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Clinical effect and safety of programmed cell death protein 1/ programmed death ligand-1 blockers in postoperative chemotherapy for advanced colorectal cancer

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► ***Original article***

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ABSTRACT

Background: This research was planned to disclose the clinical effect along with safety of programmed cell death protein 1/programmed death ligand-1 (PD-1/PD-L1) blockers in postoperative chemotherapy for advanced colorectal cancer. ***Material and Methods:*** From June 2019 to June 2021, 23 advanced colorectal cancer patients received apatinib treatment and 28 advanced colorectal cancer patients received PD-1 inhibitors in our hospital were included. The safety and clinical efficacy of 2 therapeutic regimens were compared. ***Results:*** Relative to apatinib group, the proportion of stable disease in patients accepting PD-1 blockers presented higher (P=0.010), the median progression-free survival (PFS) of patients accepting PD-1 blockers was longer (P=0.0209), the median PFS of patients with no liver metastasis who accepted PD-1 blockers presented longer (P<0.0001), the median PFS of Kirsten rat sarcoma viral oncogene homolog (KRAS) wild-type patients who received anti-PD-1 therapy presented longer (P=0.0288), and the median PFS of patients with left colon as primary site who received anti-PD-1 therapy presented longer (P=0.0105). Relative to the apatinib group, the incidence of adverse events in patients accepting PD-1 blockers was generally lower, but with no difference (P>0.05). ***Conclusion:*** PD-1/PD-L1 blockers possess certain clinical efficacy and tolerability in treating advanced colorectal cancer.

INTRODUCTION

Nowadays, colorectal cancer acts as a kind of the most common cancers entire world. In China, colorectal cancer occupies third in tumor incidence as well as fifth in mortality [1], which seriously endangers people's physical and mental health [2]. Recently, immune checkpoint inhibitors (ICIs), in especial anti-programmed cell death protein 1 (PD-1) therapeutic schedule, have dramatically altered the pattern of cancer treatment [3].

PD-1 has an integral role in the functional fine-tuning of T cells and the maintenance of immune system homeostasis, and is one of the most studied regulators [4]. PD-1 works to be a natural brake and can stimulate an immune checkpoint response in T cells [5]. Nevertheless, tumor cells utilize this checkpoint negative modulation to restrain immunity as well as evade immune surveillance [6]. This important information is helpful to initiate the development of PD-1/programmed death ligand-1 (PD-L1) blockers [7]. Currently, PD-1/PD-L1 blockers possess a momentous function in metastatic colorectal cancer (mCRC) immunotherapy [8, 9]. Therefore, treatment options have also gradually shifted from back-line therapy to first-line therapy or neoadjuvant therapy, all with success. On the one side, antiangiogenic agents cannot only normalize the tumor capillaries, but also block the transmission of autoimmune suppressive signaling in a variety of ways [10, 11]. On the other side, PD-1/PD-L1 blockers can also enhance immune function [12], so the two are closely related. This study investigated the curative effect together with safety of PD-1/PD-L1 repressors in postoperative chemotherapy for advanced colorectal cancer. Our study clarified that PD-1/PD-L1 blockers had certain clinical efficacy and tolerability in treating advanced colorectal cancer.

MATERIAL AND METHODS

Patients

Advanced colorectal cancer patients accepting apatinib or PD-1 inhibitors treatment (Jun. 2019-Jun. 2021) were enrolled in this program, including 23

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patients receiving apatinib and 28 patients receiving PD-1 inhibitors. Their clinical data were retrospectively analyzed. All patients understood the purpose and methods of the project, and signed informed consent. This research was approved by the ethics committee of The Fourth People's Hospital of Jinan. The registration date was June 2019, and the ethical number was LL-2019-06002.

Inclusion criteria

(1) The pathological diagnosis was deficient mismatch repair (dMMR) or microsatellite instability -high (MSI-H) mCRC; (2) Had previously received the third-line or above regimen; (3) Eastern Cooperative Oncology Group (ECOG) score ≤2 [13], with no myelosuppression and normal cardiopulmonary, liver and kidney function; (4) The lesion size could be accurately measured; (5) Expected survival time ≥ 3 months.

Exclusion criteria

(1) Diagnosed with other types of secondary malignancy at the same time; (2) Had risk of bleeding; (3) Diagnosed with intracranial psychiatric and neurological abnormalities; (4) Diagnosed with interstitial lung disease, thyroxine abnormalities, diffuse chronic hepatitis B, and human immunodeficiency virus (HIV). (5) History of immunodrugs.

Treatments

In the apatinib group, the initial dose of apatinib tablets (Jiangsu Hengrui Pharmaceutical Co., LTD., China) was 250 mg once daily, increased to 500 mg once daily according to patient tolerance and need.

In the PD-1/PD-L1 group, patients took molecular -targeted drugs and received intravenous PD-1 inhibitors at instructed dose at the same time. The antibodies included: Toripalimab (Shanghai Junshi Biomedical Technology Co., LTD., China), 240 mg/3 weeks (Q3W); Nivolumab (Bristol-Myers Squibb Company., China), 200 mg/2 weeks (Q2W); Sintilimab (Xinda Biopharmaceutical (Suzhou) Co., LTD., China), 200 mg/3 weeks (Q3W); Camrelizumab (Jiangsu Hengrui Pharmaceutical Co., LTD., China), 200 mg/3 weeks (Q3W).

Detection of rat sarcoma virus (RAS), Kirsten rat sarcoma viral oncogene homolog (KRAS) and B-type Raf kinase (BRAF) gene mutation

Colorectal cancer specimens fixed with formalin-embedded paraffin were extracted with EdFFEP DNA/RNA nucleic acid extraction reagent (Thermo Fisher, USA), and the mutations of *KRAS*, *RAS* along with *BRAF* genes in the specimens were detected by fluorescent PCR (Thermo Fisher, USA). The detection segments were *KRAS* (exon 2, exon 3, Exon 4), *RAS* (exon 2, exon 3), *BRAF* (Exon 15) using the human *KRAS/RAS/BRAF* gene mutation combined detection kit. If the signal showed obvious amplification curve and the ct value was < 26, the detection results were *KRAS, RAS* and *BRAF* gene mutants, and the rest were wild types.

Evaluation criteria for short-term efficacy

Tumors were measured with computerized tomography (CT, Siemens, Germany) or magnetic resonance imaging (MRI, Siemens, Germany) every 2-3 immunotherapy cycles. Tumor response before deterioration and before treatment initiation was analyzed on the basis of Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, containing complete remission (CR), partial remission (PR), stable disease (SD), or progressive disease (PD). ORR was the sum of CR plus PR. DCR was the sum of CR plus PR plus SD.

Observation indicators

(1) Clinical efficacy including ORR and DCR was compared in 2 groups

(2) The progression-free survival (PFS) was analyzed by help of Kaplan-Meier in 2 groups.

(3) Occurrence of adverse events was compared in 2 groups following the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (CTCAE5.0).

Follow-up

Follow-up recorded patients' side effects during treatment and blood biochemical test at reexamination, using the outpatient and inpatient medical record system and telephone calls, up to June 30, 2022.

Statistical analysis

The normalized distribution of variables was expressed in mean standard deviation (SE). The un-normalized distribution was expressed in median and extreme. Data were subjected for analysis by help of SPSS 21.0 software (IBM, Armonk, NY, USA) as well as GraphPad Prism 8.0 (GraphPad Software, Inc., San Diego, USA). The categorical variables in the baseline characteristics were assessed using Fisher's exact test. Kaplan-Meier survivorship was compared between groups by means of Log-rank test. $P<0.05$ meant statistical significance.

RESULTS

General data of patients

Demographic information of patients is shown in table 1. As seen, 28 patients accepted PD-1/PD-L1 inhibitors (56.9%) or 23 patients received apatinib (45.1%) as third-line therapy or above treatment. No differences were discovered in median age, gender, ECOG score, duration, primary lesion, primary tumor location, distant metastasis, drug history, lines of therapy took, anti-tumor history, and gene mutation between both groups ($P>0.05$).

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Short-term clinical efficacy in 2 groups

The clinical efficacy is shown in table 2. Relative to the apatinib group, the proportion of SD in patients receiving anti-PD-1 therapy presented higher (82.1% vs 47.8%) (P=0.010). No significance was discovered in the proportion of PR, PD, ORR along with DCR between 2 groups (P=0.709, P=0.080, P=0.709, P=0.080).

Table 1. General data of patients between 2 groups.

Characteristics	Total n (%)	PD-1/PD-L1 group n (%)	Apatinib group n (%)	*P*
Patient N (%)	51	28	23	
median age	54.2±11.9	54.6±11.7	53.7±12.02	0.724
Age group				0.718
<65	41(80.4)	22(78.6)	19(82.6)	
>65	10(19.6)	6(21.4)	4(17.4)	
Gender				0.304
Male	27(52.9)	13(46.4)	14(60.9)	
Female	24(47.1)	15(53.6)	9(39.1)	
ECOG score				0.702
0	21(41.2)	13(46.4)	8(34.8)	
1	22(43.1)	11(39.3)	11(47.8)	
2	8(15.7)	4(14.3)	4(17.4)	
Duration (diagnosis-allocation)				
<18 months	15(29.4)	10(35.7)	5(21.7)	
>18 months	36(70.6)	18(64.3)	18(78.3)	
Primary lesion				0.180
Colonic	28(54.9)	13(46.4)	15(65.2)	
Rectal	23(45.1)	15(53.6)	8(34.8)	
Colorectal	51(100.0)	28(100.0)	23(100.0)	
Primary tumor location				0.110
Left	39(76.5)	19(67.9)	20(87.0)	
Right	12(23.5)	9(32.1)	3(13.0)	
Left and right	51(100.0)	28(100.0)	23(100.0)	
Distant metastasis				
Hepar	38(74.5)	18(64.3)	20(87.0)	0.065
Lungs	43(84.3)	24(85.7)	19(82.6)	0.762
Peritoneum	13(25.5)	7(25.0)	6(26.1)	0.929
Drug history				
Fluorouracil	43(84.3)	24(85.7)	18(78.3)	0.487
Oxaliplatin	47(92.2)	26(92.9)	21(91.3)	0.837
Irinotecan	48(94.1)	26(92.9)	22(95.7)	0.673
Bevacizumab	40(78.4)	20(71.4)	20(87.0)	0.180
Cetuximab	20(39.2)	14(50.0)	6(26.1)	0.082
Regorafenib	9(17.6)	3(10.7)	6(26.1)	0.152
Fruquintinib	0	0	0	
Lines of therapy took				0.964
3	29(56.9)	16(57.1)	13(56.5)	
>3	22(43.1)	12(42.9)	10(43.5)	
Anti-tumor history				
Chemotherapy and medication	51(100.0)	28(100.0)	23(100.0)	1
Radiotherapy	9(17.6)	5(17.9)	4(17.4)	0.965
Surgery	45(88.2)	23(82.1)	22(95.7)	0.136
Gene mutation				0.853
RAS/BRAF wild	18(35.3)	13(46.4)	5(21.7)	
RAS mutant	14(27.5)	10(35.7)	4(17.4)	
BRAF mutant	1(1.9)	0(0.0)	1(4.3)	
Unknown	18(35.3)	5(17.9)	13(56.5)	

Abbreviations: N: number; PD-1: programmed cell death protein 1; PD-L1: programmed death ligand-1; ECOG: Eastern Cooperative Oncology Group; RAS: rat sarcoma virus; BRAF: B-type Raf kinase.

Median PFS in 2 groups

Relative to the apatinib group, the median PFS of patients receiving anti-PD-1 therapy presented longer [3.9 months (95% CI: 2.736-5.064) vs 6.4 months (95% CI: 5.527-7.273)] (P=0.0209, figure 1).

Table 2. Short-term clinical efficacy between 2 groups.

Achievement	Total n (%)	PD-1/PD-L1 (N=28) n (%)	Apatinib (N=23) n (%)	*p*
CR	0	0	0	1
PR	4(7.8)	2(7.1)	2(8.7)	0.709
SD	34(66.7)	23(82.1)	11(47.8)	0.010
PD	13(25.5)	3(10.7)	10(43.5)	0.080
ORR	4(7.8)	2(7.1)	2(8.7)	0.709
DCR	38(74.5)	25(89.3)	13(56.5)	0.080

Abbreviations: N: number; PD-1: programmed cell death protein 1; PD-L1: programmed death ligand-1; ECOG: Eastern Cooperative Oncology Group; RAS: rat sarcoma virus; BRAF: B-type Raf kinase.

Median PFS of patients with or without liver metastasis and KRAS mutation, as well as with left colon or right colon in 2 groups

Relative to the apatinib group, the median PFS of patients without liver metastases who received anti-PD-1 therapy presented longer (P<0.0001, figure. 2A). No significance was discovered in median PFS of patients with liver metastases between 2 groups (P>0.05, figure. 2B). Relative to the apatinib group, the median PFS of *KRAS* wild-type patients who received anti-PD-1 therapy presented longer (P=0.0288, figure. 2C). No difference was discovered in median PFS of *KRAS* mutant-type patients between 2 groups (P=0.1836, figure. 2D). Relative to the apatinib group, the median PFS of patients with left colon as primary site presented longer in patients accepting PD-1 blockers (P=0.0105, figure. 2E). No difference was discovered in patients with right primary site between 2 groups (P=0.8538, figure. 2F).

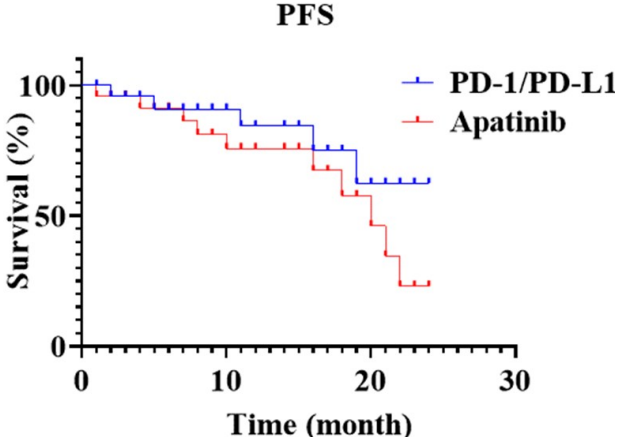

Figure 1. Kaplan-Meier analysis of median PFS between 2 groups. PFS: progression-free survival; PD-1: programmed cell death protein 1; PD-L1: programmed death ligand-1.

Adverse events in 2 groups

It was displayed in table 3 that, no differences were seen in the occurrence of adverse events containing hand-foot syndrome, hypertension, fatigue, erythema, reactive cutaneous capillary endothelial cell proliferation (RCCEP), oral mucositis,

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diarrhea, anorexia, hepatic insufficiency, hyperthyrea, hypothyrea, thrombocytopenia, neutropenia, trachyphonia, colon perforation and high myocardial enzymes levels (P>0.05). Besides, no significance was observed in the occurrence of grade > 3 adverse events between 2 groups (P>0.05).

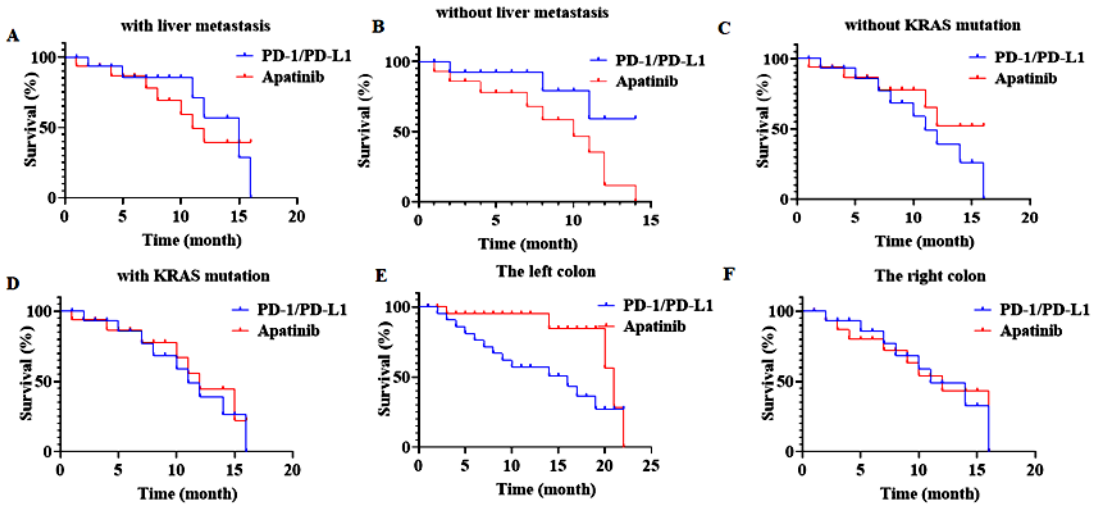

Figure 2. Kaplan-Meier analysis of median PFS of patients with or without liver metastasis and KRAS mutation, as well as with left colon or right colon between the 2 groups. PD-1: programmed cell death protein 1; PD-L1: programmed death ligand-1; KRAS: Kirsten rat sarcoma viral oncogene homolog.

Table 3. Occurrence of adverse events between 2 groups.

	All			Grade > 3		
	PD-1/PD-L1 (n = 28)	Apatinib (n = 23)	P	PD-1/PD-L1 (n = 28)	Apatinib (n = 23)	F
N (%)	28(100)	23(100)	1	3(10.7)	5(21.7)	0.281
Hand-foot syndrome	11(39.3)	10(43.5)	0.95	0	1(4.3)	0.265
Hypertension	10(35.7)	9(39.1)	0.193	0	0	1
Fatigue	7(25.0)	7(30.4)	0.665	0	0	1
Erytha	5(17.8)	4(17.30)	0.404	0	1(4.3)	0.265
RCCEP	11(39.3)	9(39.1)	0.762	0	0	1
Oral mucositis	2(7.1)	1(4.3)	0.238	0	0	1
Diarrhea	2(7.1)	0	0.425	1(3.6)	0	0.36
Anorexia	6(21.4)	3(30)	0.434	0	0	1
Hepatic insufficiency	12(42.8)	12(52.2)	0.575	2(7.1)	1(4.3)	0.673
Hyperthyrea	1(3.6)	0	0.36	0	0	1
Hypothyrea	8(28.5)	6(26.1)	0.984	0	0	1
Thrombocytopenia	5(17.8)	2(8.6)	0.493	0	0	1
Neutropenia	2(7.1)	1(4.3)	0.424	0	0	1
Trachyphonia	1(3.6)	0	0.36	0	0	1
Colon perforation	1(3.6)	2(8.6)	0.529	0	1(4.3)	0.265
High lipase levels	0	0	1	0	0	1
Interstitial pneumonia	0	0	1	0	0	1
High myocardial enzymes levels	0	1(4.3)	0.265	0	1(43)	0.265

Abbreviations: N: number; PD-1: programmed cell death protein 1; PD-L1: programmed death ligand-1; RCCEP: reactive cutaneous capillary endothelial proliferation.

DISCUSSION

Immunotherapy is a highly promising approach for treating advanced colorectal cancer. Existing studies have shown that immunotherapy based on PD-1 blockers has been authorized for treating MSI-H/dMMR mCRC cancer patients. Nevertheless, the immune response of MSI-H/dMMR mCRC cancer patients is not sufficient to support a single ICIs treatment [14, 15].

Apatinib strongly inhibits tumor progression by selectively repressing vascular endothelial growth factor receptor 2 (VEGFR2) activity [16]. Previous research has indicated that apatinib monotherapy demonstrates encouraging efficacy with manageable toxicity in chemotherapy-refractory mCRC [17]. Preclinical studies have displayed that apatinib acts synergistically with PD-1 inhibitors in mCRC models [18]. No studies comparing the efficacy of apatinib and PD-1 blockers have been currently documented.

The results of our study as shown in table 2 revealed that relative to the apatinib group, the proportion of SD in patients receiving anti-PD-1 therapy presented higher. Consistent with our findings, Zhang et al discovered that PD-1/PD-L1 blockers had encouraging clinical benefits in

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dMMR-MSI-H mCRC treatment [19]. In our study, figure 1 displayed that relative to the apatinib group, the median PFS of patients accepting PD-1 blockers presented better. Consistently, it has been reported that the combined use of apatinib and anti-PD-1 antibody had a longer PFS of MSS mCRC patients [20]. Rao *et al*. discovered that PD-1/PD-L1 blockers exhibited favorable survival in terms of survival in advanced hepatocellular carcinoma patients [21]. Studies have shown that immune escape of colorectal cancer may be linked to the pathway of PD-L1/PD-1. PD-L1 can transmit inhibitory signals downstream after binding with the receptor PD-1, and finally realize the inhibitory effect on the differentiation, maturation and proliferation of lymphocytes [22]. PD-1/PD-L1 blockers elevate $CD8^+$T expression, which is linked to better outcomes in dMMR/MSI-H mCRC patients [23].

Results shown in figure 2 suggested that in patients with no liver metastasis, the median PFS of patients accepting PD-1 blockers was superior to those were treated with apatinib. This suggested that the therapeutic regimen of PD-1/PD-L1 repressors could be beneficial in advanced colorectal cancer patients without liver metastasis. Similarly, Sun et al. pointed out those PD-1/PD-L1 repressors were considered to be the preferred treatment regimen for advanced or metastatic cancer patients without liver metastasis [24]. *KRAS* is considered to be the most commonly mutated gene in tumors, expressed in about half of the mCRC patients, occurs more frequently in the right colon and causes highly aggressive tumors and poor prognosis [25, 26]. Meanwhile, Figure 2 also showed that PD-1/PD-L1 was more effective for KRAS wild-type mCRC patients with left primary site, which was in line with previous literatures [27]. These findings implied that the PD-1/PD-L1 regimen was relatively more effective for patients with KRAS wild-type or left primary tumors.

Moreover, Table 3 displayed that compared to the apatinib group, the occurrence of adverse events in patients accepting PD-1 blockers was generally lower. Consistent with our data, Gou *et al.* indicated that PD-1 inhibitors plus apatinib exhibited certain safety in metastatic gastric cancer patients [28].

This research has several shortcomings. First of all, this research was only evaluated in the Chinese population, and further studies in other populations are required. Besides, the study was limited in duration and did not further explore the effects of chemotherapy on long-term survival of patients. Therefore, further studies should be performed in the future.

In summary, our work demonstrates that PD-1/PD-L1 blockers possess certain clinical efficacy and tolerability in treating advanced colorectal cancer.

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Conflicts of interests: The authors declare that they have no competing interests.

Ethical consideration: Written informed consent was obtained from all patients included in the study. The study protocol was approved by the Ethics Committee of The Fourth People's Hospital of Jinan. The registration date was June 2019, and the ethical number was LL-2019-06002.

Author contribution: H.G. and Q.Z.: conception and design, or analysis and interpretation of data. M.Z.: drafting the article or revising it critically for important intellectual content. H.G. and X.S.: final approval of the version to be published.

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