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ORIGINAL RESEARCH

PD-1 blockade in neoadjuvant setting of DNA mismatch repair-deficient/ microsatellite instability-high colorectal cancer

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ABSTRACT

Background: Although PD-1 blockade has significantly improved the survival of metastatic colorectal cancer with DNA Mismatch Repair-Deficient/Microsatellite Instability-High (MSI-H), the data on neoadjuvant setting is limited.

Methods: In this retrospective study, we enrolled eight patients with advanced MSI-H colorectal cancer from three hospitals. Four patients are locally advanced and four are metastatic. All the patients received at least two doses of PD-1 antibody with or without chemotherapy as neoadjuvant therapy. The aim of the present study was to evaluate the short-term efficacy and toxicities of this strategy.

Results: All the enrolled eight patients had a major response in imaging and/or pathological evaluation. Five of the seven resected patients were evaluated as pathological complete response. One patient without surgery has a clinical complete response (cCR) tumor response.

Conclusions: Neoadjuvant PD-1 blockade induced tumor regression with a major clinical and pathological response in advanced dMMR/MSI-H colorectal cancer. Further studies are required to evaluate the long-term effect of this strategy.

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Colorectal cancer; microsatellite instability; neoadjuvant; PD-1; immune checkpoint blockade

Introduction

PD-1 blockade has significantly improved the survival of metastatic colorectal cancer with DNA Mismatch Repair-Deficient (dMMR)/Microsatellite Instability-High (MSI-H).[1,2] By now, PD-1 blockade was approved as late line therapy in MSI-H metastatic colorectal cancer in USA, Switzerland, and Japan. However, previous reports demonstrated that front line use of PD-1 blockade was associated with a higher response rate compared with a late line either in Non–Small-Cell lung cancer or metastatic colorectal cancer,[3,4] suggesting that early use of PD-1 antibody might achieve better outcome. Furthermore, several studies[5-7] demonstrated that neoadjuvant therapy with an immune checkpoint inhibitor can promote neoantigen-specific T cell response, which further supports the early use of immune checkpoint inhibitor. Up to date, a very limited number of studies focusses on neoadjuvant immunotherapy in advanced dMMR/MSI-H colorectal cancer, such as NICHE study (NCT03026140), NICOLE study (NCT04123925), CHINOREC study (NCT04124601). However, most of them are in the stage of recruiting.

The current study aims to evaluate the safety and short-term effect of neoadjuvant anti-PD-1 therapy with or without chemotherapy in patients with dMMR/MSI-H locally advanced or metastatic colorectal cancer.

Results

Characteristics of the patients

From July 2017 to May 2019, we enrolled eight patients who underwent neoadjuvant anti-PD-1 therapy from three centers. The details of the enrolled patient were shown in Table 1. Among the eight patients, four patients were locally advanced (T4b or N1-2), while the other four were stage IV diseases. As the Table 2 shows, the lesion of metastasis included liver, lung, peritoneum, and distant lymph node.

As shown in Table 3, the median age of enrolled patients was 40 years (range 19–54). Four of them were male. Of all patients, two were diagnosed as multiple primary colorectal cancer, two patients were rectal cancer, and the other four patients were colon cancer. Three patients received PD-1 antibody alone as the neoadjuvant therapy, and one patient treated with anti-PD-1 and anti-CTLA4. While the other four patients were treated with anti-PD-1 and chemotherapy.

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Supplemental data for this article can be accessed on the publisher's website.

Table 1. Details of the eight patients with neoadjuvant ICB therapy.

No.	Age	Gender	Clinical TNM	Lynch	Ras/Raf mutation	Drug of ICB	Dose of ICB (mg)	Courses of ICB	Neoadjuvant Chemotherapy	Clinical Response	Surgery	Tumor Response	TRG (NCCN)
1	36	Female	rT0N0M1	Yes	No	Pembrolizumab	200	5	FOLFOX	PR	Liver metastases resection	pCR	0
2	51	Female	cT3N1M0	Yes	NA	Pembrolizumab	240	2	XELOX	PR	Subtotal colectomy	pCR	0
3	54	Male	cT4N2M1	NA	No	Pembrolizumab	200	6	Nimotuzumab + Irinotecan + Capecitabine	SD	Right hemicolectomy with lymph node dissection	pCR	0
4	51	Male	rT4N1M1	No	No	Nivolumab	200	8	-	SD	LAR and Liver metastasis resection	pCR	0
5	25	Male	rT4bN2M1	Yes	NA	Nivolumab	200	6	FOLFOX	PR	Right hemicolectomy with lymph node dissection	PR	2
6	19	Female	cT3N1M0	Yes	Kras	Pembrolizumab +Ipilimumab	200 + 50	4	-	CR		-	-
7	49	Female	cT3N1M0	Yes	Kras	Nivolumab	140	12	-	PR	Anterior resection	pCR	0
8	34	Male	cT4bN2M0	Yes	No	Pembrolizumab	200	4	-	PR	Right hemicolectomy with lymph node dissection	PR	2

ICB: Immune Checkpoint Block, pCR: pathological complete response, cCR: clinical complete response, PR: partial response, TRG: tumor regression grade, LAR: Lower anterior resection

Table 2. Details of metastasis lesion.

Patient No.	Liver	Lung	Peritoneum	Distant Lymph node
1	Multiple nodules, max: 41mm*33mm	0	0	0
3	0	Left upper lobe nodule, 10mm*6mm	0	Abdominal aortic lymph node, 25mm*35mm
4	0	0	Rectovesical pouch nodule, 29*23*34mm; One para-iliac vessel nodules, 17mm*14mm	0
5	One nodule, 9mm*8mm	0	0	Hepatic hilar lymph node, 11*15mm

Table 3. Characteristic of cohorts.

Characteristic	
Age: Median (range) – year	40 (19–54)
Sex: – no. (%)	
Male	4 (50)
Female	4 (50)
ECOG performance status score: – no. (%)	
1	6 (75)
>2	2 (25)
Tumor site: – no. (%)	
Colon cancer	4 (50)
Rectal cancer	2 (25)
Multiple primary colorectal cancer	2 (25)
Histological Grade: – no. (%)	
Medium or Well-differentiated	5 (62.5)
Poor differentiated	3 (37.5)
Pathological type: – no. (%)	
Adenocarcinoma	7 (87.5)
Mucinous adenocarcinoma	1 (12.5)
Stage: – no. (%)	
III	4 (50)
IV	4 (50)
Liver	3 (37.5)
Lung	1 (12.5)
Peritoneum	1 (12.5)
Distant Lymph Node	1 (12.5)

Table 4. Adverse events.

Adverse Events	No. of patients (%)	No. of patients (%)
Treatment-related adverse events	Grade 2	Grade 3
Any	7 (87.5)	0 (0)
Dermatologic		
Itch	3 (37.5)	0 (0)
Rash or Pruritus	4 (50)	0 (0)
Thyroiditis or Hypothyroidism	1 (12.5)	0 (0)
Gastrointestinal		
Diarrhea	1 (12.5)	0 (0)
Nausea	1 (12.5)	0 (0)
Vomit	1 (12.5)	0 (0)
Elevated Alanine Aminotransferase	2 (25)	0 (0)
Respiratory		
Cough	1 (12.5)	0 (0)
Upper respiratory infection	1 (12.5)	0 (0)
Encephalitis	0 (0)	1 (12.5)
Fatigue	1 (12.5)	0 (0)
Fever	3 (37.5)	0 (0)
Cold intolerance	1 (12.5)	0 (0)
Edema	1 (12.5)	0 (0)
Headache	1 (12.5)	0 (0)
Optic papilledema	1 (12.5)	0 (0)
Surgery-related adverse events		
Any	0 (0)	0 (0)
Anastomotic leak	0 (0)	0 (0)
Obstruction/Ileus	0 (0)	0 (0)
Surgical Site Infection	0 (0)	0 (0)
Urinary Retention	0 (0)	0 (0)
Chylous Ascites	0 (0)	0 (0)

Tumor response after neoadjuvant anti-PD-1 therapy

All the eight enrolled patients had undergone radical surgery. The median time to response was 4 months (range 1.4–12.3). The median time from neoadjuvant ICBs therapy to surgery is 140 days (range 50–219), and the median time from last neoadjuvant ICBs therapy to surgery is 30 days (range 21–73). According to iRECIST criteria, all patients were evaluated in image, of which five were partial response, two were stable disease and one were complete response. (Supplementary Figure 1). All patients with residual disease in the image underwent surgery achieved a major pathological response (Table 1). Five patients had a complete pathological response with no viable tumor cells in the metastatic lesions or the primary lesions. Two patients only had a few residual tumor cells in the resected colon and lymph nodes.

Safety and feasibility

Adverse events were shown in Table 4. All the adverse events were reported previously in other immunotherapy studies. Seven patients had at least one adverse event and only one patient had a grade 3 immune-related encephalitis, who received corticosteroids for the encephalitis. Events of clinical interests included thyroiditis or hypothyroidism (12.5%), diarrhea (12.5%), elevated alanine aminotransferase (25%), and immune-related encephalitis (12.5%). All the adverse events were under control and recovered or reduced without delay of surgery. As for the surgery-related events, there was no perioperative mortality in the surgical patients. And no patient developed postoperative complications including anastomotic leak, obstruction, infection, urinary retention, or chylous ascites.

Discussion

In the current study, we found that neoadjuvant immunotherapy had a significant pathological response in patients with advanced dMMR or MSI-H colorectal cancer. Clinical response and/or pathological response were observed in all the eight patients. Furthermore, the treatment was associated with a favorable major pathological response. These preliminary results suggest that neoadjuvant immunotherapy might be a promising strategy for advanced dMMR or MSI-H colorectal cancer.

Previous studies about anti-PD-1 in advanced dMMR colorectal cancer shows that the response rate was only about 32–53%.[2,8,9] Recently, Dr Chalabi *et al.* reported a series of MSI-H early stage colon cancer patients treated with 6 weeks neoadjuvant ipilimumab plus nivolumab.[10] All the seven enrolled dMMR CRC in Chalabi's trial had a major pathological response after neoadjuvant immunotherapy with a 57.1% pCR rate. Although patients in the current cohort are more advanced than those enrolled in Myriam Chalabi's trial, the efficacy of anti-PD-1 therapy is quite similar with a 71.4% pCR rate. One possible reason for a higher pCR rate may be that patients in our cohort received more doses of PD-1 blockade therapy compared with Myriam Chalabi's trial, which may be an important factor to improve the efficacy. Although small sample sizes in both studies, the extraordinary tumor response and consistent results suggest that early use of PD-1 antibody might achieve a better outcome. The favorable clinical and pathological outcome in the current study was also consistent with the findings in neoadjuvant anti-PD-1 therapy in lung cancer and melanoma, which reinforce the efficacy of early use of PD-1 antibody.[10]

We observed that the clinical evaluation of patients in radiograph is not accurate to show the response of neoadjuvant immunotherapy. Not only patients evaluated as PR achieved a promising pathological response, but the two patients evaluated as SD in the clinic also achieved pCR after surgery. Previous study demonstrated that radiographic evaluation may not be an accurate predictor of the pathological response.[11]To assess the response of

neoadjuvant anti-PD-1 therapy, the radiographic evaluation may not be sufficient.

In our study, we observed that neoadjuvant immunotherapy with chemotherapy had a significant tumor response. Among the four patients with very advanced disease treated with PD-1 antibody and chemotherapy, three patients achieved pCR and one achieved PR with only a few tumor residues. Previous study demonstrated that chemotherapy may improve the immunoscore and promote the CD8 + T cells infiltration in colorectal cancer.[12,13] After the tumor cells necrosis or apoptosis, the neoantigen may be released and activated the CTL. Our results support the previous findings that the combination of chemotherapy and immunotherapy might improve the efficient of PD-1 blockade for advanced MSI-H colorectal cancer.

An ideal neoadjuvant therapy should not affect the safety of surgery. We observed that neoadjuvant administration of anti-PD-1 in patients with advanced MSI-H/dMMR colorectal cancer was associated with acceptable immediate adverse events. Even when combined with chemotherapy, the toxicity profiles are consistent with other studies on pembrolizumab or nivolumab alone.[9,14,15] Meanwhile, no surgery was delayed due to adverse events and there were no any surgery-related complications such as obstruction happened. All these results seem that anti-PD-1 therapy with or without chemotherapy might be safe for patients planned surgery.

The limitations of our study include, but are not limited to, the retrospective study with only a small number of patients and the short postoperative follow-up period. Due to the nature of a retrospective study, the regimens of neoadjuvant therapy is not exactly the same. Larger and prospective studies are needed to determine the most effective duration and dosage of anti-PD-1 neoadjuvant therapy. Long-term follow-up of these studies will be necessary to define the role of neoadjuvant immune checkpoint block therapy in advanced colorectal cancers.

In conclusion, our study demonstrated that neoadjuvant anti-PD-1 therapy with or without chemotherapy is associated with promising short-term outcome and acceptable adverse events in advanced MSI-H/dMMR colorectal cancer. Further studies are warranted.

Materials and methods

Patients

We retrospective reviewed all MSI-H colorectal cancer treated with anti-PD-1. Eight patients received treatment for the purpose of neoadjuvant therapy were identified between 2017 and 2019, from three hospitals in China. All the enrolled patients were evaluated in imaging including CT, MR, PET-CT, or ultrasound colonoscopy to determine the stage of tumor before neoadjuvant therapy. The MSI and MMR status were all confirmed before anti-PD-1 therapy. The four MMR proteins (MLH1, MSH2, MSH6, PMS2) were stained and the results were confirmed by two trained pathologists. MSI status was confirmed by polymerase chain reaction (PCR) and subsequent fragment analysis of paired normal and tumor tissue or next-generation sequencing. The PCR panel include five loci: two mononucleotides (BAT25 and BAT26) and three dinucleotides (D5S346, D2S123, and D17S250).

Inclusion criteria were: diagnosis of locally advanced (T3 with ≥5 mm invasion beyond the muscularis propria or T4 for colon cancer; T3-4 or N1-2 for rectal cancer) or metastasis colorectal cancer with MSI-H or dMMR and received PD-1 antibody as neoadjuvant therapy. Patients were excluded if they had a rectal melanoma or squamous cell carcinoma, or had unresectable metastasis lesion, such as bone metastasis.

Treatment and evaluation

All patients enrolled in this study received at least two courses of anti-PD-1 therapy with or without chemotherapy. The primary tumor response was assessed according to the iRECIST criteria.[16] Surgical specimens were evaluated according to the criteria of the American Joint Committee on Cancer (seventh edition).[17] The tumor regression grading (TRG) was evaluated according to the NCCN guideline. After routine hematoxylin and eosin staining, the primary tumors or the metastasis tumor were assessed and no residual viable tumor cells were considered to have a pathological complete response. Treatment-associated adverse events were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

Disclosure of Potential Conflicts of Interest

The authors declare no potential conflicts of interest.

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Author Contributions

All authors listed have contributed sufficiently to the project to be included as authors, and all those who are qualified to be authors are listed in the author byline. All authors have read and approved the article. The authors of this study have not published or submitted any related articles from this study. This article is not under consideration elsewhere.

Data

All data in our study have been recorded at Sun Yat-sen University Cancer Center for future reference (number RDDA2019001099).

Ethical issues

All the enrolled patients approved to use PD-1 blockade as a neoadjuvant therapy before the treatment. And this retrospective study has received the full approval of the ethics committee of the Sun Yat-Sen University Cancer Center, China.

Statistical analysis

All continuous data were expressed as median with the range. All discrete variables were shown as counts and percent. The software program SPSS version 19 (SPSS Inc., Chicago, IL, USA) was used for statistical analyses.

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