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The primary aim of *World Journal of Clinical Cases* (WJCC, *World J Clin Cases*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

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Genetic mutations associated with sensitivity to neoadjuvant chemotherapy in metastatic colon cancer: A case report and review of literature

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Abstract

BACKGROUND

Colorectal liver metastases (CLM) occur in 15%-30% of patients with colorectal cancer (CRC). Advancements in next generation sequencing (NGS) can provide more precise prognoses for cancer patients and help guide clinical treatment. However, the genetic variants that predict high sensitivity to neoadjuvant chemotherapy remain unclear, especially in patients with CLM. The aim of this study was to identify the relevant genetic variants in a single CLM patient and to summarize the current evidence on mutations and single nucleotide polymorphisms (SNPs) that objectively predict sensitivity to neoadjuvant chemotherapy.

CASE SUMMARY

A 76-year-old male patient, who was diagnosed as stage IV colon cancer with liver metastases, was found to have *APC/TP53/KRAS* mutations. He showed a good therapeutic response to 12 courses of oxaliplatin regimens combined with Bevacizumab. Genetic analysis of the patient identified 5 genes with 7 detected SNPs that may be related to a better response to chemotherapy drugs. In addition, a critical literature review was performed based on a standardized appraisal form after selecting the articles. Ultimately, 21 eligible studies were appraised to assess the association between gene mutations and good prognosis. Mutations in *KRAS*, *TP53*, *SMAD4*, and *APC* were identified as being associated with a poor response to chemotherapy drugs, whereas mutations of *CREBBP* and *POLD1* were associated with longer overall survival.

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CONCLUSION

NGS can identify precise predictors of response to neoadjuvant chemotherapy, leading to improved outcomes for CRC patients.

Key Words: Colorectal liver metastases; Next generation sequencing; Neoadjuvant chemotherapy; Genetic variants; Case report

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Core Tip: Colorectal cancer has high incidence and mortality rates, with liver metastases as the main cause of death. Although chemotherapy is an effective treatment, some patients with specific gene mutations are not sensitive to chemotherapy. With advancements in next generation sequencing, we detected multiple somatic mutations in one patient with colorectal cancer who was sensitive to chemotherapy. Based on the genetic mutation of this patient, we conducted a literature review, which identified *KRAS*, *TP53*, *SMAD4*, and *APC* as being associated with a poor response to chemotherapy, whereas mutations of *CREBBP* and *POLD1* were associated with longer overall survival.

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INTRODUCTION

Colorectal cancer (CRC) has the second highest incidence rate and the third highest mortality rate globally of all forms of malignant tumor[1]. In CLM patients, colorectal liver metastases (CLM) are the main cause of death. CLM occurs in approximately 15%-30% of patients with CRC[2]. Liver resection has been proven to be an effective treatment for CLM, and it has a survival benefit over chemotherapy alone in terms of the 5-year overall survival (OS) rate (approximately 50%)[3,4].

Currently, European Society for Medical Oncology[5] and National Comprehensive Cancer Network[6] guidelines clearly state that the multiple disciplinary team (MDT) model should be adopted in the diagnosis and treatment of CLM. Notably, the Chinese Society of Clinical Oncology guidelines (version 2019)[7] recommend "some high-level medical units should try their best to treat CRC patients under the management of MDT, especially metastatic colorectal cancer (metastatic colorectal cancer, mCRC)". Subsequently, according to clinical tolerance to intensive treatments, CLM patients are divided into two categories based upon their general physical condition. For patients in poor health, the recommendations are low toxicity chemotherapy or the best supportive treatment, with re-assessment if necessary to improve quality of life and prolong survival as much as possible. For patients in good health who can tolerate intense treatment, the recommendation is to develop an active comprehensive treatment plan, or different treatment goals and individualized treatments, in order to minimize tumor size or maintain as much residual liver volume as safely possible[7].

Many studies have shown that chemotherapy combined with targeted therapies can significantly increase the response rate to treatment and improve survival time[8,9]. Heinemann *et al*[8] concluded that both FOLFIRI plus cetuximab and FOLFIRI plus bevacizumab patient groups did not differ significantly in the proportion of patients who achieved an objective response, even though FOLFIRI plus cetuximab is the preferred first-line regimen for patients with *KRAS* exon 2 wild-type metastatic colorectal cancer. However, for patients with a *RAS* gene family (*KRAS*, *NRAS*, and *HRAS*) mutation metastatic colorectal cancer, a lack of response to anti-EGFR therapy has been reported[10-12], and Bevacizumab is used as an alternative targeted therapy. Subsequently, the association between mutations in *RAS* and *BRAF* and a worse prognosis after CLM resection was also confirmed[13].



With advancements in next generation sequencing (NGS), it is now possible to detect multiple somatic mutations in clinical practice[13]. Such information can help achieve a better understanding of the effectiveness of and sensitivity to chemotherapy in cancer patients and even the emergence of drug resistance at the molecular level. The present article reviews the possible association of somatic gene mutations with the effectiveness and sensitivity of a chemotherapy regimen [oxaliplatin (XELOX) combined with Bevacizumab] through a case study of a patient with *APC/TP53/KRAS* mutations and microsatellite stable (MSS) status who was diagnosed with metastatic colorectal cancer (liver and lung). This patient showed a better objective response after 12 cycles of this chemotherapy regimen. The aim of this study is to identify possible predictors for the effectiveness of and sensitivity to this chemotherapy regimen through a panel of multi-gene testing [an 825-gene panel for solid tumors and 45 single nucleotide polymorphisms (SNPs) related to chemotherapy]. We then summarize the current best evidence of genes related to CLM through a systematic review of the literature to guide future research on predictors of the effectiveness of and sensitivity to XELOX and Bevacizumab treatment and to facilitate better clinical decision-making. This work was carried out according to the Cooperative for American Relief Everywhere (CARE) criteria[14], which is proven to improve the quality of reporting [15,16].

CASE PRESENTATION

Chief complaints

In January 2019, a 76-year-old male patient presented with the chief complaint of slight changes in bowel habits without any pain or other discomfort for 1 mo. He was admitted and treated at the Department of Gastroenterological Surgery, Peking University People's Hospital, Beijing, China.

History of present illness

There were no obvious symptoms of pain and discomfort.

History of past illness

The patient's medical history included liver cysts and gallstones for more than 20 years without specific treatment. He also had a history of hypertension for 3 years and took medication regularly. He denied a history of diabetes or other comorbidities.

Personal and family history

Parents are deceased, but his siblings are alive. He denied having any family history of genetic disease.

Physical examination

Physical examination found no obvious abnormalities.

Laboratory examinations

The tumor markers were reexamined in our hospital, and the carcinoma embryonic antigen was found to be elevated (388.1 ng/mL), while the remaining tumor markers were not abnormal.

Imaging examinations

Based on chest and abdominal computed tomography (CT) and magnetic resonance imaging (MRI), he was diagnosed with descending colon cancer with multiple metastases located in the lung and liver.

Detecting gene mutations

After discussion among the MDT, an endo-biopsy was determined to be necessary to confirm malignancy before neoadjuvant chemotherapy (Figure 1). The team also decided to determine the patient's microsatellite instable status, genetic mutations and SNPs, and tumor mutation burden (TMB) in the primary tumor tissue to guide selection of the best chemotherapeutic agent.

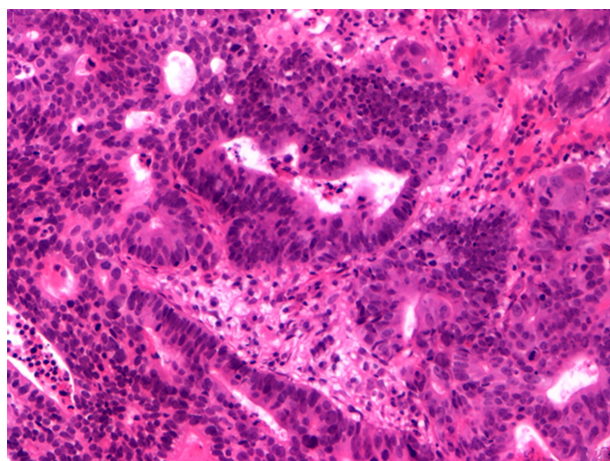


Figure 1 Result of tissue biopsy (× 200, hematoxylin-eosin staining).

FINAL DIAGNOSIS

Colorectal cancer with liver metastasis.

TREATMENT

The patient was ultimately identified as having an *APC/TP53/KRAS* mutation, MSS status, and TMB with 4.27/Mb. The XELOX regimen (XELOX 150 mg iv dl q3w, Capecitabine 1500 mg bid po d2-d15 q3w) combined with Bevacizumab (300 mg iv dl q3w) was selected for chemotherapy. After three courses of systemic combination chemotherapy, chest and abdominal CT and MRI revealed a good therapeutic response. The above-mentioned chemotherapy regimen was continued for 9 more courses (12 courses in total). The patient continued to respond well to the chemotherapy regimen (Figure 2).

OUTCOME AND FOLLOW-UP

Despite his complete response to chemotherapy, the patient ultimately passed away due to intestinal obstruction and serious cachexia on June 15, 2020, having declined to continue the chemotherapy regimen during the coronavirus disease 2019 pandemic.

DISCUSSION

Clinical questions

In light of the outcomes for this patient, we ask the following questions: (1) What is the association between these specific somatic mutations and prognosis? (2) What SNP(s) can predict treatment response to the XELOX regimen combined with Bevacizumab in patients with multiple metastases of colorectal cancer?

Literature review

Search strategy: A systematic review of the literature was conducted using the PubMed, EMBASE, and Cochrane databases through 8 September 2020. The search for specific somatic mutations was conducted using the following keywords and algorithm: “(colorectal or rectal or colon or colonic) and (liver or hepatic) and (metastasis or metastases) and (gene or mutation or *KRAS* or *TP53* or *APC* or *IKZF1* or *POLD1* or *PRKCB* or *SMAD4* or *CREBBP*).”

Literature screening and evaluation: For somatic gene mutations and their functions, we included studies that focused on the association between a specific gene mutation and overall survival (OS) or recurrence-free survival (RFS) in resectable and unresectable patients with CLM, no matter whether chemotherapy was clearly



Figure 2 Response after the 12-cycle chemotherapy regimen. A: Image on January 11, 2019 (before treatment); B: Image on April 13, 2019 (after the third treatment); C: Image on September 15, 2019 (after the sixth treatment); and D: Image on January 10, 2020 (after the twelfth treatment). Note: The spleen enlarged significantly with treatment (B and C).

described. Better OS and RFS were defined as the effectiveness of chemotherapy in this study. We included systematic reviews, meta-analyses, and cohort studies. We excluded studies that included the above-mentioned mutations but failed to report OS as a measure of prognosis, or studies in which patients received another form of intervention. Of the included studies, due to the lack of direct evidence of “genetic mutations of sensitivity to platinum-based neoadjuvant chemotherapy”, we regarded a genetic mutation of sensitivity to neoadjuvant chemotherapy to be when a published record showed a good prognosis regardless of whether the patient received adjuvant chemotherapy.

For SNPs predicting treatment response to XELOX regimens combined with Bevacizumab, the PharmGKB database (<http://www.pharmgkb.org>) was used to reference SNPs and chemotherapeutic drugs. This database focuses on genetic pharmacology and genomic pharmacology. Genetic evidence is graded using the following criteria: Level IA: Recognized by Guidelines from the Clinical Pharmacogenetics Implementation Consortium or the Genetic Pharmacology, or recognized by the International Genetic Pharmacology Research Network or other major health systems; Level IB: The relevance to drugs is supported by multiple studies that found consistent results with statistically significant differences; Level IIA: The relevance to drugs is supported by multiple studies, and the gene is known as an important drug metabolism gene with a clear function; Level IIB: The relevance to drugs is supported by multiple studies, but some studies have a small sample size or found no statistically significant differences; and Level III: The relevance to drugs is supported by a single study, but a consensus has not yet been reached.

Critical appraisal

Based on the criteria, 21 studies were identified. We appraised these 21 eligible studies using the critical appraisal questions developed by the Centre of Evidence-Based Medicine, University of Oxford.

Table 1 Summary of evidence for main gene mutations

Genes mutation	Ref.	Total No. of patients	Frequency		Prognosis	
			<i>n</i>	%	OS	RFS
KRAS ¹	Nash <i>et al</i> [19], 2010	188	51	27	Worse	
	Teng <i>et al</i> [24], 2012	292	111	38	None	
	Karagkounis <i>et al</i> [20], 2013	202	58	29	Worse	Worse
	Lin <i>et al</i> [21], 2014	154	43	28	None	
	Margonis <i>et al</i> [22], 2016	512	190	37		None
	Wang <i>et al</i> [23], 2017	300	110	37	Worse	
TP53	Tullo <i>et al</i> [25], 1999	40	19	48		Worse
	Yang <i>et al</i> [27], 2001	39	16	41	Better	Better
	Saw <i>et al</i> [26], 2002	60	35	58	None	
	De Jong <i>et al</i> [30], 2005	44	16	36	None	None
	Mollevi <i>et al</i> [28], 2007	91	46	51	Worse	
	Pilat <i>et al</i> [29], 2015	76	42	55	Worse	
	Løes <i>et al</i> [33], 2016	164	99	60	None	None
	Frankel <i>et al</i> [31], 2017	165	95	58	None	
	Chun <i>et al</i> [32], 2019	401	263	66	None	
	Mizuno <i>et al</i> [35], 2018	278	37	13	Worse	
SMAD4	Kawaguchi <i>et al</i> [36], 2019	507	56	11	Worse	Worse
APC ²	Yamashita <i>et al</i> [34], 2020	396	45	11	Worse	Worse

¹More than 150.²Represent APC and PIK3CA mutation. OS: Overall survival; RFS: Recurrence-free survival.

Somatic gene mutations

According to the literature review, *KRAS*, *TP53*, and *SMAD4* mutations may be harmful to prognosis, with pooled mutation rates of [33% (29%, 37%), *n* = 1648], [54% (48%, 60%), *n* = 1080], and [12% (10%, 14%), *n* = 785], respectively (Figure 3 and Table 1). The frequency of *APC* mutation was 11% (45/396), and it showed a negative association with better prognosis. For the other mutations, there is a lack of cohort studies focused on gene mutations and prognosis in CLM patients. Table 2 shows the current evidence of *CREBBP*, *IKZF1*, *POLD1*, and *PRKCB* mutations and gene functions. *CREBBP* and *POLD1* mutations may be related to longer OS and RFS.

Chemotherapy-related SNPs

Regarding chemotherapy-related SNPs, 5 genes with 7 detected loci were identified as potentially being related to better response to chemotherapy drugs according to the PharmGKB database; however, the grade of this evidence is relatively low (Table 3).

Advancements in NGS have enabled more precise prognosis of patients with CLM and have expanded the information available in clinical practice. It is reported that 10% of patients with CLM have mutations in *TP53*, *APC*, *RAS*, *PIK3CA*, or *SMAD4*. Notably, *TP53*, *RAS*, and *SMAD4* are associated with worse survival in patients undergoing CLM resection[17,18].

In this study, we reported a stage IV colon cancer patient with *APC/TP53/KRAS* mutations who showed a good therapeutic response after 12 courses of XELOX regimen combined with Bevacizumab. Genetic testing identified 8 relevant genes in this patient (Tables 1 and 2). In this case report, we detected 5 genes with 7 SNPs that might result in a better response to chemotherapy drugs (Table 3). However, the genetic mutations and SNPs which could be used to predict high sensitivity to neoadjuvant chemotherapy in patients with metastatic colorectal cancer remain unclear.

Table 2 Summary of evidence for other gene mutations

Genes mutation	Ref.	Summary	Conclusion
<i>CREBBP</i>	Lin <i>et al</i> [37], 2020	TMB-high (> 11 mutations/Mb), male, mutation of <i>RNF43</i> , <i>CREBBP</i> , <i>NOTCH3</i> , <i>PTCH1</i> , <i>CIC</i> , <i>DNMT1</i> and <i>SPEN</i> were all related to longer OS	<i>CREBBP</i> mutation may be related to higher immunogenicity such as TMB, high expression of mRNA related to immune response, highly infiltrating immune-active cells such as CD8 ⁺ T cells, active immune-active pathways, and DNA damage repair pathways with an increased number of mutations
	Douglas <i>et al</i> [38], 2020	When looking at the complete responder group, mutations were noted in endoscopic biopsy specimens from at least two patients in genes including <i>ARID1A</i> , <i>JAK1</i> , <i>CREBBP</i> , and <i>MTOR</i> (three patients each), that were not seen to be mutated in PR specimens	The authors identified multiple genetic variations in tumor DNA from rectal cancer patients who are poor responders to neoadjuvant chemoradiation, compared to complete responders
<i>POLD1</i>	Hühns <i>et al</i> [40], 2019	The authors performed <i>POLE</i> and <i>POLD1</i> exonuclease domain Sanger sequencing of 271 unselected colorectal carcinomas and finally identified two microsatellite-stable tumors with somatic <i>POLE</i> p.P286R variants, both with ultrahigh TMBs as demonstrated by whole exome sequencing. In two tumors, a somatic <i>POLE</i> p.V411L and a <i>POLD1</i> p.E279K, respectively, were found only focally, and TMBs were low. It is commonly assumed that compromise of one allele is sufficient, but this has not been specifically addressed	Taken together, including at least the more common DNA polymerase mutations in NGS panels allows for straightforward identification of hypermutator-type colorectal carcinomas which often may be "immunoreactive". This is important at least in young patients or when a metastasizing stage of disease has been reached and immune-checkpoint therapy enters deliberation
<i>IKZF1</i>	None	No eligible studies	No evidence
<i>PRKCB</i>	None	No eligible studies	No evidence

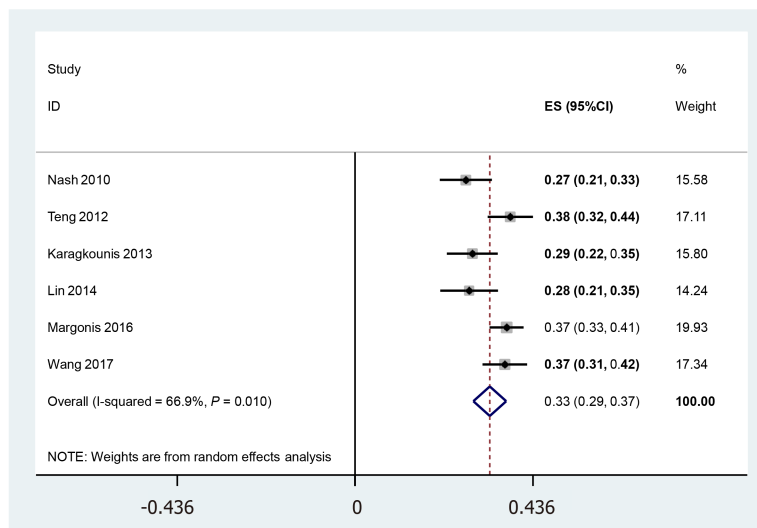
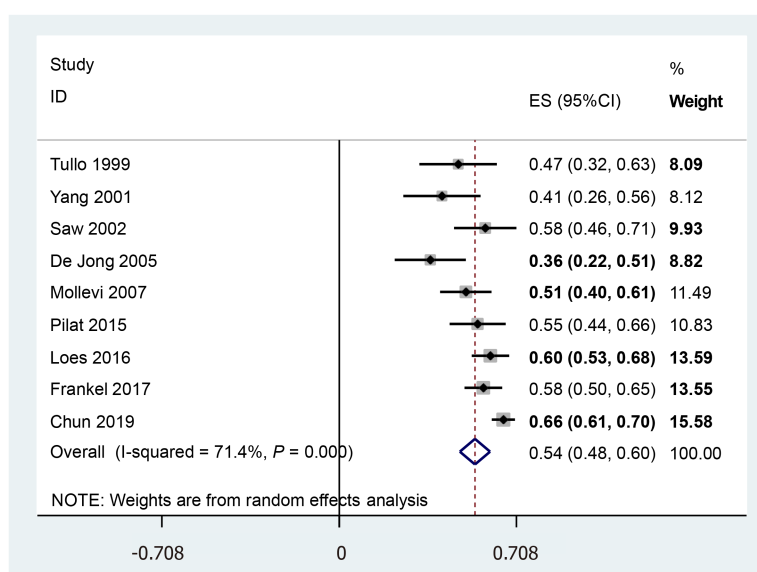
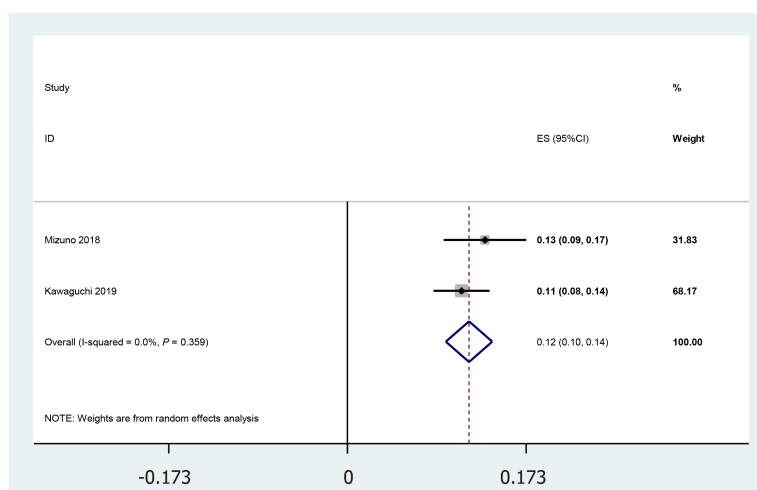
DNA: Deoxyribonucleic acid; mRNA: Messenger ribonucleic acid; NGS: Next generation sequencing; TMB: Tumor mutation burden.

Table 3 Findings of chemotherapy-related single nucleotide polymorphisms related to a better response

Genes	Detected loci	SNP results	Evidence		Summary
			Drugs	Grades	
<i>DPYD</i>	rs3918290	CC (wild-type)	5Fu-based	Level III	For patients with tumor, CC genotype may have a higher drug remission rate than CT genotype. However, there are also studies with inconsistent conclusions
	rs1801159	TT (wild-type)		Level III	For a patient with tumor, TT genotype may have a higher drug remission rate than CT or CC genotype
<i>GSTP1</i>	rs1695	AG (heterozygous mutants)	5Fu + XELOX	Level IIA	For a patient with tumor, AG genotype may have a higher drug remission rate than AA genotype, but comparing with GG genotype, AG genotype may reduce drug remission rate and relate to a poor OS
<i>ERCC2</i>	rs13181	TT (wild-type)	5Fu + Leucovorin + XELOX	Level III	For a patient with CRC, TT genotype may have a lower risk of recurrence and a longer PFS than GG genotype
	rs1052555	GG (wild-type)	Platinum compounds	Level III	For a patient with NSCLC, GG genotype may have a higher drug remission rate than AA or AG genotype
<i>ABCB1</i>	rs1045642	GG (homozygous mutants)		Level III	For a patient with CRC, GG genotype may have a higher drug remission rate than AA or AG genotype
<i>VEGFA</i>	rs25648	CC (wild-type)		Level III	For a patient with gastric cancer, CC genotype may have a higher drug remission rate than CT or TT genotype

CRC: Colorectal cancer; NSCLC: Non-small-cell lung cancer; OS: Overall survival; SNPs: Single nucleotide polymorphisms; XELOX: Oxaliplatin.

Through reviewing the literature, we found that *KRAS*[19-24], *TP53*[25-33], and *APC* [34] were potentially related to a poor prognosis after adjuvant chemotherapy or radical surgery, and so is the mutational status of *SMAD4*[35,36], which were out of eight mutations detected in the patient. However, mutations like *IKZF1* and *PRKCB* have not been studied comprehensively, especially in association with sensitivity to neoadjuvant chemotherapy. *CREBBP* seems to be mutated in patients who achieve complete remission. Lin *et al*[37] found that a high tumor mutation burden (TMB-high, mutation count > 11 mutation/Mb), male sex, *RNF43*-mutant status, and *CREBBP*-mutant status were associated with longer OS, while age ≤ 65 years, *APC*-mutant status, and *TP53*-mutant status were associated with shorter OS. Moreover, Douglas *et*

A**B****C****Figure 3 Meta-analysis of KRAS mutation rate. A: KRAS; B: TP53; C: SMAD4.**

al[38] identified 195 variants in 83 genes in tissue specimens implicated in colorectal cancer bio-pathways. Relative to partial responders, complete responders showed mutations in 10 genes, namely *ARID1A*, *PMS2*, *JAK1*, *CREBBP*, *MTOR*, *RB1*, *PRKAR1A*, *FBXW7*, *ATM* *C11orf65*, and *KMT2D*. Partial responders showed mutations in four genes: *KDM6A*, *ABL1*, *DAXX-ZBTB22*, and *KRAS*. In terms of advantages like

longer OS or greater sensitivity to chemotherapy, these genes might be associated with higher immunogenicity, such as TMB, high expression of messenger ribonucleic acid related to immune responses, highly infiltrating immune-active cells like CD8⁺ T cells, active immune-active pathways, and deoxyribonucleic acid (DNA) damage repair pathways with an increased number of mutations[37]. Yamauchi *et al*[39] investigated changes in the amount and constitution of circulating tumor DNA (ctDNA) in serial peripheral blood samples collected from patients during anti-vascular endothelial growth factor (VEGF) chemotherapy, as understanding molecular changes in tumors in response to chemotherapy is crucial for optimization of the treatment strategy for metastatic colorectal cancer. They found that mutations in *CREBBP* and *FBXW7* genes were newly detected in ctDNA at a low frequency of around 1% in the post-progression period. Moreover, they suggested that changes in ctDNA levels may be a useful predictive biomarker for survival. Furthermore, mutations in *CREBBP* and *FBXW7* genes newly detected in ctDNA in the late treatment period might reveal the rise of a minor tumor clone that could show resistance to anti-VEGF therapy.

The remaining mutation identified in this study, *POLD1*, seems to be of unknown clinical significance because of a lack of published studies. Hühns *et al*[40] performed *POLE* and *POLD1* exonuclease domain Sanger sequencing of 271 CRCs and identified two microsatellite-stable tumors with ultrahigh TMBs related to young patients (< 50-years-old, non-syndromic) and prominent T-cell infiltration. They also identified a somatic *POLE* p.A465T in a Lynch-associated tumor. Somatic *POLE* p.V411L and *POLD1* p.E279K were only found focally and with low TMBs, resulting in the assumption that the compromise of one allele might be sufficient to increase sensitivity to neoadjuvant chemotherapy.

In the results for chemotherapy-related SNPs, 5 genes with 7 loci were identified in the PharmGKB database that might predict a better response. However, the grade of the evidence is relatively low, and a consensus has not yet been reached for SNPs identified in a single study. Multiple studies or a genome-wide association study (GWAS) are needed to confirm that an SNP is relevant to drug responses, and that there is a statistically significant difference in outcomes for patients with specific SNPs.

CONCLUSION

In the present case, a weak association was observed between mutations in *CREBBP* and *POLD1* and high sensitivity to neoadjuvant chemotherapy. Future studies should identify a subgroup of patients who are excellent candidates for chemotherapy, including immune checkpoint inhibitor therapy. In addition to validating this weak evidence, a priority for future studies might be to confirm these findings in a larger sample. A GWAS of chemotherapy-related SNPs could examine whether favorable prognosis is independent of adjuvant chemotherapy.

In terms of the limitations, as a case report, this study focused on genetic mutations in only one patient, and the small sample size is an obvious limitation. However, as shown by evidence from the literature review, although the overall grade of evidence for chemotherapy-related SNPs is relatively low, an evidence-based case report and literature review might be useful for identifying predictors of sensitivity to chemotherapy in patients with metastatic colorectal cancer.

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