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

Panczyk M. Chemoresistance in colorectal cancer

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**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.

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**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.

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**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.

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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%3A%5CUsers%5Cuser%5CDesktop%5CRevision%5CTables.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%3A%5CUsers%5Cuser%5CDesktop%5CRevision%5CTables.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%3A%5CUsers%5Cuser%5CDesktop%5CRevision%5CTables.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%3A%5CUsers%5Cuser%5CDesktop%5CRevision%5CTables.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%3A%5CUsers%5Cuser%5CDesktop%5CRevision%5CTables.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%3A%5CUsers%5Cuser%5CDesktop%5CRevision%5CTables.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%3A%5CUsers%5Cuser%5CDesktop%5CRevision%5CTables.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%3A%5CUsers%5Cuser%5CDesktop%5CRevision%5CTables.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%3A%5CUsers%5Cuser%5CDesktop%5CRevision%5CTables.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%3A%5CUsers%5Cuser%5CDesktop%5CRevision%5CTables.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.