2039 [PMID: 18691054]

292 **Suzuki T**, Nishio K, Tanabe S. The MRP family and anticancer drug metabolism. *Curr Drug Metab* 2001; **2**: 367-377 [PMID: 11766988]

293 **Beretta GL**, Benedetti V, Cossa G, Assaraf YG, Bram E, Gatti L, Corna E, Carenini N, Colangelo D, Howell SB, Zunino F, Perego P. Increased levels and defective glycosylation of MRPs in ovarian carcinoma cells resistant to oxaliplatin. *Biochem Pharmacol* 2010; **79**: 1108-1117 [PMID: 20005867 DOI: 10.1016/j.bcp.2009.12.002]

294 **Theile D**, Grebhardt S, Haefeli WE, Weiss J. Involvement of drug transporters in the synergistic action of FOLFOX combination chemotherapy. *Biochem Pharmacol* 2009; **78**: 1366-1373 [PMID: 19622348 DOI: 10.1016/j.bcp.2009.07.006]

295 **Lin PC**, Lin HH, Lin JK, Lin CC, Yang SH, Li AF, Chen WS, Chang SC. Expression of ABCG2 associated with tumor response in metastatic colorectal cancer patients receiving first-line FOLFOX therapy--preliminary evidence. *Int J Biol Markers* 2013; **28**: 182-186 [PMID: 23558935 DOI: 10.5301/jbm.5000004]

296 **Wu H**, Kang H, Liu Y, Xiao Q, Zhang Y, Sun M, Liu D, Wang Z, Zhao H, Yao W, Jia T, Wang E, Zheng Z, Wei M. Association of ABCB1 genetic polymorphisms with susceptibility to colorectal cancer and therapeutic prognosis. *Pharmacogenomics* 2013; **14**: 897-911 [PMID: 23746184 DOI: 10.2217/pgs.13.78]

297 **Yue AM**, Xie ZB, Zhao HF, Guo SP, Shen YH, Wang HP. Associations of ABCB1 and XPC genetic polymorphisms with susceptibility to colorectal cancer and therapeutic prognosis in a Chinese population. *Asian Pac J Cancer Prev* 2013; **14**: 3085-3091 [PMID: 23803084]

298 **Zhang S**, Lovejoy KS, Shima JE, Lagpacan LL, Shu Y, Lapuk A, Chen Y, Komori T, Gray JW, Chen X, Lippard SJ, Giacomini KM. Organic cation transporters are determinants of oxaliplatin cytotoxicity. *Cancer Res* 2006; **66**: 8847-8857 [PMID: 16951202 DOI: 10.1158/0008-5472.CAN-06-0769]

299 **Yokoo S**, Yonezawa A, Masuda S, Fukatsu A, Katsura T, Inui K. Differential contribution of organic cation transporters, OCT2 and MATE1, in platinum agent-induced nephrotoxicity. *Biochem Pharmacol* 2007; **74**: 477-487 [PMID: 17582384 DOI: 10.1016/j.bcp.2007.03.004]

300 **Burger H**, Zoumaro-Djayoon A, Boersma AW, Helleman J, Berns EM, Mathijssen RH, Loos WJ, Wiemer EA. Differential transport of platinum compounds by the human organic cation transporter hOCT2 (hSLC22A2). *Br J Pharmacol* 2010; **159**: 898-908 [PMID: 20067471 DOI: 10.1111/j.1476-5381.2009.00569.x]

301 **Larson CA**, Blair BG, Safaei R, Howell SB. The role of the mammalian copper transporter 1 in the cellular accumulation of platinum-based drugs. *Mol Pharmacol* 2009; **75**: 324-330 [PMID: 18996970 DOI: 10.1124/mol.108.052381]

302 **Rabik CA**, Maryon EB, Kasza K, Shafer JT, Bartnik CM, Dolan ME. Role of copper transporters in resistance to platinating agents. *Cancer Chemother Pharmacol* 2009; **64**: 133-142 [PMID: 18998134 DOI: 10.1007/s00280-008-0860-1]

303 **Safaei R**. Role of copper transporters in the uptake and efflux of platinum containing drugs. *Cancer Lett* 2006; **234**: 34-39 [PMID: 16297532 DOI: 10.1016/j.canlet.2005.07.046]

304 **Holzer AK**, Manorek GH, Howell SB. Contribution of the major copper influx transporter CTR1 to the cellular accumulation of cisplatin, carboplatin, and oxaliplatin. *Mol Pharmacol* 2006; **70**: 1390-1394 [PMID: 16847145 DOI: 10.1124/mol.106.022624]

305 **Blair BG**, Larson CA, Safaei R, Howell SB. Copper transporter 2 regulates the cellular accumulation and cytotoxicity of Cisplatin and Carboplatin. *Clin Cancer Res* 2009; **15**: 4312-4321 [PMID: 19509135 DOI: 10.1158/1078-0432.CCR-09-0311]

306 **Verstraete S**, Heudi O, Cailleux A, Allain P. Comparison of the reactivity of oxaliplatin, pt(diaminocyclohexane)Cl2 and pt(diaminocyclohexane1)(OH2)2(2+) with guanosine and L-methionine. *J Inorg Biochem* 2001; **84**: 129-135 [PMID: 11330471]

307 **Kelley SL**, Basu A, Teicher BA, Hacker MP, Hamer DH, Lazo JS. Overexpression of metallothionein confers resistance to anticancer drugs. *Science* 1988; **241**: 1813-1815 [PMID: 3175622]

308 **Vescio RA**, Connors KM, Bordin GM, Robb JA, Youngkin T, Umbreit JN, Hoffman RM. The distinction of small cell and non-small cell lung cancer by growth in native-state histoculture. *Cancer Res* 1990; **50**: 6095-6099 [PMID: 2168289]

309 **Townsend DM**, Tew KD. The role of glutathione-S-transferase in anti-cancer drug resistance. *Oncogene* 2003; **22**: 7369-7375 [PMID: 14576844 DOI: 10.1038/sj.onc.1206940]

310 **Lo HW**, Ali-Osman F. Genetic polymorphism and function of glutathione S-transferases in tumor drug resistance. *Curr Opin Pharmacol* 2007; **7**: 367-374 [PMID: 17681492 DOI: 10.1016/j.coph.2007.06.009]

311 **Ali-Osman F**, Akande O, Antoun G, Mao JX, Buolamwini J. Molecular cloning, characterization, and expression in Escherichia coli of full-length cDNAs of three human glutathione S-transferase Pi gene variants. Evidence for differential catalytic activity of the encoded proteins. *J Biol Chem* 1997; **272**: 10004-10012 [PMID: 9092542]

312 **Watson MA**, Stewart RK, Smith GB, Massey TE, Bell DA. Human glutathione S-transferase P1 polymorphisms: relationship to lung tissue enzyme activity and population frequency distribution. *Carcinogenesis* 1998; **19**: 275-280 [PMID: 9498276]

313 **Ruzzo A**, Graziano F, Loupakis F, Rulli E, Canestrari E, Santini D, Catalano V, Ficarelli R, Maltese P, Bisonni R, Masi G, Schiavon G, Giordani P, Giustini L, Falcone A, Tonini G, Silva R, Mattioli R, Floriani I, Magnani M. Pharmacogenetic profiling in patients with advanced colorectal cancer treated with first-line FOLFOX-4 chemotherapy. *J Clin Oncol* 2007; **25**: 1247-1254 [PMID: 17401013 DOI: 10.1200/JCO.2006.08.1844]

314 **Chen YC**, Tzeng CH, Chen PM, Lin JK, Lin TC, Chen WS, Jiang JK, Wang HS, Wang WS. Influence of GSTP1 I105V polymorphism on cumulative neuropathy and outcome of FOLFOX-4 treatment in Asian patients with colorectal carcinoma. *Cancer Sci* 2010; **101**: 530-535 [PMID: 19922504 DOI: 10.1111/j.1349-7006.2009.01418.x]

315 **Inada M**, Sato M, Morita S, Kitagawa K, Kawada K, Mitsuma A, Sawaki M, Fujita K, Ando Y. Associations between oxaliplatin-induced peripheral neuropathy and polymorphisms of the ERCC1 and GSTP1 genes. *Int J Clin Pharmacol Ther* 2010; **48**: 729-734 [PMID: 20979931]

316 **Etienne-Grimaldi MC**, Milano G, Maindrault-Goebel F, Chibaudel B, Formento JL, Francoual M, Lledo G, André T, Mabro M, Mineur L, Flesch M, Carola E, de Gramont A. Methylenetetrahydrofolate reductase (MTHFR) gene polymorphisms and FOLFOX response in colorectal cancer patients. *Br J Clin Pharmacol* 2010; **69**: 58-66 [PMID: 20078613 DOI: 10.1111/j.1365-2125.2009.03556.x]

317 **Boige V**, Mendiboure J, Pignon JP, Loriot MA, Castaing M, Barrois M, Malka D, Trégouët DA, Bouché O, Le Corre D, Miran I, Mulot C, Ducreux M, Beaune P, Laurent-Puig P. Pharmacogenetic assessment of toxicity and outcome in patients with metastatic colorectal cancer treated with LV5FU2, FOLFOX, and FOLFIRI: FFCD 2000-05. *J Clin Oncol* 2010; **28**: 2556-2564 [PMID: 20385995 DOI: 10.1200/JCO.2009.25.2106]

318 **Braun MS**, Richman SD, Thompson L, Daly CL, Meade AM, Adlard JW, Allan JM, Parmar MK, Quirke P, Seymour MT. Association of molecular markers with toxicity outcomes in a randomized trial of chemotherapy for advanced colorectal cancer: the FOCUS trial. *J Clin Oncol* 2009; **27**: 5519-5528 [PMID: 19858398 DOI: 10.1200/JCO.2008.21.6283]

319 **Paré L**, Marcuello E, Altés A, del Río E, Sedano L, Salazar J, Cortés A, Barnadas A, Baiget M. Pharmacogenetic prediction of clinical outcome in advanced colorectal cancer patients receiving oxaliplatin/5-fluorouracil as first-line chemotherapy. *Br J Cancer* 2008; **99**: 1050-1055 [PMID: 18797464 DOI: 10.1038/sj.bjc.6604671]

320 **Kweekel DM**, Koopman M, Antonini NF, Van der Straaten T, Nortier JW, Gelderblom H, Punt CJ, Guchelaar HJ. GSTP1 Ile105Val polymorphism correlates with progression-free survival in MCRC patients treated with or without irinotecan: a study of the Dutch Colorectal Cancer Group. *Br J Cancer* 2008; **99**: 1316-1321 [PMID: 18797455 DOI: 10.1038/sj.bjc.6604654]

321 **Kweekel DM**, Gelderblom H, Antonini NF, Van der Straaten T, Nortier JW, Punt CJ, Guchelaar HJ. Glutathione-S-transferase pi (GSTP1) codon 105 polymorphism is not associated with oxaliplatin efficacy or toxicity in advanced colorectal cancer patients. *Eur J Cancer* 2009; **45**: 572-578 [PMID: 19084393 DOI: 10.1016/j.ejca.2008.10.015]

322 **Sweeney C**, McClure GY, Fares MY, Stone A, Coles BF, Thompson PA, Korourian S, Hutchins LF, Kadlubar FF, Ambrosone CB. Association between survival after treatment for breast cancer and glutathione S-transferase P1 Ile105Val polymorphism. *Cancer Res* 2000; **60**: 5621-5624 [PMID: 11059750]

323 **Allan JM**, Wild CP, Rollinson S, Willett EV, Moorman AV, Dovey GJ, Roddam PL, Roman E, Cartwright RA, Morgan GJ. Polymorphism in glutathione S-transferase P1 is associated with susceptibility to chemotherapy-induced leukemia. *Proc Natl Acad Sci U S A* 2001; **98**: 11592-11597 [PMID: 11553769 DOI: 10.1073/pnas.191211198]

324 **Stoehlmacher J**, Park DJ, Zhang W, Groshen S, Tsao-Wei DD, Yu MC, Lenz HJ. Association between glutathione S-transferase P1, T1, and M1 genetic polymorphism and survival of patients with metastatic colorectal cancer. *J Natl Cancer Inst* 2002; **94**: 936-942 [PMID: 12072547]

325 **Le Morvan V**, Smith D, Laurand A, Brouste V, Bellott R, Soubeyran I, Mathoulin-Pelissier S, Robert J. Determination of ERCC2 Lys751Gln and GSTP1 Ile105Val gene polymorphisms in colorectal cancer patients: relationships with treatment outcome. *Pharmacogenomics* 2007; **8**: 1693-1703 [PMID: 18085999 DOI: 10.2217/14622416.8.12.1693]

326 **Ye F**, Liu Z, Tan A, Liao M, Mo Z, Yang X. XRCC1 and GSTP1 polymorphisms and prognosis of oxaliplatin-based chemotherapy in colorectal cancer: a meta-analysis. *Cancer Chemother Pharmacol* 2013; **71**: 733-740 [PMID: 23299794 DOI: 10.1007/s00280-012-2067-8]

327 **Chai H**, Pan J, Zhang X, Zhang X, Shen X, Li H, Zhang K, Yang C, Sheng H, Gao H. ERCC1 C118T associates with response to FOLFOX4 chemotherapy in colorectal cancer patients in Han Chinese. *Int J Clin Exp Med* 2012; **5**: 186-194 [PMID: 22567180]

328 **Hong J**, Han SW, Ham HS, Kim TY, Choi IS, Kim BS, Oh DY, Im SA, Kang GH, Bang YJ, Kim TY. Phase II study of biweekly S-1 and oxaliplatin combination chemotherapy in metastatic colorectal cancer and pharmacogenetic analysis. *Cancer Chemother Pharmacol* 2011; **67**: 1323-1331 [PMID: 20734048 DOI: 10.1007/s00280-010-1425-7]

329 **Lamas MJ**, Duran G, Balboa E, Bernardez B, Touris M, Vidal Y, Gallardo E, Lopez R, Carracedo A, Barros F. Use of a comprehensive panel of biomarkers to predict response to a fluorouracil-oxaliplatin regimen in patients with metastatic colorectal cancer. *Pharmacogenomics* 2011; **12**: 433-442 [PMID: 21449681 DOI: 10.2217/pgs.10.196]

330 **Goekkurt E**, Al-Batran SE, Hartmann JT, Mogck U, Schuch G, Kramer M, Jaeger E, Bokemeyer C, Ehninger G, Stoehlmacher J. Pharmacogenetic analyses of a phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil and leucovorin plus either oxaliplatin or cisplatin: a study of the arbeitsgemeinschaft internistische onkologie. *J Clin Oncol* 2009; **27**: 2863-2873 [PMID: 19332728 DOI: 10.1200/JCO.2008.19.1718]

331 **Faivre S**, Chan D, Salinas R, Woynarowska B, Woynarowski JM. DNA strand breaks and apoptosis induced by oxaliplatin in cancer cells. *Biochem Pharmacol* 2003; **66**: 225-237 [PMID: 12826265]

332 **Reed E**. ERCC1 and clinical resistance to platinum-based therapy. *Clin Cancer Res* 2005; **11**: 6100-6102 [PMID: 16144907 DOI: 10.1158/1078-0432.CCR-05-1083]

333 **Kweekel DM**, Gelderblom H, Guchelaar HJ. Pharmacology of oxaliplatin and the use of pharmacogenomics to individualize therapy. *Cancer Treat Rev* 2005; **31**: 90-105 [PMID: 15847979 DOI: 10.1016/j.ctrv.2004.12.006]

334 **Reardon JT**, Vaisman A, Chaney SG, Sancar A. Efficient nucleotide excision repair of cisplatin, oxaliplatin, and Bis-aceto-ammine-dichloro-cyclohexylamine-platinum(IV) (JM216) platinum intrastrand DNA diadducts. *Cancer Res* 1999; **59**: 3968-3971 [PMID: 10463593]

335 **Yu JJ**, Lee KB, Mu C, Li Q, Abernathy TV, Bostick-Bruton F, Reed E. Comparison of two human ovarian carcinoma cell lines (A2780/CP70 and MCAS) that are equally resistant to platinum, but differ at codon 118 of the ERCC1 gene. *Int J Oncol* 2000; **16**: 555-560 [PMID: 10675489]

336 **Lunn RM**, Helzlsouer KJ, Parshad R, Umbach DM, Harris EL, Sanford KK, Bell DA. XPD polymorphisms: effects on DNA repair proficiency. *Carcinogenesis* 2000; **21**: 551-555 [PMID: 10753184]

337 **Duell EJ**, Wiencke JK, Cheng TJ, Varkonyi A, Zuo ZF, Ashok TD, Mark EJ, Wain JC, Christiani DC, Kelsey KT. Polymorphisms in the DNA repair genes XRCC1 and ERCC2 and biomarkers of DNA damage in human blood mononuclear cells. *Carcinogenesis* 2000; **21**: 965-971 [PMID: 10783319]

338 **Vilmar A**, Sørensen JB. Excision repair cross-complementation group 1 (ERCC1) in platinum-based treatment of non-small cell lung cancer with special emphasis on carboplatin: a review of current literature. *Lung Cancer* 2009; **64**: 131-139 [PMID: 18804893 DOI: 10.1016/j.lungcan.2008.08.006]

339 **Park DJ**, Zhang W, Stoehlmacher J, Tsao-Wei D, Groshen S, Gil J, Yun J, Sones E, Mallik N, Lenz HJ. ERCC1 gene polymorphism as a predictor for clinical outcome in advanced colorectal cancer patients treated with platinum-based chemotherapy. *Clin Adv Hematol Oncol* 2003; **1**: 162-166 [PMID: 16224397]

340 **Bohanes P**, Labonte MJ, Lenz HJ. A review of excision repair cross-complementation group 1 in colorectal cancer. *Clin Colorectal Cancer* 2011; **10**: 157-164 [PMID: 21855036 DOI: 10.1016/j.clcc.2011.03.024]

341 **Uchida K**, Danenberg PV, Danenberg KD, Grem JL. Thymidylate synthase, dihydropyrimidine dehydrogenase, ERCC1, and thymidine phosphorylase gene expression in primary and metastatic gastrointestinal adenocarcinoma tissue in patients treated on a phase I trial of oxaliplatin and capecitabine. *BMC Cancer* 2008; **8**: 386 [PMID: 19105824 DOI: 10.1186/1471-2407-8-386]

342 **Lenz HJ**, Zhang W, Shi MM, Jacques C, Barrett JC, Danenberg KD, Hoffmann AC, Trarbach T, Folprecht G, Meinhardt G, Yang D. ERCC-1 gene expression levels and outcome to FOLFOX chemotherapy in patients enrolled in CONFIRM1 and CONFIRM2. *J Clin Oncol* 2008; **26**: 4131 [PMID: WOS: 000208457401311]

343 **Yu JJ**, Mu C, Lee KB, Okamoto A, Reed EL, Bostick-Bruton F, Mitchell KC, Reed E. A nucleotide polymorphism in ERCC1 in human ovarian cancer cell lines and tumor tissues. *Mutat Res* 1997; **382**: 13-20 [PMID: 9360634]

344 **Viguier J**, Boige V, Miquel C, Pocard M, Giraudeau B, Sabourin JC, Ducreux M, Sarasin A, Praz F. ERCC1 codon 118 polymorphism is a predictive factor for the tumor response to oxaliplatin/5-fluorouracil combination chemotherapy in patients with advanced colorectal cancer. *Clin Cancer Res* 2005; **11**: 6212-6217 [PMID: 16144923 DOI: 10.1158/1078-0432.CCR-04-2216]

345 **Martinez-Balibrea E**, Abad A, Aranda E, Sastre J, Manzano JL, Díaz-Rubio E, Gómez-España A, Aparicio J, García T, Maestu I, Martínez-Cardús A, Ginés A, Guino E. Pharmacogenetic approach for capecitabine or 5-fluorouracil selection to be combined with oxaliplatin as first-line chemotherapy in advanced colorectal cancer. *Eur J Cancer* 2008; **44**: 1229-1237 [PMID: 18448328 DOI: 10.1016/j.ejca.2008.03.025]

346 **Chang PM**, Tzeng CH, Chen PM, Lin JK, Lin TC, Chen WS, Jiang JK, Wang HS, Wang WS. ERCC1 codon 118 C→T polymorphism associated with ERCC1 expression and outcome of FOLFOX-4 treatment in Asian patients with metastatic colorectal carcinoma. *Cancer Sci* 2009; **100**: 278-283 [PMID: 19068092 DOI: 10.1111/j.1349-7006.2008.01031.x]

347 **Goldberg RM**, McLeod HL, Sargent DJ, Morton RF, Green EM, Fuchs C, Ramanathan RK, Williamson SK, Findlay BP, Pitot HC, Alberts SR. Genetic polymorphisms, toxicity, and response rate in African Americans (AA) with metastatic colorectal cancer (MCRC) compared to Caucasians (C) when treated with IFL, FOLFOX or IROX in Intergroup N9741*. J Clin Oncol* 2006; **24**: 146S-146S

348 **Ruzzo A**, Graziano F, Kawakami K, Watanabe G, Santini D, Catalano V, Bisonni R, Canestrari E, Ficarelli R, Menichetti ET, Mari D, Testa E, Silva R, Vincenzi B, Giordani P, Cascinu S, Giustini L, Tonini G, Magnani M. Pharmacogenetic profiling and clinical outcome of patients with advanced gastric cancer treated with palliative chemotherapy. *J Clin Oncol* 2006; **24**: 1883-1891 [PMID: 16622263 DOI: 10.1200/JCO.2005.04.8322]

349 **Liu B**, Wei J, Zou Z, Qian X, Nakamura T, Zhang W, Ding Y, Feng J, Yu L. Polymorphism of XRCC1 predicts overall survival of gastric cancer patients receiving oxaliplatin-based chemotherapy in Chinese population. *Eur J Hum Genet* 2007; **15**: 1049-1053 [PMID: 17593927 DOI: 10.1038/sj.ejhg.5201884]

350 **Braun MS**, Richman SD, Quirke P, Daly C, Adlard JW, Elliott F, Barrett JH, Selby P, Meade AM, Stephens RJ, Parmar MK, Seymour MT. Predictive biomarkers of chemotherapy efficacy in colorectal cancer: results from the UK MRC FOCUS trial. *J Clin Oncol* 2008; **26**: 2690-2698 [PMID: 18509181 DOI: 10.1200/JCO.2007.15.5580]

351 **Monzo M**, Moreno I, Navarro A, Ibeas R, Artells R, Gel B, Martinez F, Moreno J, Hernandez R, Navarro-Vigo M. Single nucleotide polymorphisms in nucleotide excision repair genes XPA, XPD, XPG and ERCC1 in advanced colorectal cancer patients treated with first-line oxaliplatin/fluoropyrimidine. *Oncology* 2007; **72**: 364-370 [PMID: 18204222 DOI: 10.1159/000113534]

352 **Keam B**, Im SA, Han SW, Ham HS, Kim MA, Oh DY, Lee SH, Kim JH, Kim DW, Kim TY, Heo DS, Kim WH, Bang YJ. Modified FOLFOX-6 chemotherapy in advanced gastric cancer: Results of phase II study and comprehensive analysis of polymorphisms as a predictive and prognostic marker. *BMC Cancer* 2008; **8**: 148 [PMID: 18505590 DOI: 10.1186/1471-2407-8-148]

353 **Park DJ**, Stoehlmacher J, Zhang W, Tsao-Wei DD, Groshen S, Lenz HJ. A Xeroderma pigmentosum group D gene polymorphism predicts clinical outcome to platinum-based chemotherapy in patients with advanced colorectal cancer. *Cancer Res* 2001; **61**: 8654-8658 [PMID: 11751380]

354 **Shi Q**, Wang LE, Bondy ML, Brewster A, Singletary SE, Wei Q. Reduced DNA repair of benzo[a]pyrene diol epoxide-induced adducts and common XPD polymorphisms in breast cancer patients. *Carcinogenesis* 2004; **25**: 1695-1700 [PMID: 15090466 DOI: 10.1093/carcin/bgh167]

355 **Qiao Y**, Spitz MR, Shen H, Guo Z, Shete S, Hedayati M, Grossman L, Mohrenweiser H, Wei Q. Modulation of repair of ultraviolet damage in the host-cell reactivation assay by polymorphic XPC and XPD/ERCC2 genotypes. *Carcinogenesis* 2002; **23**: 295-299 [PMID: 11872635]

356 **Ruzzo A**, Graziano F, Loupakis F, Santini D, Catalano V, Bisonni R, Ficarelli R, Fontana A, Andreoni F, Falcone A, Canestrari E, Tonini G, Mari D, Lippe P, Pizzagalli F, Schiavon G, Alessandroni P, Giustini L, Maltese P, Testa E, Menichetti ET, Magnani M. Pharmacogenetic profiling in patients with advanced colorectal cancer treated with first-line FOLFIRI chemotherapy. *Pharmacogenomics J* 2008; **8**: 278-288 [PMID: 17549067 DOI: 10.1038/sj.tpj.6500463]

357 **Yin M**, Yan J, Martinez-Balibrea E, Graziano F, Lenz HJ, Kim HJ, Robert J, Im SA, Wang WS, Etienne-Grimaldi MC, Wei Q. ERCC1 and ERCC2 polymorphisms predict clinical outcomes of oxaliplatin-based chemotherapies in gastric and colorectal cancer: a systemic review and meta-analysis. *Clin Cancer Res* 2011; **17**: 1632-1640 [PMID: 21278243 DOI: 10.1158/1078-0432.CCR-10-2169]

358 **Kim SH**, Kwon HC, Oh SY, Lee DM, Lee S, Lee JH, Roh MS, Kim DC, Park KJ, Choi HJ, Kim HJ. Prognostic value of ERCC1, thymidylate synthase, and glutathione S-transferase pi for 5-FU/oxaliplatin chemotherapy in advanced colorectal cancer. *Am J Clin Oncol* 2009; **32**: 38-43 [PMID: 19194123 DOI: 10.1097/COC.0b013e31817be58e]

359 **Lunn RM**, Langlois RG, Hsieh LL, Thompson CL, Bell DA. XRCC1 polymorphisms: effects on aflatoxin B1-DNA adducts and glycophorin A variant frequency. *Cancer Res* 1999; **59**: 2557-2561 [PMID: 10363972]

360 **Monaco R**, Rosal R, Dolan MA, Pincus MR, Brandt-Rauf PW. Conformational effects of a common codon 399 polymorphism on the BRCT1 domain of the XRCC1 protein. *Protein J* 2007; **26**: 541-546 [PMID: 17899335 DOI: 10.1007/s10930-007-9095-y]

361 **Gurubhagavatula S**, Liu G, Park S, Zhou W, Su L, Wain JC, Lynch TJ, Neuberg DS, Christiani DC. XPD and XRCC1 genetic polymorphisms are prognostic factors in advanced non-small-cell lung cancer patients treated with platinum chemotherapy. *J Clin Oncol* 2004; **22**: 2594-2601 [PMID: 15173214 DOI: 10.1200/JCO.2004.08.067]

362 **Suh KW**, Kim JH, Kim do Y, Kim YB, Lee C, Choi S. Which gene is a dominant predictor of response during FOLFOX chemotherapy for the treatment of metastatic colorectal cancer, the MTHFR or XRCC1 gene? *Ann Surg Oncol* 2006; **13**: 1379-1385 [PMID: 17009149 DOI: 10.1245/s10434-006-9112-y]

363 **Liang J**, Jiang T, Yao RY, Liu ZM, Lv HY, Qi WW. The combination of ERCC1 and XRCC1 gene polymorphisms better predicts clinical outcome to oxaliplatin-based chemotherapy in metastatic colorectal cancer. *Cancer Chemother Pharmacol* 2010; **66**: 493-500 [PMID: 19960344 DOI: 10.1007/s00280-009-1186-3]

364 **Stoehlmacher J**, Ghaderi V, Iobal S, Groshen S, Tsao-Wei D, Park D, Lenz HJ. A polymorphism of the XRCC1 gene predicts for response to platinum based treatment in advanced colorectal cancer. *Anticancer Res* 2001; **21**: 3075-3079 [PMID: 11712813]

365 **Raymond E**, Faivre S, Woynarowski JM, Chaney SG. Oxaliplatin: mechanism of action and antineoplastic activity. *Semin Oncol* 1998; **25**: 4-12 [PMID: 9609103]

366 **Chaney SG**, Campbell SL, Bassett E, Wu Y. Recognition and processing of cisplatin- and oxaliplatin-DNA adducts. *Crit Rev Oncol Hematol* 2005; **53**: 3-11 [PMID: 15607931 DOI: 10.1016/j.critrevonc.2004.08.008]

367 **Jascur T**, Boland CR. Structure and function of the components of the human DNA mismatch repair system. *Int J Cancer* 2006; **119**: 2030-2035 [PMID: 16804905 DOI: 10.1002/ijc.22023]

368 **Wheeler JM**, Beck NE, Kim HC, Tomlinson IP, Mortensen NJ, Bodmer WF. Mechanisms of inactivation of mismatch repair genes in human colorectal cancer cell lines: the predominant role of hMLH1. *Proc Natl Acad Sci U S A* 1999; **96**: 10296-10301 [PMID: 10468602]

369 **Peltomäki P**. Role of DNA mismatch repair defects in the pathogenesis of human cancer. *J Clin Oncol* 2003; **21**: 1174-1179 [PMID: 12637487]

370 **Plumb JA**, Strathdee G, Sludden J, Kaye SB, Brown R. Reversal of drug resistance in human tumor xenografts by 2'-deoxy-5-azacytidine-induced demethylation of the hMLH1 gene promoter. *Cancer Res* 2000; **60**: 6039-6044 [PMID: 11085525]

371 **Fink D**, Nebel S, Aebi S, Zheng H, Cenni B, Nehmé A, Christen RD, Howell SB. The role of DNA mismatch repair in platinum drug resistance. *Cancer Res* 1996; **56**: 4881-4886 [PMID: 8895738]

372 **Vaisman A**, Varchenko M, Umar A, Kunkel TA, Risinger JI, Barrett JC, Hamilton TC, Chaney SG. The role of hMLH1, hMSH3, and hMSH6 defects in cisplatin and oxaliplatin resistance: correlation with replicative bypass of platinum-DNA adducts. *Cancer Res* 1998; **58**: 3579-3585 [PMID: 9721864]

373 **Barry MA**, Behnke CA, Eastman A. Activation of programmed cell death (apoptosis) by cisplatin, other anticancer drugs, toxins and hyperthermia. *Biochem Pharmacol* 1990; **40**: 2353-2362 [PMID: 2244936]

374 **Jung Y**, Lippard SJ. Direct cellular responses to platinum-induced DNA damage. *Chem Rev* 2007; **107**: 1387-1407 [PMID: 17455916 DOI: 10.1021/cr068207j]

375 **Nehmé A**, Baskaran R, Nebel S, Fink D, Howell SB, Wang JY, Christen RD. Induction of JNK and c-Abl signalling by cisplatin and oxaliplatin in mismatch repair-proficient and -deficient cells. *Br J Cancer* 1999; **79**: 1104-1110 [PMID: 10098743 DOI: 10.1038/sj.bjc.6690176]

376 **Raymond E**, Faivre S, Chaney S, Woynarowski J, Cvitkovic E. Cellular and molecular pharmacology of oxaliplatin. *Mol Cancer Ther* 2002; **1**: 227-235 [PMID: 12467217]

377 **Fink D**, Zheng H, Nebel S, Norris PS, Aebi S, Lin TP, Nehmé A, Christen RD, Haas M, MacLeod CL, Howell SB. In vitro and in vivo resistance to cisplatin in cells that have lost DNA mismatch repair. *Cancer Res* 1997; **57**: 1841-1845 [PMID: 9157971]

378 **Ahmad S**. Platinum-DNA interactions and subsequent cellular processes controlling sensitivity to anticancer platinum complexes. *Chem Biodivers* 2010; **7**: 543-566 [PMID: 20232326 DOI: 10.1002/cbdv.200800340]

379 **Wang D**, Lippard SJ. Cellular processing of platinum anticancer drugs. *Nat Rev Drug Discov* 2005; **4**: 307-320 [PMID: 15789122 DOI: 10.1038/nrd1691]

380 **Adimoolam S**, Ford JM. p53 and regulation of DNA damage recognition during nucleotide excision repair. *DNA Repair (Amst)* 2003; **2**: 947-954 [PMID: 12967652]

381 **Vekris A**, Meynard D, Haaz MC, Bayssas M, Bonnet J, Robert J. Molecular determinants of the cytotoxicity of platinum compounds: the contribution of in silico research. *Cancer Res* 2004; **64**: 356-362 [PMID: 14729645]

382 **Fojta M**, Pivonkova H, Brazdova M, Kovarova L, Palecek E, Pospisilova S, Vojtesek B, Kasparkova J, Brabec V. Recognition of DNA modified by antitumor cisplatin by "latent" and "active" protein p53. *Biochem Pharmacol* 2003; **65**: 1305-1316 [PMID: 12694871]

383 **Masui K**, Gini B, Wykosky J, Zanca C, Mischel PS, Furnari FB, Cavenee WK. A tale of two approaches: complementary mechanisms of cytotoxic and targeted therapy resistance may inform next-generation cancer treatments. *Carcinogenesis* 2013; **34**: 725-738 [PMID: 23455378 DOI: 10.1093/carcin/bgt086]

384 **Casado E**, De Castro J, Belda-Iniesta C, Cejas P, Feliu J, Sereno M, González-Barón M. Molecular markers in colorectal cancer: genetic bases for a customised treatment. *Clin Transl Oncol* 2007; **9**: 549-554 [PMID: 17921101]

385 **Silvestri A**, Pin E, Huijbers A, Pellicani R, Parasido EM, Pierobon M, Petricoin E, Liotta L, Belluco C. Individualized therapy for metastatic colorectal cancer. *J Intern Med* 2013; **274**: 1-24 [PMID: 23527888 DOI: 10.1111/joim.12070]

386 **Kim ST**, Lee J, Park SH, Park JO, Lim HY, Kang WK, Kim JY, Kim YH, Chang DK, Rhee PL, Kim DS, Yun H, Cho YB, Kim HC, Yun SH, Lee WY, Chun HK, Park YS. Clinical impact of microsatellite instability in colon cancer following adjuvant FOLFOX therapy. *Cancer Chemother Pharmacol* 2010; **66**: 659-667 [PMID: 20033812 DOI: 10.1007/s00280-009-1206-3]

387 **Zaanan A**, Fléjou JF, Emile JF, Des GG, Cuilliere-Dartigues P, Malka D, Lecaille C, Validire P, Louvet C, Rougier P, de Gramont A, Bonnetain F, Praz F, Taïeb J. Defective mismatch repair status as a prognostic biomarker of disease-free survival in stage III colon cancer patients treated with adjuvant FOLFOX chemotherapy. *Clin Cancer Res* 2011; **17**: 7470-7478 [PMID: 21998335 DOI: 10.1158/1078-0432.CCR-11-1048]

388 **Postma C**, Koopman M, Buffart TE, Eijk PP, Carvalho B, Peters GJ, Ylstra B, van Krieken JH, Punt CJ, Meijer GA. DNA copy number profiles of primary tumors as predictors of response to chemotherapy in advanced colorectal cancer. *Ann Oncol* 2009; **20**: 1048-1056 [PMID: 19150955 DOI: 10.1093/annonc/mdn738]

389 **Lee AJ**, Endesfelder D, Rowan AJ, Walther A, Birkbak NJ, Futreal PA, Downward J, Szallasi Z, Tomlinson IP, Howell M, Kschischo M, Swanton C. Chromosomal instability confers intrinsic multidrug resistance. *Cancer Res* 2011; **71**: 1858-1870 [PMID: 21363922 DOI: 10.1158/0008-5472.CAN-10-3604]

390 **Jover R**, Nguyen TP, Pérez-Carbonell L, Zapater P, Payá A, Alenda C, Rojas E, Cubiella J, Balaguer F, Morillas JD, Clofent J, Bujanda L, Reñé JM, Bessa X, Xicola RM, Nicolás-Pérez D, Castells A, Andreu M, Llor X, Boland CR, Goel A. 5-Fluorouracil adjuvant chemotherapy does not increase survival in patients with CpG island methylator phenotype colorectal cancer. *Gastroenterology* 2011; **140**: 1174-1181 [PMID: 21185836 DOI: 10.1053/j.gastro.2010.12.035]

391 **Iacopetta B**, Kawakami K, Watanabe T. Predicting clinical outcome of 5-fluorouracil-based chemotherapy for colon cancer patients: is the CpG island methylator phenotype the 5-fluorouracil-responsive subgroup? *Int J Clin Oncol* 2008; **13**: 498-503 [PMID: 19093176 DOI: 10.1007/s10147-008-0854-3]

392 **Shen L**, Catalano PJ, Benson AB, O'Dwyer P, Hamilton SR, Issa JP. Association between DNA methylation and shortened survival in patients with advanced colorectal cancer treated with 5-fluorouracil based chemotherapy. *Clin Cancer Res* 2007; **13**: 6093-6098 [PMID: 17947473 DOI: 10.1158/1078-0432.CCR-07-1011]

393 **Miyaki Y**, Suzuki K, Koizumi K, Kato T, Saito M, Kamiyama H, Maeda T, Shibata K, Shiya N, Konishi F. Identification of a potent epigenetic biomarker for resistance to camptothecin and poor outcome to irinotecan-based chemotherapy in colon cancer. *Int J Oncol* 2012; **40**: 217-226 [PMID: 21901246 DOI: 10.3892/ijo.2011.1189]

394 **Kasahara K**, Arao T, Sakai K, Matsumoto K, Sakai A, Kimura H, Sone T, Horiike A, Nishio M, Ohira T, Ikeda N, Yamanaka T, Saijo N, Nishio K. Impact of serum hepatocyte growth factor on treatment response to epidermal growth factor receptor tyrosine kinase inhibitors in patients with non-small cell lung adenocarcinoma. *Clin Cancer Res* 2010; **16**: 4616-4624 [PMID: 20679350 DOI: 10.1158/1078-0432.CCR-10-0383]

395 **Pierobon M**, Calvert V, Belluco C, Garaci E, Deng J, Lise M, Nitti D, Mammano E, De Marchi F, Liotta L, Petricoin E. Multiplexed cell signaling analysis of metastatic and nonmetastatic colorectal cancer reveals COX2-EGFR signaling activation as a potential prognostic pathway biomarker. *Clin Colorectal Cancer* 2009; **8**: 110-117 [PMID: 19739273 DOI: 10.3816/CCC.2009.n]

396 **de Wit M**, Fijneman RJ, Verheul HM, Meijer GA, Jimenez CR. Proteomics in colorectal cancer translational research: biomarker discovery for clinical applications. *Clin Biochem* 2013; **46**: 466-479 [PMID: 23159294 DOI: 10.1016/j.clinbiochem.2012.10.039]

397 **McShane LM**, Altman DG, Sauerbrei W, Taube SE, Gion M, Clark GM. REporting recommendations for tumor MARKer prognostic studies (REMARK). *Nat Clin Pract Urol* 2005; **2**: 416-422 [PMID: 16482653]

398 **Walther A**, Johnstone E, Swanton C, Midgley R, Tomlinson I, Kerr D. Genetic prognostic and predictive markers in colorectal cancer. *Nat Rev Cancer* 2009; **9**: 489-499 [PMID: 19536109 DOI: 10.1038/nrc2645]

399 **Heinemann V**, Douillard JY, Ducreux M, Peeters M. Targeted therapy in metastatic colorectal cancer -- an example of personalised medicine in action. *Cancer Treat Rev* 2013; **39**: 592-601 [PMID: 23375249 DOI: 10.1016/j.ctrv.2012.12.011]

400 **Vijayaraghavan A**, Efrusy MB, Göke B, Kirchner T, Santas CC, Goldberg RM. Cost-effectiveness of KRAS testing in metastatic colorectal cancer patients in the United States and Germany. *Int J Cancer* 2012; **131**: 438-445 [PMID: 21898389 DOI: 10.1002/ijc.26400]

401 **Longley DB**, Allen WL, Johnston PG. Drug resistance, predictive markers and pharmacogenomics in colorectal cancer. *Biochim Biophys Acta* 2006; **1766**: 184-196 [PMID: 16973289 DOI: 10.1016/j.bbcan.2006.08.001]

402 **Sommer H**, Santi DV. Purification and amino acid analysis of an active site peptide from thymidylate synthetase containing covalently bound 5-fluoro-2'-deoxyuridylate and methylenetetrahydrofolate. *Biochem Biophys Res Commun* 1974; **57**: 689-695 [PMID: 4275130]

403 **Santos A**, Zanetta S, Cresteil T, Deroussent A, Pein F, Raymond E, Vernillet L, Risse ML, Boige V, Gouyette A, Vassal G. Metabolism of irinotecan (CPT-11) by CYP3A4 and CYP3A5 in humans. *Clin Cancer Res* 2000; **6**: 2012-2020 [PMID: 10815927]

404 **Strassburg CP**, Lankisch TO, Manns MP, Ehmer U. Family 1 uridine-5'-diphosphate glucuronosyltransferases (UGT1A): from Gilbert's syndrome to genetic organization and variability. *Arch Toxicol* 2008; **82**: 415-433 [PMID: 18491077 DOI: 10.1007/s00204-008-0314-x]

405 **Paillas S**, Causse A, Marzi L, de Medina P, Poirot M, Denis V, Vezzio-Vie N, Espert L, Arzouk H, Coquelle A, Martineau P, Del Rio M, Pattingre S, Gongora C. MAPK14/p38α confers irinotecan resistance to TP53-defective cells by inducing survival autophagy. *Autophagy* 2012; **8**: 1098-1112 [PMID: 22647487 DOI: 10.4161/auto.20268]

406 **Kroetz DL**. Role for drug transporters beyond tumor resistance: hepatic functional imaging and genotyping of multidrug resistance transporters for the prediction of irinotecan toxicity. *J Clin Oncol* 2006; **24**: 4225-4227 [PMID: 16895999 DOI: 10.1200/JCO.2006.07.2355]

407 **Han JY**, Lim HS, Park YH, Lee SY, Lee JS. Integrated pharmacogenetic prediction of irinotecan pharmacokinetics and toxicity in patients with advanced non-small cell lung cancer. *Lung Cancer* 2009; **63**: 115-120 [PMID: 18221820 DOI: 10.1016/j.lungcan.2007.12.003]

408 **Rabik CA**, Dolan ME. Molecular mechanisms of resistance and toxicity associated with platinating agents. *Cancer Treat Rev* 2007; **33**: 9-23 [PMID: 17084534 DOI: 10.1016/j.ctrv.2006.09.006]

409 **Salgado J**, Zabalegui N, Gil C, Monreal I, Rodríguez J, García-Foncillas J. Polymorphisms in the thymidylate synthase and dihydropyrimidine dehydrogenase genes predict response and toxicity to capecitabine-raltitrexed in colorectal cancer. *Oncol Rep* 2007; **17**: 325-328 [PMID: 17203168]

410 **Park DJ**, Stoehlmacher J, Zhang W, Tsao-Wei D, Groshen S, Lenz HJ. Thymidylate synthase gene polymorphism predicts response to capecitabine in advanced colorectal cancer. *Int J Colorectal Dis* 2002; **17**: 46-49 [PMID: 12018454]

411 **Marsh S**, McKay JA, Cassidy J, McLeod HL. Polymorphism in the thymidylate synthase promoter enhancer region in colorectal cancer. *Int J Oncol* 2001; **19**: 383-386 [PMID: 11445856]

412 **Schwab M**, Zanger UM, Marx C, Schaeffeler E, Klein K, Dippon J, Kerb R, Blievernicht J, Fischer J, Hofmann U, Bokemeyer C, Eichelbaum M. Role of genetic and nongenetic factors for fluorouracil treatment-related severe toxicity: a prospective clinical trial by the German 5-FU Toxicity Study Group. *J Clin Oncol* 2008; **26**: 2131-2138 [PMID: 18299612 DOI: 10.1200/JCO.2006.10.4182]

413 **Hitre E**, Budai B, Adleff V, Czeglédi F, Horváth Z, Gyergyay F, Lövey J, Kovács T, Orosz Z, Láng I, Kásler M, Kralovánszky J. Influence of thymidylate synthase gene polymorphisms on the survival of colorectal cancer patients receiving adjuvant 5-fluorouracil. *Pharmacogenet Genomics* 2005; **15**: 723-730 [PMID: 16141798]

414 **Lecomte T**, Ferraz JM, Zinzindohoué F, Loriot MA, Tregouet DA, Landi B, Berger A, Cugnenc PH, Jian R, Beaune P, Laurent-Puig P. Thymidylate synthase gene polymorphism predicts toxicity in colorectal cancer patients receiving 5-fluorouracil-based chemotherapy. *Clin Cancer Res* 2004; **10**: 5880-5888 [PMID: 15355920 DOI: 10.1158/1078-0432.CCR-04-0169]

415 **Dotor E**, Cuatrecases M, Martínez-Iniesta M, Navarro M, Vilardell F, Guinó E, Pareja L, Figueras A, Molleví DG, Serrano T, de Oca J, Peinado MA, Moreno V, Germà JR, Capellá G, Villanueva A. Tumor thymidylate synthase 1494del6 genotype as a prognostic factor in colorectal cancer patients receiving fluorouracil-based adjuvant treatment. *J Clin Oncol* 2006; **24**: 1603-1611 [PMID: 16575011 DOI: 10.1200/JCO.2005.03.5253]

416 **Robien K**, Ulrich CM. 5,10-Methylenetetrahydrofolate reductase polymorphisms and leukemia risk: a HuGE minireview. *Am J Epidemiol* 2003; **157**: 571-582 [PMID: 12672676]

417 **Deenen MJ**, Tol J, Burylo AM, Doodeman VD, de Boer A, Vincent A, Guchelaar HJ, Smits PH, Beijnen JH, Punt CJ, Schellens JH, Cats A. Relationship between single nucleotide polymorphisms and haplotypes in DPYD and toxicity and efficacy of capecitabine in advanced colorectal cancer. *Clin Cancer Res* 2011; **17**: 3455-3468 [PMID: 21498394 DOI: 10.1158/1078-0432.CCR-10-2209]

418 **Magné N**, Etienne-Grimaldi MC, Cals L, Renée N, Formento JL, Francoual M, Milano G. Dihydropyrimidine dehydrogenase activity and the IVS14+1G& gt; A mutation in patients developing 5FU-related toxicity. *Br J Clin Pharmacol* 2007; **64**: 237-240 [PMID: 17335544 DOI: 10.1111/j.1365-2125.2007.02869.x]

419 **van Kuilenburg AB**, Meijer J, Mul AN, Meinsma R, Schmid V, Dobritzsch D, Hennekam RC, Mannens MM, Kiechle M, Etienne-Grimaldi MC, Klümpen HJ, Maring JG, Derleyn VA, Maartense E, Milano G, Vijzelaar R, Gross E. Intragenic deletions and a deep intronic mutation affecting pre-mRNA splicing in the dihydropyrimidine dehydrogenase gene as novel mechanisms causing 5-fluorouracil toxicity. *Hum Genet* 2010; **128**: 529-538 [PMID: 20803296 DOI: 10.1007/s00439-010-0879-3]

420 **Johnson MR**, Wang K, Diasio RB. Profound dihydropyrimidine dehydrogenase deficiency resulting from a novel compound heterozygote genotype. *Clin Cancer Res* 2002; **8**: 768-774 [PMID: 11895907]

421 **Gross E**, Ullrich T, Seck K, Mueller V, de Wit M, von Schilling C, Meindl A, Schmitt M, Kiechle M. Detailed analysis of five mutations in dihydropyrimidine dehydrogenase detected in cancer patients with 5-fluorouracil-related side effects. *Hum Mutat* 2003; **22**: 498 [PMID: 14635116 DOI: 10.1002/humu.9201]

422 **Morel A**, Boisdron-Celle M, Fey L, Soulie P, Craipeau MC, Traore S, Gamelin E. Clinical relevance of different dihydropyrimidine dehydrogenase gene single nucleotide polymorphisms on 5-fluorouracil tolerance. *Mol Cancer Ther* 2006; **5**: 2895-2904 [PMID: 17121937 DOI: 10.1158/1535-7163.MCT-06-0327]

423 **Tanaka D**, Hishida A, Matsuo K, Iwata H, Shinoda M, Yamamura Y, Kato T, Hatooka S, Mitsudomi T, Kagami Y, Ogura M, Tajima K, Suyama M, Naito M, Yamamoto K, Tamakoshi A, Hamajima N. Polymorphism of dihydropyrimidine dehydrogenase (DPYD) Cys29Arg and risk of six malignancies in Japanese. *Nagoya J Med Sci* 2005; **67**: 117-124 [PMID: 17375478]

424 **Kleibl Z**, Fidlerova J, Kleiblova P, Kormunda S, Bilek M, Bouskova K, Sevcik J, Novotny J. Influence of dihydropyrimidine dehydrogenase gene (DPYD) coding sequence variants on the development of fluoropyrimidine-related toxicity in patients with high-grade toxicity and patients with excellent tolerance of fluoropyrimidine-based chemotherapy. *Neoplasma* 2009; **56**: 303-316 [PMID: 19473056]

425 **Gross E**, Busse B, Riemenschneider M, Neubauer S, Seck K, Klein HG, Kiechle M, Lordick F, Meindl A. Strong association of a common dihydropyrimidine dehydrogenase gene polymorphism with fluoropyrimidine-related toxicity in cancer patients. *PLoS One* 2008; **3**: e4003 [PMID: 19104657 DOI: 10.1371/journal.pone.0004003]

426 **Sistonen J**, Smith C, Fu YK, Largiadèr CR. A new DPYD genotyping assay for improving the safety of 5-fluorouracil therapy. *Clin Chim Acta* 2012; **414**: 109-111 [PMID: 22935545 DOI: 10.1016/j.cca.2012.08.015]

427 **Mueller F**, Büchel B, Köberle D, Schürch S, Pfister B, Krähenbühl S, Froehlich TK, Largiader CR, Joerger M. Gender-specific elimination of continuous-infusional 5-fluorouracil in patients with gastrointestinal malignancies: results from a prospective population pharmacokinetic study. *Cancer Chemother Pharmacol* 2013; **71**: 361-370 [PMID: 23139054 DOI: 10.1007/s00280-012-2018-4]

428 **Wei X**, Elizondo G, Sapone A, McLeod HL, Raunio H, Fernandez-Salguero P, Gonzalez FJ. Characterization of the human dihydropyrimidine dehydrogenase gene. *Genomics* 1998; **51**: 391-400 [PMID: 9721209 DOI: 10.1006/geno.1998.5379]

429 **He YF**, Wei W, Zhang X, Li YH, Li S, Wang FH, Lin XB, Li ZM, Zhang DS, Huang HQ, Hu B, Jiang WQ. Analysis of the DPYD gene implicated in 5-fluorouracil catabolism in Chinese cancer patients. *J Clin Pharm Ther* 2008; **33**: 307-314 [PMID: 18452418 DOI: 10.1111/j.1365-2710.2008.00898.x]

430 **Zhang XP**, Bai ZB, Chen BA, Feng JF, Yan F, Jiang Z, Zhong YJ, Wu JZ, Chen L, Lu ZH, Tong N, Zhang ZD, Xu PP, Peng MX, Zhang WJ, Wang S. Polymorphisms of dihydropyrimidine dehydrogenase gene and clinical outcomes of gastric cancer patients treated with fluorouracil-based adjuvant chemotherapy in Chinese population. *Chin Med J (Engl)* 2012; **125**: 741-746 [PMID: 22490566]

431 **van Kuilenburg AB**, Dobritzsch D, Meinsma R, Haasjes J, Waterham HR, Nowaczyk MJ, Maropoulos GD, Hein G, Kalhoff H, Kirk JM, Baaske H, Aukett A, Duley JA, Ward KP, Lindqvist Y, van Gennip AH. Novel disease-causing mutations in the dihydropyrimidine dehydrogenase gene interpreted by analysis of the three-dimensional protein structure. *Biochem J* 2002; **364**: 157-163 [PMID: 11988088]

432 **Loganayagam A**, Arenas-Hernandez M, Fairbanks L, Ross P, Sanderson JD, Marinaki AM. The contribution of deleterious DPYD gene sequence variants to fluoropyrimidine toxicity in British cancer patients. *Cancer Chemother Pharmacol* 2010; **65**: 403-406 [PMID: 19795123 DOI: 10.1007/s00280-009-1147-x]

433 **Collie-Duguid ES**, Etienne MC, Milano G, McLeod HL. Known variant DPYD alleles do not explain DPD deficiency in cancer patients. *Pharmacogenetics* 2000; **10**: 217-223 [PMID: 10803677]

434 **Ezzeldin HH**, Lee AM, Mattison LK, Diasio RB. Methylation of the DPYD promoter: an alternative mechanism for dihydropyrimidine dehydrogenase deficiency in cancer patients. *Clin Cancer Res* 2005; **11**: 8699-8705 [PMID: 16361556 DOI: 10.1158/1078-0432.CCR-05-1520]

435 **Seck K**, Riemer S, Kates R, Ullrich T, Lutz V, Harbeck N, Schmitt M, Kiechle M, Diasio R, Gross E. Analysis of the DPYD gene implicated in 5-fluorouracil catabolism in a cohort of Caucasian individuals. *Clin Cancer Res* 2005; **11**: 5886-5892 [PMID: 16115930 DOI: 10.1158/1078-0432.CCR-04-1784]

436 **Loganayagam A**, Arenas Hernandez M, Corrigan A, Fairbanks L, Lewis CM, Harper P, Maisey N, Ross P, Sanderson JD, Marinaki AM. Pharmacogenetic variants in the DPYD, TYMS, CDA and MTHFR genes are clinically significant predictors of fluoropyrimidine toxicity. *Br J Cancer* 2013; **108**: 2505-2515 [PMID: 23736036 DOI: 10.1038/bjc.2013.262]

437 **Boisdron-Celle M**, Remaud G, Traore S, Poirier AL, Gamelin L, Morel A, Gamelin E. 5-Fluorouracil-related severe toxicity: a comparison of different methods for the pretherapeutic detection of dihydropyrimidine dehydrogenase deficiency. *Cancer Lett* 2007; **249**: 271-282 [PMID: 17064846 DOI: 10.1016/j.canlet.2006.09.006]

438 **Westra JL**, Hollema H, Schaapveld M, Platteel I, Oien KA, Keith WN, Mauritz R, Peters GJ, Buys CH, Hofstra RM, Plukker JT. Predictive value of thymidylate synthase and dihydropyrimidine dehydrogenase protein expression on survival in adjuvantly treated stage III colon cancer patients. *Ann Oncol* 2005; **16**: 1646-1653 [PMID: 16012177 DOI: 10.1093/annonc/mdi316]

439 **Belvedere O**, Puglisi F, Di Loreto C, Cataldi P, Guglielmi A, Aschele C, Sobrero A. Lack of correlation between immunohistochemical expression of E2F-1, thymidylate synthase expression and clinical response to 5-fluorouracil in advanced colorectal cancer. *Ann Oncol* 2004; **15**: 55-58 [PMID: 14679120]

440 **Paradiso A**, Xu J, Mangia A, Chiriatti A, Simone G, Zito A, Montemurro S, Giuliani F, Maiello E, Colucci G. Topoisomerase-I, thymidylate synthase primary tumour expression and clinical efficacy of 5-FU/CPT-11 chemotherapy in advanced colorectal cancer patients. *Int J Cancer* 2004; **111**: 252-258 [PMID: 15197779 DOI: 10.1002/ijc.20208]

441 **Lindebjerg J**, Nielsen JN, Hoeffding LD, Jakobsen A. Immunohistochemical expression of thymidylate synthase as predictor of response to capecitabine in patients with advanced colorectal adenocarcinoma. *APMIS* 2005; **113**: 600-602 [PMID: 16218935 DOI: 10.1111/j.1600-0463.2005.apm\_201.x]

442 **Karlberg M**, Ohrling K, Edler D, Hallström M, Ullén H, Ragnhammar P. Prognostic and predictive value of thymidylate synthase expression in primary colorectal cancer. *Anticancer Res* 2010; **30**: 645-651 [PMID: 20332484]

443 **Jensen SA**, Vainer B, Sørensen JB. The prognostic significance of thymidylate synthase and dihydropyrimidine dehydrogenase in colorectal cancer of 303 patients adjuvantly treated with 5-fluorouracil. *Int J Cancer* 2007; **120**: 694-701 [PMID: 17096352 DOI: 10.1002/ijc.22318]

444 **Oi K**, Makino M, Ozaki M, Takemoto H, Yamane N, Nakamura S, Ikeguchi M, Kaibara N. Immunohistochemical dihydropyrimidine dehydrogenase expression is a good prognostic indicator for patients with Dukes' C colorectal cancer. *Anticancer Res* 2004; **24**: 273-279 [PMID: 15015608]

445 **Lassmann S**, Hennig M, Rosenberg R, Nährig J, Schreglmann J, Krause F, Poignee-Heger M, Nekarda H, Höfler H, Werner M. Thymidine phosphorylase, dihydropyrimidine dehydrogenase and thymidylate synthase mRNA expression in primary colorectal tumors-correlation to tumor histopathology and clinical follow-up. *Int J Colorectal Dis* 2006; **21**: 238-247 [PMID: 16132996 DOI: 10.1007/s00384-005-0767-9]

446 **Gustavsson B**, Kaiser C, Carlsson G, Wettergren Y, Odin E, Lindskog EB, Niyikiza C, Ma D. Molecular determinants of efficacy for 5-FU-based treatments in advanced colorectal cancer: mRNA expression for 18 chemotherapy-related genes. *Int J Cancer* 2009; **124**: 1220-1226 [PMID: 19051292 DOI: 10.1002/ijc.23852]

447 **Tokunaga Y**, Takahashi K, Saito T. Clinical role of thymidine phosphorylase and dihydropyrimidine dehydrogenase in colorectal cancer treated with postoperative fluoropyrimidine. *Hepatogastroenterology* 2005; **52**: 1715-1721 [PMID: 16334763]

448 **Petrioli R**, Bargagli G, Lazzi S, Pascucci A, Francini E, Bellan C, Conca R, Martellucci I, Fiaschi AI, Lorenzi B, Francini G. Thymidine phosphorylase expression in metastatic sites is predictive for response in patients with colorectal cancer treated with continuous oral capecitabine and biweekly oxaliplatin. *Anticancer Drugs* 2010; **21**: 313-319 [PMID: 20016369 DOI: 10.1097/CAD.0b013e328334d88a]

449 **Sameshima S**, Tomozawa S, Horikoshi H, Motegi K, Hirayama I, Koketsu S, Okada T, Kojima M, Kon Y, Sawada T. 5-Fluorouracil-related gene expression in hepatic artery infusion-treated patients with hepatic metastases from colorectal carcinomas. *Anticancer Res* 2008; **28**: 389-393 [PMID: 18383874]

450 **Dong Q**, Huang S, Li Y, Liu J. [Expressions of orotate phosphoribosyltransferase in colorectal carcinoma and its correlations with toxicities of chemotherapy]. *Nan Fang Yi Ke Da Xue Xue Bao* 2012; **32**: 1179-1181 [PMID: 22931617]

451 **Ishibashi K**, Sobajima J, Ohsawa T, Yokoyama M, Miyazaki T, Nakada H, Gonda T, Ishida H. [Expression of mRNA levels of thymidylate synthase, thymidine phosphorylase, dihydropyrimidine dehydrogenase and orotate phosphoribosyltransferase in diffusely infiltrating colorectal cancer]. *Gan To Kagaku Ryoho* 2007; **34**: 1073-1077 [PMID: 17637543]

452 **Yamada T**, Tanaka N, Yokoi K, Ishikawa N, Seya T, Horiba K, Kanazawa Y, Shirakawa T, Ohkawa K, Kudoh H, Koizumi M, Yoshioka M, Shinji S, Yamashita K, Tajiri T. [Prediction of sensitivity to 5-fluorouracil (5-fu) by metabolic and target enzyme activities in colon cancer]. *Gan To Kagaku Ryoho* 2006; **33**: 1603-1609 [PMID: 17108726]

453 **Kinoshita M**, Kodera Y, Hibi K, Nakayama G, Inoue T, Ohashi N, Ito Y, Koike M, Fujiwara M, Nakao A. Gene expression profile of 5-fluorouracil metabolic enzymes in primary colorectal cancer: potential as predictive parameters for response to fluorouracil-based chemotherapy. *Anticancer Res* 2007; **27**: 851-856 [PMID: 17465211]

454 **de Jong FA**, Kehrer DF, Mathijssen RH, Creemers GJ, de Bruijn P, van Schaik RH, Planting AS, van der Gaast A, Eskens FA, Janssen JT, Ruit JB, Verweij J, Sparreboom A, de Jonge MJ. Prophylaxis of irinotecan-induced diarrhea with neomycin and potential role for UGT1A1\*28 genotype screening: a double-blind, randomized, placebo-controlled study. *Oncologist* 2006; **11**: 944-954 [PMID: 16951398 DOI: 10.1634/theoncologist.11-8-944]

455 **Kweekel DM**, Gelderblom H, Van der Straaten T, Antonini NF, Punt CJ, Guchelaar HJ, Dutch Colorectal Cancer Group. UGT1A1\*28 genotype and irinotecan dosage in patients with metastatic colorectal cancer: a Dutch Colorectal Cancer Group study. *Br J Cancer* 2008; **99**: 275-282 [PMID: 18594531 DOI: 10.1038/sj.bjc.6604461]

456 **Minami H**, Sai K, Saeki M, Saito Y, Ozawa S, Suzuki K, Kaniwa N, Sawada J, Hamaguchi T, Yamamoto N, Shirao K, Yamada Y, Ohmatsu H, Kubota K, Yoshida T, Ohtsu A, Saijo N. Irinotecan pharmacokinetics/pharmacodynamics and UGT1A genetic polymorphisms in Japanese: roles of UGT1A1\*6 and \*28. *Pharmacogenet Genomics* 2007; **17**: 497-504 [PMID: 17558305 DOI: 10.1097/FPC.0b013e328014341f]

457 **Lamas MJ**, Duran G, Balboa E, Bernardez B, Candamio S, Vidal Y, Mosquera A, Giraldez JM, Lopez R, Carracedo A, Barros F. The value of genetic polymorphisms to predict toxicity in metastatic colorectal patients with irinotecan-based regimens. *Cancer Chemother Pharmacol* 2012; **69**: 1591-1599 [PMID: 22535333 DOI: 10.1007/s00280-012-1866-2]

458 **Shulman K**, Cohen I, Barnett-Griness O, Kuten A, Gruber SB, Lejbkowicz F, Rennert G. Clinical implications of UGT1A1\*28 genotype testing in colorectal cancer patients. *Cancer* 2011; **117**: 3156-3162 [PMID: 21287524 DOI: 10.1002/cncr.25735]

459 **Martinez-Balibrea E**, Abad A, Martínez-Cardús A, Ginés A, Valladares M, Navarro M, Aranda E, Marcuello E, Benavides M, Massutí B, Carrato A, Layos L, Manzano JL, Moreno V. UGT1A and TYMS genetic variants predict toxicity and response of colorectal cancer patients treated with first-line irinotecan and fluorouracil combination therapy. *Br J Cancer* 2010; **103**: 581-589 [PMID: 20628391 DOI: 10.1038/sj.bjc.6605776]

460 **Rhodes KE**, Zhang W, Yang D, Press OA, Gordon M, Vallböhmer D, Schultheis AM, Lurje G, Ladner RD, Fazzone W, Iqbal S, Lenz HJ. ABCB1, SLCO1B1 and UGT1A1 gene polymorphisms are associated with toxicity in metastatic colorectal cancer patients treated with first-line irinotecan. *Drug Metab Lett* 2007; **1**: 23-30 [PMID: 19356014]

461 **Ando Y**, Saka H, Asai G, Sugiura S, Shimokata K, Kamataki T. UGT1A1 genotypes and glucuronidation of SN-38, the active metabolite of irinotecan. *Ann Oncol* 1998; **9**: 845-847 [PMID: 9789606]

462 **Innocenti F**, Liu W, Chen P, Desai AA, Das S, Ratain MJ. Haplotypes of variants in the UDP-glucuronosyltransferase1A9 and 1A1 genes. *Pharmacogenet Genomics* 2005; **15**: 295-301 [PMID: 15864130]

463 **Ramírez J**, Liu W, Mirkov S, Desai AA, Chen P, Das S, Innocenti F, Ratain MJ. Lack of association between common polymorphisms in UGT1A9 and gene expression and activity. *Drug Metab Dispos* 2007; **35**: 2149-2153 [PMID: 17761781 DOI: 10.1124/dmd.107.015446]

464 **Roco A**, Quiñones L, Agúndez JA, García-Martín E, Squicciarini V, Miranda C, Garay J, Farfán N, Saavedra I, Cáceres D, Ibarra C, Varela N. Frequencies of 23 functionally significant variant alleles related with metabolism of antineoplastic drugs in the chilean population: comparison with caucasian and asian populations. *Front Genet* 2012; **3**: 229 [PMID: 23130019 DOI: 10.3389/fgene.2012.00229]

465 **Bethke L**, Webb E, Sellick G, Rudd M, Penegar S, Withey L, Qureshi M, Houlston R. Polymorphisms in the cytochrome P450 genes CYP1A2, CYP1B1, CYP3A4, CYP3A5, CYP11A1, CYP17A1, CYP19A1 and colorectal cancer risk. *BMC Cancer* 2007; **7**: 123 [PMID: 17615053 DOI: 10.1186/1471-2407-7-123]

466 **Yang X**, Zhang B, Molony C, Chudin E, Hao K, Zhu J, Gaedigk A, Suver C, Zhong H, Leeder JS, Guengerich FP, Strom SC, Schuetz E, Rushmore TH, Ulrich RG, Slatter JG, Schadt EE, Kasarskis A, Lum PY. Systematic genetic and genomic analysis of cytochrome P450 enzyme activities in human liver. *Genome Res* 2010; **20**: 1020-1036 [PMID: 20538623 DOI: 10.1101/gr.103341.109]

467 **Dai Z**, Papp AC, Wang D, Hampel H, Sadee W. Genotyping panel for assessing response to cancer chemotherapy. *BMC Med Genomics* 2008; **1**: 24 [PMID: 18547414 DOI: 10.1186/1755-8794-1-24]

468 **Balcerczak E**, Panczyk M, Piaskowski S, Pasz-Walczak G, Sałagacka A, Mirowski M. ABCB1/MDR1 gene polymorphisms as a prognostic factor in colorectal cancer. *Int J Colorectal Dis* 2010; **25**: 1167-1176 [PMID: 20533057 DOI: 10.1007/s00384-010-0961-2]

469 **Panczyk M**, Balcerczak E, Piaskowski S, Jamroziak K, Pasz-Walczak G, Mirowski M. ABCB1 gene polymorphisms and haplotype analysis in colorectal cancer. *Int J Colorectal Dis* 2009; **24**: 895-905 [PMID: 19415305 DOI: 10.1007/s00384-009-0724-0]

470 **He T**, Mo A, Zhang K, Liu L. ABCB1/MDR1 gene polymorphism and colorectal cancer risk: a meta-analysis of case-control studies. *Colorectal Dis* 2013; **15**: 12-18 [PMID: 23279665 DOI: 10.1111/j.1463-1318.2012.02919.x]

471 **Zhao L**, Li K, Li W, Yang Z. Association between the C3435T polymorphism of ABCB1/MDR1 gene (rs1045642) and colorectal cancer susceptibility : a meta-analysis based on 11,339 subjects. *Tumour Biol* 2013; **34**: 1949-1957 [PMID: 23504525 DOI: 10.1007/s13277-013-0740-0]

472 **Campa D**, Sainz J, Pardini B, Vodickova L, Naccarati A, Rudolph A, Novotny J, Försti A, Buch S, von Schönfels W, Schafmayer C, Völzke H, Hoffmeister M, Frank B, Barale R, Hemminki K, Hampe J, Chang-Claude J, Brenner H, Vodicka P, Canzian F. A comprehensive investigation on common polymorphisms in the MDR1/ABCB1 transporter gene and susceptibility to colorectal cancer. *PLoS One* 2012; **7**: e32784 [PMID: 22396794 DOI: 10.1371/journal.pone.0032784]

473 **He T**, Mo A, Zhang K, Liu L. ABCB1/MDR1 polymorphism and colorectal cancer risk: a meta-analysis of case-control studies. *Colorectal Dis* 2013; **15**:12-8 [PMID: 22176633 DOI: 10.1111/j.1463-1318.2011.02919.x]

474 **Lara PN**, Natale R, Crowley J, Lenz HJ, Redman MW, Carleton JE, Jett J, Langer CJ, Kuebler JP, Dakhil SR, Chansky K, Gandara DR. Phase III trial of irinotecan/cisplatin compared with etoposide/cisplatin in extensive-stage small-cell lung cancer: clinical and pharmacogenomic results from SWOG S0124. *J Clin Oncol* 2009; **27**: 2530-2535 [PMID: 19349543 DOI: 10.1200/JCO.2008.20.1061]

475 **Zhou Q**, Sparreboom A, Tan EH, Cheung YB, Lee A, Poon D, Lee EJ, Chowbay B. Pharmacogenetic profiling across the irinotecan pathway in Asian patients with cancer. *Br J Clin Pharmacol* 2005; **59**: 415-424 [PMID: 15801936 DOI: 10.1111/j.1365-2125.2004.02330.x]

476 **Wang Z**, Sew PH, Ambrose H, Ryan S, Chong SS, Lee EJ, Lee CG. Nucleotide sequence analyses of the MRP1 gene in four populations suggest negative selection on its coding region. *BMC Genomics* 2006; **7**: 111 [PMID: 16684361 DOI: 10.1186/1471-2164-7-111]

477 **Cecchin E**, D'Andrea M, Lonardi S, Zanusso C, Pella N, Errante D, De Mattia E, Polesel J, Innocenti F, Toffoli G. A prospective validation pharmacogenomic study in the adjuvant setting of colorectal cancer patients treated with the 5-fluorouracil/leucovorin/oxaliplatin (FOLFOX4) regimen. *Pharmacogenomics J* 2013; **13**: 403-409 [PMID: 22868256 DOI: 10.1038/tpj.2012.31]

478 **Campa D**, Müller P, Edler L, Knoefel L, Barale R, Heussel CP, Thomas M, Canzian F, Risch A. A comprehensive study of polymorphisms in ABCB1, ABCC2 and ABCG2 and lung cancer chemotherapy response and prognosis. *Int J Cancer* 2012; **131**: 2920-2928 [PMID: 22473764 DOI: 10.1002/ijc.27567]

479 **Sun N**, Sun X, Chen B, Cheng H, Feng J, Cheng L, Lu Z. MRP2 and GSTP1 polymorphisms and chemotherapy response in advanced non-small cell lung cancer. *Cancer Chemother Pharmacol* 2010; **65**: 437-446 [PMID: 19568750 DOI: 10.1007/s00280-009-1046-1]

480 **Tian C**, Ambrosone CB, Darcy KM, Krivak TC, Armstrong DK, Bookman MA, Davis W, Zhao H, Moysich K, Gallion H, DeLoia JA. Common variants in ABCB1, ABCC2 and ABCG2 genes and clinical outcomes among women with advanced stage ovarian cancer treated with platinum and taxane-based chemotherapy: a Gynecologic Oncology Group study. *Gynecol Oncol* 2012; **124**: 575-581 [PMID: 22112610 DOI: 10.1016/j.ygyno.2011.11.022]

481 **Akaba K**, Kimura T, Sasaki A, Tanabe S, Ikegami T, Hashimoto M, Umeda H, Yoshida H, Umetsu K, Chiba H, Yuasa I, Hayasaka K. Neonatal hyperbilirubinemia and mutation of the bilirubin uridine diphosphate-glucuronosyltransferase gene: a common missense mutation among Japanese, Koreans and Chinese. *Biochem Mol Biol Int* 1998; **46**: 21-26 [PMID: 9784835]

482 **Tamura A**, Watanabe M, Saito H, Nakagawa H, Kamachi T, Okura I, Ishikawa T. Functional validation of the genetic polymorphisms of human ATP-binding cassette (ABC) transporter ABCG2: identification of alleles that are defective in porphyrin transport. *Mol Pharmacol* 2006; **70**: 287-296 [PMID: 16608919 DOI: 10.1124/mol.106.023556]

483 **Campa D**, Pardini B, Naccarati A, Vodickova L, Novotny J, Försti A, Hemminki K, Barale R, Vodicka P, Canzian F. A gene-wide investigation on polymorphisms in the ABCG2/BRCP transporter and susceptibility to colorectal cancer. *Mutat Res* 2008; **645**: 56-60 [PMID: 18775442 DOI: 10.1016/j.mrfmmm.2008.08.001]

484 **Di Martino MT**, Arbitrio M, Leone E, Guzzi PH, Rotundo MS, Ciliberto D, Tomaino V, Fabiani F, Talarico D, Sperlongano P, Doldo P, Cannataro M, Caraglia M, Tassone P, Tagliaferri P. Single nucleotide polymorphisms of ABCC5 and ABCG1 transporter genes correlate to irinotecan-associated gastrointestinal toxicity in colorectal cancer patients: a DMET microarray profiling study. *Cancer Biol Ther* 2011; **12**: 780-787 [PMID: 21892003 DOI: 10.4161/cbt.12.9.17781]

485 **Cortejoso L**, García MI, García-Alfonso P, González-Haba E, Escolar F, Sanjurjo M, López-Fernández LA. Differential toxicity biomarkers for irinotecan- and oxaliplatin-containing chemotherapy in colorectal cancer. *Cancer Chemother Pharmacol* 2013; **71**: 1463-1472 [PMID: 23543295 DOI: 10.1007/s00280-013-2145-6]

486 **Kweekel DM**, Antonini NF, Nortier JW, Punt CJ, Gelderblom H, Guchelaar HJ. Explorative study to identify novel candidate genes related to oxaliplatin efficacy and toxicity using a DNA repair array. *Br J Cancer* 2009; **101**: 357-362 [PMID: 19536092 DOI: 10.1038/sj.bjc.6605134]

487 **Ma H**, Xu L, Yuan J, Shao M, Hu Z, Wang F, Wang Y, Yuan W, Qian J, Wang Y, Xun P, Liu H, Chen W, Yang L, Jin G, Huo X, Chen F, Shugart YY, Jin L, Wei Q, Wu T, Shen H, Huang W, Lu D. Tagging single nucleotide polymorphisms in excision repair cross-complementing group 1 (ERCC1) and risk of primary lung cancer in a Chinese population. *Pharmacogenet Genomics* 2007; **17**: 417-423 [PMID: 17502833 DOI: 10.1097/01.fpc.0000239975.77088.17]

**P-Reviewers:** Fang BL, Lakatos PL, Nishida T **S-Editor:** Gou SX  **L-Editor: E-Editor:**

Figure 1 5-fluorouracil is converted to three major active metabolites. (1) fluorodeoxyuridine monophosphate (FdUMP); (2) fluorodeoxyuridine triphosphate (FdUTP); and (3) fluorouridine triphosphate (FUTP). The main mechanism of 5-fluorouracil (5-FU) activation is conversion to fluorouridine monophosphate (FUMP) either directly by orotate phosphoribosyl transferase (OPRT), or indirectly *via* fluorouridine (FUR) through the sequential action of uridine phosphorylase and uridine kinase. FUMP is then phosporylated to fluorouridine diphosphate (FUDP), which can be either further phosphorylated to the active metabolite fluorouridine triphosphate (FUTP), or converted to fluorodeoxyuridine diphosphate (FdUDP) by ribonucleotide reductase. In turn, FdUDP can either be phosphorylated or dephosphorylated to generate the active metabolites FdUTP and FdUMP respectively. An alternative activation pathway involves the thymidine phosphorylase catalyzed conversion of 5-FU to 5-fluoro-2’-deoxyuridine (5-FUDR), which is then phosphorylated by thymidine kinase to the thymidylate synthase inhibitor, FdUMP. Dihydropyrimidine dehydrogenase (DPD)-mediated conversion of 5-FU to dihydrofluorouracil (DHFU) is the rate-limiting step of 5-FU catabolism in normal and tumour cells[401].

Figure 2 Methylentetrahydrofolate reductase plays an important role in the action of 5-fluorouracil, an inhibitor of thymidylate synthase. Methylentetrahydrofolate reductase (MTHFR) catalyses a unidirectional reaction that lowers the levels of 5,10-methylenetetrahydrofolate (CH2THF) by rising levels of 5-methyltetrahydrofolate (CH3THF) which is used for biological methylation. Other factors, such as vitamin B12 and homocysteine, are involved in biological methylation processes. The addition of folinic acid (leucovorin) to 5-FU improves the response rates and survival of CRC patients. Thymidylate synthase (TS) catalyses the reductive methylation of deoxyuridine monophosphate (dUMP) to deoxythymidine monophosphate (dTMP) with the reduced folate CH2THF as the methyl donor. This reaction provides the sole *de novo* source of thymidylate, which is necessary for DNA replication and repair. TS contains a nucleotide-binding site and a binding site for CH2THF. The 5-FU metabolite FdUMP binds to the nucleotide-binding site of TS, forming a stable ternary complex with the enzyme and CH2THF which blocks binding of the normal substrate dUMP, thereby inhibiting dTMP synthesis. Inhibition of thymidylate synthesis causes disruption of nucleotide levels that results in DNA damage[402].

**Figure 3** **Some of the described polymorphisms affect inter-individual differences in patient sensitivity to 5-fluorouracil treatment.** Polymorphisms in the thymidylate synthase gene(*TYMS* gene), 5’ and 3’ untranslated regions (5’UTR and 3’UTR), exons (E1-E7), binding site for upstream stimulating factor (USF), variable number tandem repeats (VNTR), single nucleotide polymorphism (SNP), deletion/insertion polymorphism (Del/Ins), two-tandem repeats(*TSER\*2*), three-tandem repeats(*TSER\*3*), *TSER\*3* G>C (single nucleotide polymorphism of *TSER\*3*). Regulation of *TYMS* gene expression. TSER polymorphism (TS 2R/3R repeat) is a tandem repeat upstream of the *TYMS* translational start site containing either double (2R) or triple (3R) repeats of 28-bp sequences. These tandem repeats regulate transcription and translation of *TYMS*. Additional functional variants of the *TYMS* gene have been identified and TSER 2R/3R repeat is now studied together with a G to C SNP within the second repeat of the 3R allele. TSER 3RC/3RC genotype causes lower transcriptional activity of *TYMS*, comparable with the TS 2R/2R genotype. TS 1494del6bp is another functional variant of the *TYMS* gene and has been shown to decrease RNA stability and therefore influence TS mRNA and TS protein expression *in vitro*[52].

**Figure 4 A schematic map of the human *DPYD* gene is shown with the location of SNP *DPYD\*2A* (IVS14+1G>A); exon 14 is skipped as a result of the G>A translocation at intron 14.**

Figure 5 Irinotecan is metabolized to APC or NPC and potential other intermediate metabolites (M1, M2) *via* a cytochrome P450 mediated process. Neither 7-ethyl-10-[4-N-(5-aminopentanoic acid)-1-piperidino] carbonyloxycamptothecin (APC) nor 7-ethyl-10-(4-amino-1-piperidino) carbonyloxycamptothecin (NPC) contributes directly to irinotecan *in vivo* activity. NPC is further converted to SN-38 (7-ethyl-10-hydroxy-camptothecin) by carboxylesterase. All of irinotecan’s metabolites are pH sensitive and thus are at risk of transforming from inactive to active products, and vice versa. SN-38 is subsequently conjugated predominantly by the enzyme UDP-glucuronosyltransferase 1A1 (UGT1A1) to form a glucuronide metabolite (SN-38G)[403].

**Figure 6 Graphic representation of the human *UGT1A* gene locus encoding the UGT1A enzymes and the major *UGT1A1*, *1A7* and *1A9* polymorphisms that are responsible for glucuronidation of SN-38.** Individual first exons are positioned at the 5’ end of the chromosome and common exons 2–5 at the 3’ end. Individual exon 1 sequences are combined with exon 2–5 sequence, which is present in every UDP-glycosyltransferase 1A1 (*UGT1A1*) transcript, the intervening sequence of the primary transcript is eliminated by splicing[404]. The promoter variant, *UGT1A1\*28*, *\*36* and *\*37* which results from a TA insertion/deletion in the (TA)6TAA element of the *UGT1A1* promoter region. This alteration leads to decreased/increased gene expression[184].

**Figure 7 UDP-glycosyltransferase 1 family.**A: The active metabolite of irinotecan, SN-38 is a DNA topoisomerase I (TOP1) inhibitor which leads to cancer cell death. TOP1 is a nuclear enzyme required in replication, responsible for unwinding DNA and preventing lethal strand breaks. SN-38 is cytotoxic and destabilizes the TOP1-DNA covalent complex formed in colorectal cancerous cells. SN-38 causes irreversible double strand breaks which lead to S phase arrest followed by cell death. To do so, SN-38 attaches to the complexes and blocks future replication forks preventing repairs of double strand breaks[405]; B: Irinotecan uptake and transport into the liver is facilitated by: OATP1B1 (SLCO1B1), ABCB1, MRP1 (ABCC1), MRP2 (ABCC2), and MXR (ABCG2). Specifically, ABCB1 is present on the bile membrane and is responsible for the secretion of irinotecan and its metabolites into the liver[406]. Irinotecan is metabolized in the liver and converted to SN-38, the active metabolite and TOP1 inhibitor, by carboxylesterases (CE) mediated hydrolysis. SN-38 is then glucoronized to SN-38 glucoronic acid (SN-38G) and detoxified in the liver *via* conjugation by the UGT1A family, which releases SN-38G into the intestines for elimination[407]. Approximately 70% of SN-38 becomes SN-38G, which has 1/100 of the antitumour activity and is virtually inactive. In the intestinal lumen, bacterial β-glucoronidases can reverse the reaction and transform inactive SN-38G back into the active form SN-38. This is a factor contributing to varied toxicity, specifically dose limiting diarrhoea[198].

**Figure 8 Intracellular drug accumulation.** Free fraction of oxaliplatin is biotransformed non-enzymatically and subsequently forms complexes with chloride, glutathione (GSH), methionine (Met) and cysteine (Cys). Oxaliplatin undergoes non-enzymatic conversion in physiologic solutions to active derivatives *via* displacement of the labile oxalate ligand. Several transient reactive species are formed, including monoaquo DACH (1,2-diaminocyclohexane) platinum ([Pt(H2O)Cl(DACH)]+) and diaquo DACH platinum ([Pt(H2O)2(DACH)]2+), which covalently bind with macromolecules. There is no evidence of cytochrome P450-mediated metabolism *in vitro*. The major route of platinum elimination is renal excretion. The main mechanism of action is mediated through the formation of DNA adducts which is thought to be related to the anti-tumour effects of oxaliplatin. An important factor is the induction of apoptosis by the primary DNA-Pt lesions, which is possibly enhanced by a contribution of targets other than DNA. Several influx and efflux transporters like organic cation transporters (OCTs) 1, 2 and 3 (SLC22A1, SLC22A2 and SLC22A3), copper efflux transporters (CTRs), P-type ATPases, ATP7A and ATP7B have been identified, which may play an important role in determining tumour sensitivity and/or resistance to oxaliplatin[408].

Figure 9 Nucleotide excision repair pathway. (1) DNA damage formed by platinum agents leads to DNA double helix distortion. Several distinct complexes are involved in sequential steps than can be summarized as DNA damage recognition (XPCHR23B), damage demarcation, and verification (TFIIH), assembly of a preincision complex (RPA and XPA) and helix unwinding (XPB and XPD); (2) Endonuclease recruitment with dual incision of the damaged strand on the 5’ side (ERCC1-XPF heterodimers) and 3’ side (XPG) followed by the removal of the excised oligomer; (3) DNA repair synthesis to fill in the resulting gap; and (4) ligation. ERCC1: Excision repair cross-complementation group 1; Pol σ/ε - polymerase σ/ε; RFC: Replication factor C; TFIIH: Transcription factor II H; XP (A,B,C,D,F,G): Xeroderma pigmentosum complementation group (A,B,C,D,F,G)[340].

Table 1 Some common polymorphisms of genes *TYMS, MTHFR, DPYD* and *UMPS* and their potential impact on the functioning of proteins associated with the pharmacology of 5-fluorouracil

|  |  |  |  |
| --- | --- | --- | --- |
| **dbSNP rs cluster ID** | **Type of polymorphism** | **Function** | **Ref.** |
| Thymidylate synthase (*TYMS*) (OMIM # 188350) | | | |
| rs45445694 | VNTR |  | [43-51,68,409-413] |
| TSER\*2/ TSER\*3 | TSER polymorphism (TS 2R/3R repeat) is a tandem repeat upstream of the *TYMS* translational start site containing either double (2R) or triple (3R) repeats of 28-bp sequences |
| [http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 45445694](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=45445694) | | |
| rs34743033 | SNP |  | [44-46,49,50,414] |
| TSER\*3G>C | TSER\*2/\*3 repeat is studied together with a G to C SNP within the second repeat of the TSER\*3 allele |
| TSER\*3C allele = decrease transcriptional activity of *TYMS* |
| [http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 34743033](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=34743033) | | |
| rs151264360 | Del/Ins |  | [44,46,49,51,72,415] |
| TS 1494del6bp | -6-bp deletion, decreased stability of TS mRNA |
| +6-bp insertion, increased stability of TS mRNA |
| [http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 151264360](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=151264360) | | |
| Methylenetetrahydrofolate reductase (*MTHFR*) [OMIM # 607093] | | | |
| rs1801133 | SNP |  | [66-69,72,313,316,362] |
| 677C>T | At codon 222 in exon 4 (Ala → Val) |
| Reduces enzymatic activity and increased thermolability |
| [http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 1801133](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=1801133) | | |
| rs1801131 | SNP |  | [67-69,72,313,316] |
| 1298A>C | At codon 429 in exon 7 (Glu → Ala) |
| Reduces MTHFR activity |
| [http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 1801131](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=1801131) | | |
| rs4846051 a | SNPs |  | [71,416] |
| 1305T>C | At codon 435 (synonymous), effect unknown |
| rs201095365 b | 1798G>A | At codon 600 (Glu → Lys), effect unknown |
| [a http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 4846051](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=4846051) | | |
| [b http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 201095365](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=201095365) | | |
| Dihydropyrimidine dehydrogenase (*DPYD*) [OMIM # 612779] | | | |
| rs3918290 | SNP |  | [88,412,417,418] |
| IVS14+1G>A | Exon 14 is skipped as a result of the G → A translocation at intron 14, inactive enzyme is formed |
| [http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 3918290](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=3918290) | | |
| rs75017182 | SNP |  | [92,419] |
| c.1129– 5923C>G | Cryptic splice donor site leads to a 44 bp fragment of intron 10 insert in mrna, frameshift and premature stop codon in exon 11 |
| Associated with toxicity |
| [http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 75017182](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=75017182) | | |
|  | SNPs |  | [92,417] |
| ----- | IVS5+18G>A | G → A translocation at intron 5, effect unknown |
| ----- | IVS6+139G>A | G → A translocation at intron 6, effect unknown |
| ----- | IVS9–51T>G | T → G translocation at intron 9, effect unknown |
| rs1801265 | SNP |  | [85,420-424] |
| 85T>C | At codon 29 in exon 2 (Cys → Arg) |
| Decreased expression |
| [http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 1801265](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=1801265) | | |
| rs2297595 | SNP |  | [420,421,424-427] |
| 496A>G | At codon 166 in exon 6 (Met → Val) |
| Significantly conserved site close to the Fe-S motif, may disrupt electron transport |
| [http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 2297595](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=2297595) | | |
|  | SNP |  | [421,424,427-430] |
| rs1801159 | 1627A>G | At codon 543 in exon 13 (Ile → Val) |
| Decreased expression |
| [http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 1801159](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=1801159) | | |
| rs55886062 | SNP |  | [92,422,431-434] |
| 1679T>G | At codon 560 in exon 13 (Ile → Ser) |
| Might destabilize FMN (flavine mononucleotide) binding domain |
| [http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 55886062](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=55886062) | | |
| rs1801160 | SNP |  | [424,428] |
| 2194G>A | At codon 732 in exon 18 (Val → Ile) |
| Decreased expression |
| [http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 1801160](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=1801160) | | |
| rs67376798 | SNP |  | [92,412,417,422,425,426,432,435-437] |
| 2846A>T | At codon 949 in exon 22 (Asp → Val) |
| Significantly conserved site near the Fe-S motif, may disrupt cluster formation and electron transport and lead to lower DPD activity |
| [http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 67376798](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=67376798) | | |
| Uridine monophosphate synthetase (*UMPS*) [OMIM #613891] | | | |
| rs121917890 a | SNPs |  | [[122-126]](file:///C:\Users\user\Desktop\Revision\Tables.xlsx#RANGE!_ENREF_200) |
| 213A>G | At codon 96 (Arg → Gly), effect unknown |
| rs121917892 b | 326T>G | At codon 109 (Val → Gly), effect unknown |
| rs1801019 c | 638G>C | At codon 213 (Gly → Ala), increase activity |
| rs2291078 d | 1050T>A | At codon 350 (synonymous), effect unknown |
| rs121917891 e | 1285G>C | At codon 429 (Gly → Arg), effect unknown |
| rs3772809 f | 1336A>G | At codon 446 (Ile → Val), effect unknown |
| [a http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 121917890](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=121917890) | | |
| [b http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 121917892](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=121917892) | | |
| [c http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 1801019](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=1801019) | | |
| [d http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 2291078](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=2291078) | | |
| [e http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 121917891](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=121917891) | | |
| [f http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 3772809](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=3772809) | | |

SNP: Single nucleotide polymorphism.

**Table 2 Gene/protein expression or metabolic enzyme activity in colorectal cancer cells and correlation with outcome of patients receiving fluoropyrimidine-based chemotherapy**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Treatment setting** | **Method** | **Patients (*n* )** | | **Better response to chemotherapy** | **Form of the disease** | **References** |
|
| Thymidylate synthase (*TYMS*) [OMIM # 188350] | | | | | | |
| 5-FU | RT-PCR | | 29 | Low expression | mCRC | Iyevleva *et al*[24] |
| 5-FU | RT-PCR | | 39 | Low expression | CRC | Ishida *et al*[25] |
| 5-FU | IHC | | 57 | Low expression | mCRC | Hosokawa *et al*[26] |
| 5-FU | IHC | | 62 | Low expression | aCRC | Ciaparrone *et al*[27] |
| 5-FU | RT-PCR | | 92 | Low expression | CRC | Nakajima *et al*[28] |
| 5-FU | RT-PCR | | 309 | Low expression | CRC | Kornmann *et al*[29] |
| 5-FU | IHC | | 391 | Not significant | aCRC | Westra *et al*[438] |
| 5-FU | IHC | | 945 | Not significant | CRC | Soong *et al*[107] |
| FUdR | IHC | | 36 | Low expression | mCRC | Davies *et al*[31] |
| 5-FU/LV or 5-FU | RT-PCR | | 29 | Low expression | mCRC | Kornmann *et al*[32] |
| 5-FU/LV | RT-PCR | | 33 | Low expression | aCRC | Salonga *et al*[17] |
| 5-FU/LV | RT-PCR | | 36 | Low expression | mCRC | Lenz *et al*[7] |
| 5-FU/LV | RT-PCR | | 42 | Low expression | CRC | Leichman *et al*[19] |
| 5-FU/LV | RIA | | 102 | Low expression | mCRC | Etienne *et al*[33] |
| 5-FU/OX | RT-PCR | | 45 | Low expression | aCRC | Shirota *et al*[34] |
| 5-FU/MTX | IHC | | 108 | Low expression | aCRC | Paradiso *et al*[35] |
| 5-FU or 5-FU/MTX or 5-FU/LV | IHC | | 24 | Not significant | aCRC | Belvedere *et al*[439] |
| 5-FU or 5-FU/MTX or 5-FU/LV | IHC | | 27 | Not significant | mCRC | Aschele *et al*[23] |
| 5-FU or 5-FU/MTX or 5-FU/LV | IHC | | 48 | Low expression | mCRC | Aschele *et al*[36] |
| 5-FU/LV/CPT-11 | RT-PCR | | 13 | Low expression | aCRC | Yanagisaw *et al*[37] |
| 5-FU/LV/CPT-11 | IHC | | 54 | Low expression | aCRC | Bendardaf *et al*[38] |
| 5-FU/LV/CPT-11 | IHC | | 57 | Not significant | aCRC | Paradiso *et al*[440] |
| UFT/LV | RT-PCR | | 37 | Low expression | mCRC | Ichikawa *et al*[39] |
| Capecitabine | RT-PCR | | 37 | Not significant | aCRC | Vallbohmer *et al*[97] |
| Capecitabine | IHC | | 39 | Not significant | CRC | Lindebjerg *et al*[441] |
| Capecitabine/CPT-11 | IHC | | 556 | Not significant | aCRC | Koopman *et al*[110] |
| 5-FU-based therapy | IHC | | 681 | Not significant | CRC | Karlberg *et al*[442] |
| Dihydropyrimidine dehydrogenase (*DPYD*) [OMIM # 612779] | | | | | | |
| 5-FU | RT-PCR | | 29 | Not significant | mCRC | Iyevleva *et al*[24] |
| 5-FU | RT-PCR | | 39 | Not significant | CRC | Ishida *et al*[25] |
| 5-FU | IHC | | 62 | Low expression | aCRC | Ciaparrone *et al*[27] |
| 5-FU | IHC | | 303 | Low expression | CRC | Jensen *et al*[443] |
| 5-FU | RT-PCR | | 309 | Low expression | CRC | Kornmann *et al*[29] |
| 5-FU | IHC | | 391 | Not significant | aCRC | Westra *et al*[438] |
| 5-FU | IHC | | 945 | Not significant | CRC | Soong *et al*[107] |
| 5-FU/LV | RT-PCR | | 33 | Low expression | aCRC | Salonga *et al*[17] |
| UFT/LV | RT-PCR | | 37 | Low expression | mCRC | Ichikawa *et al*[39] |
| 5-FU/LV/CPT-11 | RT-PCR | | 13 | Not significant | aCRC | Yanagisawa *et al*[37] |
| Capecitabine | RT-PCR | | 37 | Low expression | aCRC | Vallbohmer *et al*[97] |
| Capecitabine/CPT-11 | RT-PCR | | 67 | Not significant | aCRC | Meropol *et al*[98] |
| Capecitabine/CPT-11 | IHC | | 556 | Low expression | aCRC | Koopman *et al*[110] |
| 5-FU-based therapy | ELISA | | 64 | Low expression | aCRC | Oi *et al*[444] |
| 5-FU-based therapy | RT-PCR | | 102 | Low expression | CRC | Lassman *et al*[445] |
| 5-FU-based therapy | RT-PCR | | 144 | Low expression | aCRC | Gustavsson *et al*[446] |
| 5-FU-based therapy | IHC | | 150 | Low expression | aCRC | Tokunaga *et al*[447] |
| Thymidine phosphorylase(*TYMP*) [OMIM # 131222] | | | | | | |
| 5-FU | IHC | | 62 | Not significant | aCRC | Ciaparrone *et al*[27] |
| 5-FU | IHC | | 945 | Not significant | CRC | Soong *et al*[107] |
| 5-FU/LV | RT-PCR | | 33 | Low expression | aCRC | Salonga *et al*[17] |
| 5-FU/LV/CPT-11 | RT-PCR | | 13 | Not significant | aCRC | Yanagisawa *et al*[37] |
| Capecitabine | RT-PCR | | 37 | Not significant | aCRC | Vallbohmer *et al*[97] |
| Capecitabine/OX | IHC | | 41 | High expression | mCRC | Petrioli *et al*[448] |
| Capecitabine/CPT-11 | RT-PCR | | 67 | High expression | aCRC | Meropol *et al*[98] |
| Capecitabine/CPT-11 | IHC | | 556 | Not significant | aCRC | Koopman *et al*[110] |
| 5-FU-based therapy | RT-PCR | | 144 | Low expression | aCRC | Gustavsson *et al*[446] |
| 5-FU-based therapy | IHC | | 150 | Low expression | aCRC | Tokunaga *et al*[447] |
| Uridine monophosphate synthetase (*UMPS*) [OMIM #613891] | | | | | | |
| 5-FU | RT-PCR | | 38 | Not significant | mCRC | Sameshima *et al*[449] |
| 5-FU | RT-PCR | | 39 | Not significant | CRC | Ishida *et al*[25] |
| 5-FU/LV/OX | RT-PCR | | 58 | Not significant | CRC | Dong *et al*[450] |
| 5-FU/LV/cis-platin | RT-PCR | | 22 | High expression | mCRC | Matsuyama *et al*[113] |
| UFT | RIA | | 40 | High expression | CRC | Ichikawa *et al*[114] |
| UFT | RIA | | 124 | High expression | CRC | Ochiai *et al*[115] |
| UFT | IHC | | 150 | High expression | CRC | Tokunaga *et al*[116] |
| UFT | IHC | | 160 | High expression | CRC | Tokunaga *et al*[117] |
| UFT/LV | RT-PCR | | 37 | High expression | mCRC | Ichikawa *et al*[118] |
| UFT/LV | RT-PCR | | 103 | High expression | CRC | Yamada *et al*[119] |
| 5-FU-based therapy | RT-PCR | | 10 | Not significant | CRC | Ishibashi *et al*[451] |
| 5-FU-based therapy | RIA | | 11 | Not significant | CRC | Yamada *et al*[452] |
| 5-FU-based therapy | RT-PCR | | 52 | Not significant | CRC | Kinoshita *et al*[453] |
| 5-FU-based therapy | RIA | | 54 | High expression | CRC | Fujii *et al*[120] |
| 5-FU-based therapy | RIA | | 90 | High expression | CRC | Ochiai *et al*[121] |

5-FU: 5-fluorouracil; LV: Leucovorin; FUdR: 5-fluorodeoxyuridine; MTX: Methotrexate; OX: Oxaliplatin; UFT: Compound tegafur tablets; CPT-11: Irinotecan; CTX: Cetuximab; RT-PCR: Reverse trascriptase polimerase chain reaction; IHC: Immunohistochemistry; ELISA: Enzyme-linked immunosorbent ssay; RIA: Radioimmunoassay; CRC: Colorectal cancer; aCRC: Advanced colorectal cancer; mCRC: Metastatic colorectal cancer

Table 3 Selected common polymorphisms of *UGT1A1, UGT1A7, UGT1A9, CES2, CYP3A4, CYP3A5, MDR1, MRP1, MRP2, BCRP, OATP1B1* genes and their potential impact on functioning of proteins related to CPT-11 pharmacology

|  |  |  |  |
| --- | --- | --- | --- |
| **dbSNP rs cluster ID** | **Type of polymorphism** | **Function** | **Ref.** |
| UDP-glycosyltransferase 1A1 (*UGT1A1*) [OMIM # 191740] | | | |
| rs8175347 | VNTR |  | [177,178,180,182,191,192,197,219,317,356,454-460] |
| -53(TA)6>7 | *UGT1A1\*28,* reduced activity |
| -53(TA)6>5 | *UGT1A1\*36,* increased activity |
| -53(TA)6>8 | *UGT1A1\*37,* reduced activity |
| [http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 8175347](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=8175347) | | |
| rs3755319 | SNP |  | [[187]](file:///C:\Users\user\Desktop\Revision\Tables.xlsx#RANGE!_ENREF_263) |
| -3279T>G | *UGT1A1\*60,* reduced activity |
| [http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 3755319](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=3755319) | | |
| rs10929302 a | SNP |  | [192,404] |
| -3156G>A | *UGT1A1\*93,* reduced activity |
| rs887829 b | -3140G>A | effect unknown |
| [a http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 10929302](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=10929302) | | |
| [b http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 887829](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=887829) | | |
| rs4148323 | SNP |  | [186,191,461] |
| 211G>A | Gly71Arg, *UGT1A1\*6*, reduced activity |
| [http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 4148323](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=4148323) | | |
| rs35350960 | SNP |  | [172,174,189] |
| 686C>A | Pro229Gln, *UGT1A1\*27,* reduced activity |
| [http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 35350960](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=35350960) | | |
| rs34993780 | SNP |  | [170,174,189] |
| 1456T>G | Tyr486Asp, *UGT1A1\*7,* reduced activity |
| [http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 34993780](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=34993780) | | |
| UDP-glycosyltransferase 1A7 (*UGT1A7*) [OMIM #606432] | | | |
| rs17868323 a | SNP |  | [188,189,197,237] |
| 387T>G | Asn129Lys, *UGT1A7\*2* and *\*3*, increased activity |
| rs17863778 b | 391C>A | Arg131Lys, *UGT1A7\*2* and *\*3*, increased activity |
| rs11692021 c | 622C>T | Trp208Arg, *UGT1A7\*3* and *\*4,* reduced activity |
| [a http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 17868323](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=17868323) | | |
| [b http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 17863778](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=17863778) | | |
| [c http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 11692021](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=11692021) | | |
| UDP-glycosyltransferase 1A9 (*UGT1A9*) [OMIM #606434] | | | |
| rs45625337 | VNTR |  | [190,197,462] |
| –118(T)9>10 | *UGT1A9\*22,* increased activity |
| [http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 45625337](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=45625337) | | |
| rs2741049 | SNP |  | [197,463] |
| IVS1+399C>T | effect unknown |
| [http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 2741049](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=2741049) | | |
| Carboxylesterase 2 *(CES2)* [OMIM #605278] | | | |
| ----- | SNP |  | [159,161,166] |
| 1A>T | Met1Leu*, CES\*5* |
| rs72547531 a | 100C>T | Arg98Trp, *CES\*2* |
| rs72547532 b | 424G>A | Val206Met, *CES\*3* |
| rs8192924 c | 617G>A | Arg270His, *CES\*6* |
| rs11075646 d | 830C>G | synonymous |
| rs72547533 e | IVS8-2A>G | splicing defect, *CES\*4* |
| [a http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 72547531](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=72547531) | | |
| [b http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 72547532](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=72547532) | | |
| [c http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 8192924](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=8192924) | | |
| [d http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 11075646](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=11075646) | | |
| [e http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 72547533](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=72547533) | | |
| Cytochrome P450, subfamily IIIA, polypeptide 4 (*CYP3A4*) [OMIM #124010] | | | |
| rs2740574 a | SNP |  | [211,464,465] |
| -392A>G | *CYP3A4\*1b*, altered pharmacokinetics and toxicity |
| rs4986907 b | 485G>A | *CYP3A4\*15*, Arg162Gln |
| rs4986908 c | 520G>C | *CYP3A4\*10*, Asp174His |
| rs12721627 d | 554C>G | *CYP3A4\*16*, Thr185Ser |
| rs4987161 e | 566T>C | *CYP3A4\*17*, Phe189Ser, altered pharmacokinetics |
| rs55785340 f | 664T>C | *CYP3A4\*2*, Ser222Pro, altered pharmacokinetics and toxicity |
| rs28371759 g | 878T>C | *CYP3A4\*18*, Leu293Pro, altered pharmacokinetics and toxicity |
| [a http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 2740574](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=2740574) | | |
| [b http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 4986907](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=4986907) | | |
| [c http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 4986908](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=4986908) | | |
| [d http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 12721627](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=12721627) | | |
| [e http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 4987161](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=4987161) | | |
| [f http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 55785340](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=55785340) | | |
| [g http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 28371759](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=28371759) | | |
| rs4986910 | SNP |  | [210,465] |
| 1334T>C | *CYP3A4\*3*, Met444Thr |
| [http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 4986910](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=4986910) | | |
| Cytochrome P450, subfamily IIIA, polypeptide 5 (*CYP3A5*) [OMIM #605325] | | | |
| rs776746 | SNP |  | [179,464-467] |
| 6986A>G | synonymous |
| [http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 776746](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=776746) | | |
| Multidrug resistance 1 (*MDR1*, *ABCB1*) [OMIM #171050] | | | |
| rs1128503 | SNP |  | [210,211,217,460,467-469] |
| 1236C>T | synonymous, CTP-11 or SN-38 AUC ↑ |
| [http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 1128503](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=1128503) | | |
| rs2032582 | SNP |  | [217,468-470] |
| 2677G>T/A | Ser893Ala or Ser893Thr |
| [http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 2032582](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=2032582) | | |
| rs1045642 | SNP |  | [179,217,468-475] |
| 3435C>T | synonymous, CTP-11 AUC ↑ |
| [http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 1045642](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=1045642) | | |
| rs10276036 | SNP |  | [[207]](file:///C:\Users\user\Desktop\Revision\Tables.xlsx#RANGE!_ENREF_282) |
| IVS9-44A>G | effect unknown |
| [http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 10276036](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=10276036) | | |
| Multidrug resistance-associated protein 1 (*MRP1, ABCC1*) [OMIM #158343] | | | |
| rs35605 | SNP |  | [210,476] |
| 1684T>C | synonymous |
| [http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 35605](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=35605) | | |
| rs17287570 | SNP |  | [[237]](file:///C:\Users\user\Desktop\Revision\Tables.xlsx#RANGE!_ENREF_308) |
| c.1677+4951A>C | effect unknown |
| rs3765129 | SNP |  | [207,210,476] |
| IVS11-48C>T | effect unknown |
| [http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 3765129](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=3765129) | | |
| rs2074087 | SNP |  | [476,477] |
| IVC18-30C>G | effect unknown |
| [http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 2074087](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=2074087) | | |
| Multidrug resistance-associated protein 2 (*MRP2, ABCC2*) [OMIM #601107] | | | |
| rs1885301 | SNP |  | [[477]](file:///C:\Users\user\Desktop\Revision\Tables.xlsx#RANGE!_ENREF_549) |
| -1549A>G | effect unknown |
| [http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 1885301](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=1885301) | | |
| rs2804402 | SNP |  | [[207]](file:///C:\Users\user\Desktop\Revision\Tables.xlsx#RANGE!_ENREF_282) |
| -1019A>G | effect unknown |
| [http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 2804402](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=2804402) | | |
| rs717620 | SNP |  | [[477-479]](file:///C:\Users\user\Desktop\Revision\Tables.xlsx#RANGE!_ENREF_549) |
| -24C>T | effect unknown |
| [http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 717620](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=717620) | | |
| rs2273697 | SNP |  | [467,479,480] |
| 1249G>A | Val417Ile, effect unknown |
| [http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 2273697](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=2273697) | | |
| rs3740066 | SNP |  | [477,479,481] |
| 3972C>T | synonymous, CTP-11 or APC or SN-38G AUC ↑ |
| [http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 3740066](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=3740066) | | |
| Breast cancer resistance protein (*BCRP, ABCG2*) [OMIM #603756] | | | |
| rs2622604 a | SNP |  | [[237]](file:///C:\Users\user\Desktop\Revision\Tables.xlsx#RANGE!_ENREF_308) |
| c.-19-17758A>G | synonymous |
| rs3109823 b | c.-19-3436G>A | synonymous |
| [a http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 2622604](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=2622604) | | |
| [b http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 3109823](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=3109823) | | |
| rs2231142 | SNP |  | [239-244,482] |
| 421C>A | Gln141Lys, no significant changes in CPT-11 pharmacokinetics |
| [http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 2231142](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=2231142) | | |
| rs2231137 | SNP |  | [242,467,482] |
| 34G>A | Val12Met, higher drug resistance *in vitro* (SN-38) |
| [http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 2231137](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=2231137) | | |
| rs1481012 | SNP |  | [[483]](file:///C:\Users\user\Desktop\Revision\Tables.xlsx#RANGE!_ENREF_555) |
| c.841+179T>C | synonymous |
| [http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 1481012](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=1481012) | | |
| Organic anion-transporting polypeptide 1B1 (*OATP1B1, SLCO1B1*) [OMIM #604843] | | | |
| rs2306283 | SNP |  | [247-249,460,467,484] |
| 388A>G | Asn130Asp, effect unknown |
| [http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 2306283](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=2306283) | | |
| rs4149056 | SNP |  | [247-249,460] |
| 521T>C | Val174Ala, effect unknown |
| [http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 4149056](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=4149056) | | |

SNP: Single nucleotide polymorphism.

Table 4 Selected common polymorphisms of *MDR1*, *GSTP1*, *ERCC1*, *ERCC2*, *XRCC1* gene and their potential impact on functioning of proteins related to OX pharmacology

|  |  |  |  |
| --- | --- | --- | --- |
| **dbSNP rs cluster ID** | **Type of polymorphism** | **Function** | **Ref.** |
| Multidrug resistance 1 (*MDR1*, *ABCB1*) [OMIM #171050] | | | |
| rs1128503 | SNP |  | [152,296,318,485] |
| 1236C>T | synonymous, effect unknown |
| [http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 1128503](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=1128503) | | |
| rs2032582 | SNP |  | [152,296] |
| 2677G>T/A | Ser893Ala or Ser893Thr, the GG genotype carriers have the highest while the AT genotype carriers have the lowest levels of ABCB1 expression |
| [http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 2032582](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=2032582) | | |
| rs1045642 | SNP |  | [152,296,350,485] |
| 3435C>T | synonymous, TT genotype carriers have lower intestinal ABCB1 expression |
| [http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 1045642](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=1045642) | | |
| Glutathione S-transferase π (*GSTP1*) [OMIM #134660] | | | |
| rs1138272 | SNP |  | [311,477] |
| 341C>T | Ala114Val, altered enzyme kinetics, altered toxicity |
| [http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 1138272](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=1138272) | | |
| rs1695 | SNP |  | [51,180,311-329,467,477] |
| 313A>G | Ile105Val, decreased enzymatic activity, altered toxicity |
| [http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 1695](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=1695) | | |
| Excision repair cross-complementation group 1 (*ERCC1*) [OMIM #126380] | | | |
| rs11615 | SNP |  | [51,313,344,345,357,486] |
| 354T>C | synonymous, decrease transcriptional activity of *ERCC1* |
| [http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 11615](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=11615) | | |
| rs3212948 | SNP |  | [[487]](file:///C:\Users\user\Desktop\Revision\Tables.xlsx#RANGE!_ENREF_559) |
| 321+74C>G | intronic SNP (intron 2), protective effect of the C allele to cancer risk |
| [http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 3212948](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=3212948) | | |
| Excision repair cross-complementation group 2 (*ERCC2, XPD*) [OMIM #126340] | | | |
| rs13181 | SNP |  | [51,313,336,337,350,351,353,356,357,486] |
| 2251A>C | Lys751Gln, the Gln allele is associated with a higher DNA adduct level or lower DNA repair capacity |
| [http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 13181](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=13181) | | |
| rs1799793 | SNP |  | [313,336,337,353] |
| 862G>A | Asp312Asn, lower DNA repair capacity for the Asn allele than the Asp allele |
| [http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 1799793](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=1799793) | | |
| X-ray cross complementation factor (*XRCC1*) [OMIM #194360] | | | |
| rs25487 | SNP |  | [51,313,349,350,361-364,486] |
| Arg399Gln, reduced base excision repair function for Gln allele than the Arg allele |
| 1196A>G |
| [http://www.ncbi.nlm.nih.gov/SNP/snp\_ref.cgi?rs = 25487](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=25487) | | |

SNP: Single nucleotide polymorphism.