Original Article

# PD-1 blockade combined with chemotherapy and bevacizumab in DNA mismatch repair-proficient/microsatellite stable colorectal liver metastases

**Qianqian Men[1#], Yinghua Duan[2#], Fengyun Pei[3,4#], Qijun Yao[3,4#], Wan He[5], Yandong Zhao[6], Lishuo Shi[7], Guangjian Liu[8*], Jun Huang[3,4,9,10*]**

[1]Graceland Medical Center, The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, China; [2]Department of Traditional Chinese Medicine, the First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China; [3]Department of Colorectal Surgery, The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, China; [4]Department of General Surgery, The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, China; [5]Department of Oncology, Shenzhen People's Hospital (The Second Clinical Medical College, Jinan University; The First Affiliated Hospital, Southern University of Science and Technology), Shenzhen, China; [6]Department of Pathology, The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, China; [7]Clinical Research Center, The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, China; [8]Department of Medical Ultrasonic, The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, China; [9]Guangdong Provincial Key Laboratory of Colorectal and Pelvic Floor Diseases, the Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, China; [10]Guangdong Institute of Gastroenterology, Guangzhou, China

*Contributions:* (I) Conception and design: J Huang, G Liu; (II) Administrative support: J Huang; (III) Provision of study materials or patients: J Huang, Q Men; (IV) Collection and assembly of data: Y Duan, F Pei, Q Yao; (V) Data analysis and interpretation: W He, Y Zhao, L Shi; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work as co-first authors.

[*]These authors contributed equally to this work.

*Correspondence to:* Jun Huang, MD, PhD. Department of Colorectal Surgery, The Sixth Affiliated Hospital, Sun Yat-sen University, Yuancunerheng Road, Guangzhou 510655, China; Department of General Surgery, The Sixth Affiliated Hospital, Sun Yat-sen University, Yuancunerheng Road, Guangzhou 510655, China; Guangdong Provincial Key Laboratory of Colorectal and Pelvic Floor Diseases, The Sixth Affiliated Hospital, Sun Yat-sen University, Yuancunerheng Road, Guangzhou 510655, China; Guangdong Institute of Gastroenterology, Yuancunerheng Road, Guangzhou 510655, China. Email: huangj97@mail.sysu.edu.cn; Guangjian Liu, MD, PhD. Department of Medical Ultrasonic, The Sixth Affiliated Hospital, Sun Yat-sen University, Yuancunerheng Road, Guangzhou 510655, China. Email: liugj@mail.sysu.edu.cn.

**Background:** Single-agent immunotherapy is less effective in patients with DNA mismatch repair-proficient/microsatellite stable (pMMR/MSS) metastatic colorectal cancer (mCRC). Whether pMMR/MSS mCRC patients benefit from combination immunotherapy remains unclear. This study aimed to evaluate the efficacy and safety of anti-programmed cell death protein 1 (PD-1) therapy combined with chemotherapy and bevacizumab in pMMR/MSS colorectal liver metastases (CRLM) patients.

**Methods:** A total of 12 patients with pMMR/MSS CRLM treated at The Sixth Affiliated Hospital of Sun Yat-sen University were enrolled. All patients were treated with at least 4 doses of PD-1 monoclonal antibody combined with chemotherapy and bevacizumab as neoadjuvant/adjuvant therapy.

**Results:** A total of 10 of the 12 patients received the combined therapies before primary tumor resection; the disease control rate (DCR) was 100% (10/10), and the objective response rate (ORR) was 70% (7/10). The ORR of liver metastases was 75% (9/12). Pathological complete response (pCR) was achieved in 1 primary tumor patient and 2 patients with hepatic lesions. A total of 5 patients underwent simultaneous resection of the primary tumor and liver metastases; 9 patients underwent microwave ablation for liver metastases. A total of 7 patients were assessed as having no evidence of disease (NED) with a median progression-free survival (PFS) interval of 9.2 (1.5–15.8) months after multimodality treatments for both primary and metastatic lesions. No severe immune-related adverse events (irAEs) and operational complications were observed.

**Conclusions:** PD-1 blockade combined with chemotherapy and bevacizumab might be safe and effective

 

for patients with pMMR/MSS CRLM. This treatment strategy might lead to better tumor regression and a higher chance of achieving NED.

**Keywords:** Colorectal cancer (CRC); liver metastases; mismatch repair-proficient/microsatellite stable (pMMR/MSS); programmed cell death protein 1 blockade (PD-1 blockade); bevacizumab

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## Introduction

Colorectal cancer (CRC) is the third most common cancer and the second most common cause of cancer-related death worldwide (1-3). About 20% of CRC patients have liver metastasis at the time of diagnosis, and 40% of patients have liver metastasis during the early disease course after surgical resection. For 30% of CRC patients, the liver is the only site of metastasis (4). Surgical resection of liver metastases is the most effective treatment for patients with colorectal cancer liver metastases (CRLM), especially those with limited or few liver metastases (5). Among this subgroup of patients, the 5-year overall survival (OS) rate ranges from 20% to 58% (6-8), but the 90-day mortality rate is 4%, and the complication rate is 40% (9).

Ablation therapy is usually reserved for CRLM patients who are not suitable for surgery. Previous studies have shown that 5-year OS rates, 5-year recurrence-free survival (RFS), and local recurrence rate are 27–50%, 0–34%, and 11–37% in CRLM patients treated with ablative therapy (8,10). Chemotherapy, non-surgical local treatment, and local or liver-targeted therapy and treatment are effective methods for treating CRLM. The objective response rates (ORRs) of first-line treatment for metastatic colorectal cancer (mCRC) range from 34% to 66%; whereas the range for second-line treatment is 30% to 40% (11).

Bevacizumab targets vascular endothelial growth factor A (VEGF-A) and plays a role in anti-angiogenesis, as well as immune regulation (12). The interaction between angiogenesis and immune regulation makes bevacizumab an interesting combination of immunotherapy, and related clinical trials are currently underway. Programmed cell death protein 1 (PD-1) blockade has been recommended as the first-line treatment in DNA mismatch repair-deficient/microsatellite instability-high (dMMR/MSI-H) mCRC (13,14). It is worth investigating whether DNA mismatch repair-proficient/microsatellite stable (pMMR/MSS) CRLM patients benefit from PD-1 blockade combination therapy. This study aimed to evaluate the short-term efficacy and safety of anti-PD-1 therapy combined with chemotherapy and bevacizumab in pMMR/MSS CRLM patients. We present this article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-940/rc).

### Highlight box

**Key findings**

- This study found that programmed cell death protein 1 (PD-1) blockade combined with chemotherapy and bevacizumab might be safe and effective for patients with DNA mismatch repair-proficient/microsatellite stable (pMMR/MSS) colorectal liver metastases (CRLM).

**What is known and what is new?**

- Single-agent immunotherapy is less effective in patients with pMMR/MSS CRLM.
- We found that PD-1 blockade combined with chemotherapy and bevacizumab in patients with pMMR/MSS CRLM might lead to better tumor regression and a higher chance of achieving no evidence of disease.

**What is the implication, and what should change now?**

- The therapy regimen of PD-1 blockade combined with chemotherapy and bevacizumab was associated with favorable disease control rate and objective response rate and an acceptable safety profile for patients with pMMR/MSS CRLM. The mechanism of action of the treatment combination deserves further analysis.

## Methods

We retrospectively reviewed 12 pMMR/MSS CRLM patients who were treated with anti-PD-1 combined with chemotherapy and bevacizumab. All enrolled patients underwent imaging evaluations, including computed tomography (CT), magnetic resonance (MR), positron emission tomography (PET), or ultrasound colonoscopy,

 

to determine the tumor stage before neoadjuvant/adjuvant therapy. The microsatellite instability (MSI) and mismatch repair (MMR) status of the tumors were all confirmed before the starting of anti-PD-1 therapy. The 4 MMR proteins (MLH1, MSH2, MSH6, and PMS2) were evaluated by staining, and the results were confirmed by a trained pathologist. MSI status was confirmed by immunohistochemistry (IHC) or next-generation sequencing (NGS). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of The Sixth Affiliated Hospital, Sun Yat-sen University (No. 2022ZSLYEC-39), and all the enrolled patients agreed to receive PD-1 blockade combined chemotherapy and bevacizumab as a neoadjuvant/adjuvant therapy before the treatment. The requirement for individual consent for this retrospective analysis was waived.

### *Treatment and evaluation*

All enrolled patients received at least 4 courses of anti-PD-1 therapy combined with chemotherapy and bevacizumab. The response of the primary tumor was assessed according to the Immune Response Evaluation Criteria In Solid Tumors (iRECIST) (15). Surgical specimens were evaluated according to the American Joint Committee on Cancer criteria (7th edition) (16). The tumor regression grade (TRG) was determined according to National Comprehensive Cancer Network (NCCN) guidelines. Primary and metastatic tumors were assessed by routine hematoxylin and eosin (HE) and IHC staining. No residual viable tumor cells was defined as pathological complete response (pCR). No evidence of disease (NED) was defined as no residual tumor after resection or no blood supply to the ablated lesions assessed by ultrasound contrast and magnetic resonance imaging (MRI) and negative tumor marker analyses. Treatment-related adverse events (AEs) were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (17). The last patient follow-up was conducted on 31 July 2022.

### *Statistical analysis*

All continuous data are expressed as the median with ranges. All discrete variables are presented as counts and percentages. The software program SPSS 26.0 (IBM Corp., Armonk, NY, USA) was used for statistical analyses.

## Results

### *Patient characteristics*

From August 2020 to July 2022, 12 patients with pMMR/MSS CRLM who were treated at The Sixth Affiliated Hospital of Sun Yat-sen University and received anti-PD-1 therapy (sintilimab injection) combined with systemic chemotherapy and targeted therapy were enrolled. The details of the enrolled patients are shown in *Table 1*. All 12 patients with pMMR/MSS had stage IV CRLM, and 2 had liver metastases 2 years after primary tumor surgery. *Table 2* shows the location, size, and number of liver metastases, the surgical resection or ablative treatment administered, and the patients' response to the treatment. As shown in *Table 3*, the median age of the enrolled patients was 53.5 years (range, 38–63 years); 8 of the patients were male. There were 6 patients diagnosed with rectal cancer, 2 with right colon cancer; and 4 with left colon cancer. The pathological tumor type was adenocarcinoma. A total of 10 patients received anti-PD-1 combined with chemotherapy and targeted neoadjuvant therapy.

### *Tumor response after neoadjuvant anti-PD-1 therapy*

All 12 patients were confirmed to have pMMR/MSS by IHC or NGS. A total of 10 of the 12 patients received combined therapy before primary tumor resection, with a median time from neoadjuvant therapy to surgery of 121.5 days (range, 62–161 days). The disease control rate (DCR) was 100% (10/10) and ORR was 70% (7/10) in primary tumors, and the ORR of liver metastases was 75% (9/12) after the combined therapy (*Table 4*). Comparison of the primary tumors before and after treatment is shown in *Figure 1A* (P<0.001); comparison of the rate of radiological and pathological residual cancer of the primary lesion is shown in *Figure 1B* (P=0.009). Meanwhile, *Figure 1C* shows the comparison of the liver metastases before and after treatment (P<0.001); *Figure 1D* displays comparison of the rate of radiological and pathological residual cancer of the liver metastases (P=0.09). There was 1 patient with a primary tumor and 2 with liver metastasis who achieved pCR. A total of 5 patients underwent simultaneous resection of the primary tumor and liver metastases, whereas 9 patients underwent microwave ablation for liver metastases. A total of 7 patients were assessed as having NED with a median progression-free survival (PFS) interval of 9.2 months after multimodality treatments for both primary and metastatic lesions.

 

**Table 1** Cohort clinical characteristics and treatment details

| No. | Age (years) | Gender | Clinical TNM | MMR or MSI status | BRAF | KRAS | Drug of ICB | Courses of ICB before surgery | Chemotherapy and targeted therapy | Clinical response | Surgery | Pathological tumor response | TRG | NED |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 59 | Male | cT3N0M1 | pMMR/MSS | Wt | Wt | Sintilimab | 6 | mFOLFOX6 + bevacizumab | PR | Left hemicolectomy + hepatectomy + ablation | PR | 1 | – |
| 2 | 45 | Male | M1 | pMMR/MSS | Wt | Wt | Sintilimab | 8 | mFOLFOX6 + bevacizumab | SD | Ablation | – | – | Yes |
| 3 | 47 | Male | cT3N1bM1c | pMMR/MSS | Wt | Wt | Sintilimab | 4 | mFOLFOX6/ Xeloda + bevacizumab | PR | Lower anterior resection + ablation | PR | 3 | – |
| 4 | 54 | Male | cT4aN2bM1 | pMMR/MSS | Mt | Wt | Sintilimab | 4 | mFOLFXOX6 + bevacizumab | PR | Lower anterior resection + ablation | PR | 1 | Yes |
| 5 | 55 | Male | cT4aN1bM1 | pMMR/MSS | Wt | Wt | Sintilimab | 5 | mFOLFOX6 + bevacizumab | PR | Lower anterior resection + hepatectomy | PR | 2 | Yes |
| 6 | 55 | Male | cT4aN2aM1 | pMMR/MSS | Wt | Wt | Sintilimab | 6 | mFOLFOX6 + bevacizumab | PR | Left hemicolectomy + hepatectomy + ablation | PR | 2 | Yes |
| 7 | 52 | Male | cT3N2bM1 | pMMR/MSS | Wt | Wt | Sintilimab | 7 | mFOLFOX6 + bevacizumab | PR to PD | Ablation | – | – | – |
| 8 | 38 | Female | cT3N1bM1 | pMMR/MSS | Wt | Wt | Sintilimab | 5 | mFOLFOX6 + bevacizumab | PR | Right hemicolectomy + hepatectomy + ablation | PR | 2 | – |
| 9 | 63 | Female | cT4aN2M1c | pMMR/MSS | Wt | Wt | Sintilimab | 5 | mFOLFOX6 + bevacizumab | PR | Left hemicolectomy + ablation | pCR | 0 | Yes |
| 10 | 52 | Female | M1 | pMMR/MSS | Wt | Wt | Sintilimab | 4 | mFOLFOX6 + bevacizumab | SD | Hepatectomy + ablation | PR | – | – |
| 11 | 69 | Male | cT4aN1bM1 | pMMR/MSS | – | – | Sintilimab | 6 | mFOLFOX6 + bevacizumab | PR | Right hemicolectomy + hepatectomy | PR | 2 | Yes |
| 12 | 53 | Female | cT4aN2bM1 | pMMR/MSS | – | – | Sintilimab | 5 | mFOLFOX6 + bevacizumab | PR | Lower anterior resection | pCR | 2 | Yes |

MSI, microsatellite instability; MMR, mismatch repair; ICB, immune checkpoint block; pCR, pathological complete response; PR, partial response; SD, stable disease; PD, progressive disease; pMMR, mismatch repair-proficient; MSS, microsatellite stable; NED, no evidence of disease; Mt, mutant; Wt, wild-type; TRG, tumor regression grade; TNM, tumor, node, metastasis.

**Table 2** Details about the liver metastases

| No. | Timing of metastases | Location | Count | Resection | Ablation | Clinical response | Pathological response |
|---|---|---|---|---|---|---|---|
| 1 | Synchronous | S3/S5/S8/S7 | 3 | Yes | Yes | PR | PR |
| 2 | Metachronous | S7 | 1 | No | Yes | SD | – |
| 3 | Synchronous | S6 | >3 | No | Yes | PR | – |
| 4 | Synchronous | S8 | 1 | No | Yes | PR | – |
| 5 | Synchronous | S2 | 1 | Yes | No | cCR | pCR |
| 6 | Synchronous | S5/S6/S8 | 3 | Yes | Yes | PR | PR |
| 7 | Synchronous | S2/S5/S6/S7 | >3 | No | Yes | PR | – |
| 8 | Synchronous | S2/S5/S8 | >3 | Yes | Yes | PR | PR |
| 9 | Synchronous | S1/S4/S7 | 3 | No | Yes | PR | – |
| 10 | Metachronous | S3/S4/S8 | >3 | Yes | Yes | SD | PR |
| 11 | Synchronous | S6 | 1 | Yes | No | PR | PR |
| 12 | Synchronous | S2/S3/S6/S7/S8 | >3 | No | No | PR | pCR |

cCR, clinical complete response; pCR, pathological complete response; PR, partial response; SD, stable disease.

**Table 3** Characteristics of cohorts

| Characteristic | Values |
|---|---|
| Age, years, median [range] | 53.5 [38–63] |
| ≥60, n (%) | 2 (16.7) |
| <60, n (%) | 10 (83.3) |
| Sex, n (%) | |
| Male | 8 (66.7) |
| Female | 4 (33.3) |
| ECOG performance status score, n (%) | |
| 0 | 8 (66.7) |
| 1 | 3 (25.0) |
| ≥2 | 1 (8.3) |
| Primary tumor location, n (%) | |
| Right-side | 2 (16.7) |
| Left-side | 4 (33.3) |
| Rectum | 6 (50.0) |
| Histological type, n (%) | |
| Medium or well-differentiated | 11 (91.7) |
| Poor differentiated | 1 (8.3) |
| Pathological type, n (%) | |
| Adenocarcinoma | 12 (100.0) |
| Stage, n (%) | |
| IV | 12 (100.0) |

ECOG, Eastern Cooperative Oncology Group.

### *Safety and feasibility*

AEs are shown in *Table 5*. All AEs had been previously reported in other immunotherapy studies (18-21). A total of 10 patients experienced at least 1 AE. Events of clinical interest included hand-foot syndrome (41.7%), nausea (33.3%), elevated alanine aminotransferase (16.7%), rash or pruritus (16.7%), diarrhea (8.3%), thyroiditis or hypothyroidism (8.3%), and chylous ascites (8.3%). All AEs were level 1–2; no level 3 AEs occurred. All AEs were secondary to chemotherapy or surgery, which were controlled or reduced, and the patients returned to normal; no surgeries were delayed. No perioperative mortality was observed among the patients who received surgery. Postoperative complications such as infection, anastomotic leakage, obstruction, urinary retention, and other complications occurred.

## Discussion

Targeting immune checkpoint molecules, such as PD-1, has achieved lasting clinical benefits in patients with dMMR/MSI-H mCRC, which contributes only 5% of mCRC (22,23). The liver is one of the most common sites of CRC metastasis. Hepatectomy is the mainstay treatment with a 5-year survival rate of 40–60% (24). Conversion therapy has been used for patients with unresectable liver metastases. Preoperative chemotherapy and new therapeutic strategies

 

**Table 4** ORR in primary tumors and liver metastases (based on radiological changes in maximum tumor diameter)

| Case | Primary tumor | | | | Liver metastases | | | |
|---|---|---|---|---|---|---|---|---|
| | Before treatment (mm) | Posttreatment (mm) | ORR, % | PTRR, % | Before treatment (mm) | Posttreatment (mm) | ORR, % | PTRR, % |
| 1 | 39.3 | 17.7 | 55 | 10 | 47.3 | 22.7 | 52 | 10 |
| 2 | – | – | – | 40 | 31.5 | 30.8 | 2.2 | – |
| 3 | 72.2 | 57.1 | 20.9 | 80 | 20.4 | 12.7 | 37.8 | – |
| 4 | 55.1 | 42.8 | 22.3 | 1 | 14.6 | 14 | 4.1 | – |
| 5 | 62.4 | 43.3 | 30.6 | 45 | 13.8 | 0 | 100 | 0 |
| 6 | 36.4 | 13.7 | 62.4 | – | 35.2 | 15.6 | 54.8 | – |
| 7 | 57 | 14 | 75.4 | – | 40.9 | 18.5 | 54.8 | – |
| 8 | 30.2 | 16.8 | 44.4 | 50 | 39.7 | 14.3 | 64 | 50 |
| 9 | 109.8 | 93.1 | 15.2 | 0 | 39.7 | 17.4 | 56.2 | – |
| 10 | – | – | – | – | 68 | 65 | 4.4 | 70 |
| 11 | 59.9 | 37.16 | 38 | 2 | 16.04 | 11.75 | 26.7 | <1 |
| 12 | 65.55 | 28.97 | 55.8 | 12 | 49.3 | 16.96 | 65.6 | 0 |

ORR, objective response rate; PTRR, pathological tumor residue rate.

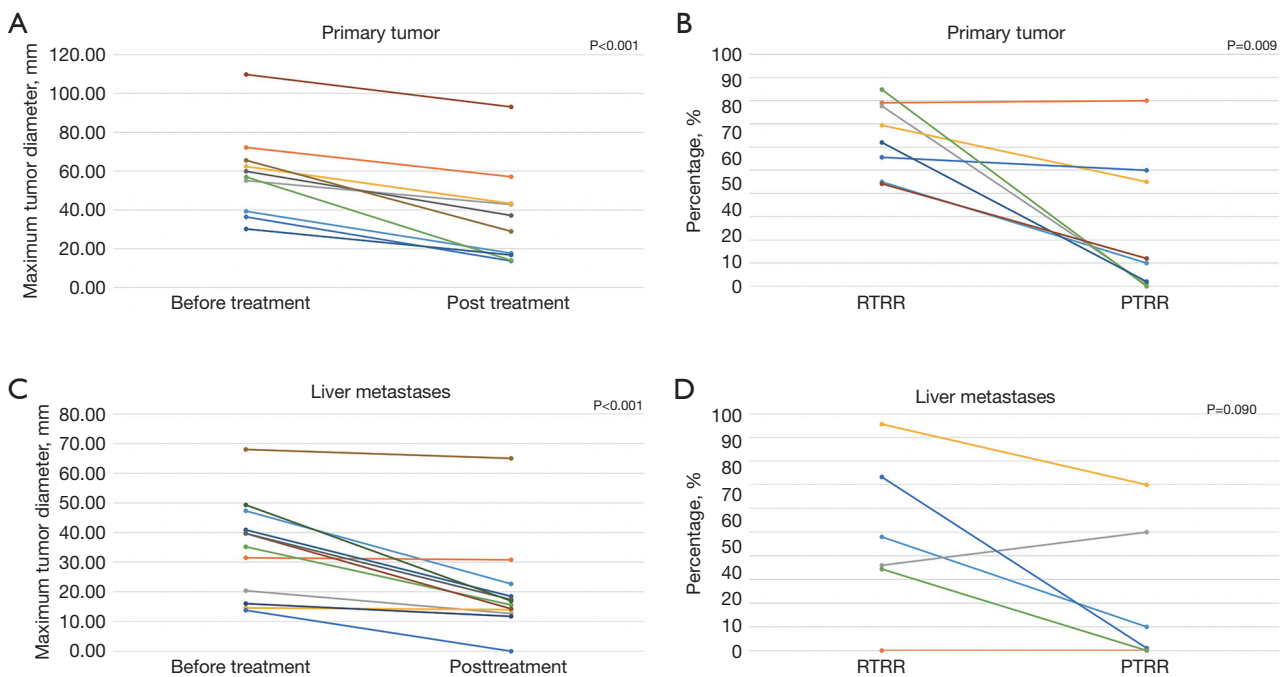


**Figure 1** Affective outcomes after treatment by the maximum diameter of the tumor, RTRR and PTRR. (A) Comparison of the primary tumors before and after treatment; (B) comparison of the rate of radiological and pathological residual cancer of the primary lesion; (C) comparison of the liver metastases before and after treatment; (D) comparison of the rate of radiological and pathological residual cancer of the liver metastases. RTRR, radiological tumor residue rate; PTRR, pathological tumor residue rate.

 

**Table 5** Adverse events observed in the cohort

| Adverse events | Grade 1–2, n (%) | Grade ≥3, n (%) | Any grade, n (%) | Immune-related adverse reactions | Adverse reactions secondary to chemotherapy or surgery |
|---|---|---|---|---|---|
| Hand-foot syndrome | 5 (41.7) | 0 | 5 (41.7) | No | Yes |
| Itch | 1 (8.3) | 0 | 1 (8.3) | No | Yes |
| Rash or pruritus | 2 (16.7) | 0 | 2 (16.7) | No | Yes |
| Elevated alanine aminotransferase | 2 (16.7) | 0 | 2 (16.7) | No | Yes |
| Nausea | 4 (33.3) | 0 | 4 (33.3) | No | Yes |
| Vomit | 2 (16.7) | 0 | 2 (16.7) | No | Yes |
| Diarrhea | 1 (8.3) | 0 | 1 (8.3) | No | Yes |
| Thyroiditis or hypothyroidism | 1 (8.3) | 0 | 1 (8.3) | No | Yes |
| Myocarditis | 1 (8.3) | 0 | 1 (8.3) | No | Yes |
| Upper respiratory infection | 1 (8.3) | 0 | 1 (8.3) | No | Yes |
| Cough | 1 (8.3) | 0 | 1 (8.3) | No | Yes |
| Fever | 2 (16.7) | 0 | 2 (16.7) | No | Yes |
| Cold intolerance | 1 (8.3) | 0 | 1 (8.3) | No | Yes |
| Fatigue | 3 (25.0) | 0 | 3 (25.0) | No | Yes |
| Headache | 1 (8.3) | 0 | 1 (8.3) | No | Yes |
| Surgery-related adverse events | | | | | |
| Surgical site infection | 0 | 0 | 0 | | |
| Anastomotic leak | 0 | 0 | 0 | | |
| Obstruction/ileus | 0 | 0 | 0 | | |
| Chylous ascites | 1 (8.3) | 0 | 1 (8.3) | No | Yes |
| Urinary retention | 0 | 0 | 0 | | |
| All | 10 (83.3) | 0 | 10 (83.3) | No | Yes |

were used to shrink the tumor and promote resection (25). Ye *et al.* showed that patients who received targeted therapy or chemotherapy in combination with hepatectomy had significantly longer median survival compared to those who did not undergo hepatectomy (46.4 *vs.* 25.7 months in the targeted treatment group and 36.0 *vs.* 19.6 months in the chemotherapy alone group) (26). The final analysis of the TRICC0808 trial showed that patients who underwent hepatectomy after treatment with mFOLFOX6 and bevacizumab had better long-term survival outcomes, although most of the patients eventually relapsed. Therefore, hepatectomy after chemotherapy may improve the survival of CRLM patients, although achieving a cure remains challenging (27).

Previous research has evaluated the efficacy of atezolizumab in combination with bevacizumab and/or FOLFOX in patients with mCRC. Patients who received atezolizumab, bevacizumab, and FOLFOX as the first-line treatment had an ORR of 52% and a median PFS of 14.1 months, with no significant benefit (28). In this study, 10 of the 12 patients received the combined therapies before primary tumor resection. The DCR of the primary tumors was 100%, and the ORR was 70%. The ORR of the liver metastases was 75% (9/12) after treatment. The therapeutic effect on both the primary tumors and liver metastases was statistically significant (P<0.001), and there was also a statistically significant reduction in radiological and pathological residual cancer in the primary lesion (P=0.009). These preliminary results suggest that neoadjuvant immunotherapy combined with chemotherapy plus targeted

 

therapy might be a promising strategy for pMMR/MSS CRLM patients.

A previous study on anti-PD-1 in dMMR mCRC reported a response rate of 32–53% (22). In the NICHE phase I/II trial, 4 of 15 pMMR tumors achieved pathological remission (3 cases of major remission and 1 partial remission). The difference in response between dMMR and pMMR patients is mainly attributed to variations in tumor load/neoantigens and T cell tumor mutation burden. Higher numbers of tumor-infiltrating PD-1$^+$CD8$^+$ T cells and Th1 T cells have been shown to predict the response of dMMR/MSI-H population to checkpoint blockade (29,30). Additionally, a study on the adjuvant ipilimumab combined with nivolumab in early-stage MSS CRC demonstrated a 27% pathological response rate, further supporting the notion that CRC can be targeted by immunotherapy and is not an immune desert (31). Recently, the combination of vascular endothelial growth factor receptor (VEGFR) inhibitors and anti-PD-1 antibodies has shown encouraging clinical activity in patients with MSS mCRC (32,33). Increasing evidence indicates that vascular endothelial growth factor (VEGF) can inhibit the maturation of dendritic cells, reduce the expression of MHC I, increase the expression of checkpoint molecules, and inhibit the activation of CD8$^+$ T cells by recruiting bone marrow-derived inhibitory cells (34). The R0 hepatectomy rate of mFOLFOX6 combined with bevacizumab was 44.4%, with a favorable outcome rate of 23.1% and a low rate of surgical complications (27). Chemotherapy drugs may lead to liver injury, such as steatohepatitis and sinusoidal obstruction, as well as surgical complications (35). In contrast, the combination of bevacizumab and oxaliplatin can reduce hyperemia (36). The radiologic response rate was high (55.6%), and the pathological response rate was significant (the main response with necrosis of >1/3 of the tumor =42.5%). Based on these findings, the combination of bevacizumab and oxaliplatin is acceptable for patients who are not suitable for liver metastasis resection, and is not limited to the Kras wild-type population (27).

It is well known that bevacizumab targets VEGF-A and has both anti-angiogenesis and immune-modulating effects (12). There is a lack of biomarkers to guide bevacizumab treatment strategies. The interaction between angiogenesis and immunotherapy makes bevacizumab an interesting combination of immunotherapy, and ongoing clinical trials are investigating its potential. These reports suggest that immune checkpoint inhibition combined with bevacizumab may play a role in neoadjuvant therapy for patients with localized liver disease (37). Previous research has shown that chemotherapy can improve the immune score and promote CD8$^+$ T cell infiltration in CRC (38). After tumor cell necrosis or apoptosis, neoantigens can be released and activate cytotoxic T lymphocytes (CTLs) (39). In this study, 5 patients underwent simultaneous resection of the primary tumor and liver metastases, whereas other patients underwent microwave ablation for liver metastases. pCR was achieved in 1 patient with a primary tumor and 2 patients with hepatic lesions. A total of 7 patients were assessed as NED, with a median PFS interval of 9.2 months after multimodality treatments for both primary and metastatic lesions. Therefore, it was concluded that the combination of chemotherapy and targeted therapy with immunotherapy might improve the efficiency of PD-1 blockade for pMMR/MSS CRLM. In this study, neoadjuvant/adjuvant therapy with anti-PD-1 was associated with acceptable AEs. Even when used in combination with chemotherapy and targeted therapy, the toxicity profile was consistent with that observed in other studies using pembrolizumab or nivolumab alone (22). Moreover, there were no AEs leading to surgical delays, and only 1 adverse reaction was recorded secondary to surgery. These results suggest that PD-1 blockade combined with chemotherapy and targeted therapy might be a safe option for CRLM patients planning to undergo surgery.

Certainly, there were some limitations in this study. This study was a retrospectively pilot small cohort with a short postoperative follow-up period. Notably, the response to immunotherapy combined with chemotherapy and targeted therapy was relatively poor in the 2 metachronous CRLM patients. One patient with potentially resectable synchronous CRLM achieved a significant response while presenting with extrahepatic metastases and progression of intrahepatic metastases after the sixth course of the combined therapy, but the primary tumor remained in clinical complete response (cCR). Furthermore, current clinical trials of immunotherapy and targetable therapy mainly focus on patients with primary liver cancer, with limited reports on resectable or potentially resectable CRLM. To determine the role of neoadjuvant immune checkpoint blocking therapy in patients with pMMR/MSS CRLM, more cases and long-term follow-up studies are needed. The abstract of this study has been selected for online publication in 2022 ASCO Annual Meeting (submission ID: 362684, abstract number for publication: e15547).

 

## Conclusions

Although this study has limitations such as its small sample size and retrospective design, we believe that PD-1 blockade combined with chemotherapy and bevacizumab might be safe and effective for patients with pMMR/MSS CRLM. This treatment strategy might lead to better tumor regression and a higher chance of achieving NED. Further phase II clinical studies are required to evaluate the long-term effectiveness of this combined therapeutic approach.

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## Footnote

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*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of The Sixth Affiliated Hospital, Sun Yat-sen University (No. 2022ZSLYEC-39), and all the enrolled patients agreed to receive PD-1 blockade combined chemotherapy and bevacizumab as a neoadjuvant/adjuvant therapy before the treatment. The requirement for individual consent for this retrospective analysis was waived.



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