Efficacy of regorafenib combined with PD-1 inhibitors in elderly patients with advanced metastatic colorectal cancer

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Abstract

Objective: This is the first trial that wants to investigate the treatment patterns, clinical outcomes and prognostic factors of regorafenib plus PD-1 inhibitors therapy to Chinese elderly patients with advanced colorectal cancer.

Methods: A cohort of metastatic colorectal cancer patients with 60 years or older received treatment of regorafenib combined with PD-1 inhibitors was included in our analysis. The endpoints included overall survival (OS), progression free survival (PFS), and prognostic factors.

Results: In total, 24 patients were enrolled. The median age was 68 years; 62.5% were female. The median OS and PFS were 15.03 months (95% CI 7.0-23.0) and 4.0 months (95% CI 1.8-6.2), respectively. The objective response rate was 8.3% and disease control rate was 70.8%. When compared with PFS and OS in different initial daily doses group of regorafenib (such as 40, 80, 120 or 160 mg), we concluded that there were no significantly difference between these groups. And similar results were found in final daily doses groups. However, in terms of final daily doses, it showed a trend toward better PFS in > 80mg group compared to $\leq$ 80 mg group (median PFS was 10.0 months in >80mg group versus 3.5 months in $\leq$ 80mg group) . Patients with previous treated with regorafenib had longer median PFS than those without it (6.3 versus 2.8 months).

Conclusions: This real-world evidence confirms that Chinese elderly patients with advanced colorectal cancer may benefit from treatment of regorafenib combined with PD-1 inhibitors, similarly with this combination therapy strategies in all age patients.

Introduction

Colorectal cancer (CRC), as one of the most prevalent types of cancer in China, is still a leading cause of cancer related mortality^[1]. Based on a multicenter retrospective study from China, the median age of metastatic CRC (mCRC) cases at diagnosis was 58 years, and almost half mCRC patients were age 60 year or older^[2]. Therapeutic decisions involving elderly patients are a serious issue in oncology, because this group is characterized by a higher incidence of significant co-morbidities (cardiovascular disorders, metabolic disorders and liver disorders), decreased regenerative capacity of bone marrow (higher incidence and intensity of hematological complications of chemotherapy) as well as worse general performance^[3]. Making all anticancer drugs available to elderly patients with mCRC is important to achieve the maximal benefit for long-term survival and maintain their quality of life.

Regorafenib, an oral small-molecule multikinase inhibitor, has demonstrated significantly improved survival in two randomized, double-blind, placebo-controlled phase 3 trials (CORRECT and CONCUR)^[4, 5]. Therefore, it is recommended as a standard third- or later-line therapy for refractory metastatic colorectal cancer (mCRC) by Chinese Society of Clinical Oncology (CSCO) guideline and other international guidelines^[6-8]. Immune checkpoint inhibitors have showed promising therapeutic outcomes in advanced

colorectal cancer with bearing mismatch repair-deficiency/microsatellite instability-high (dMMR/MSI-H) tumors in recent years^[7–10]. However, patients with mismatch repair-proficient/microsatellite stable (pMMR/MSS) colorectal cancer, who account for 95% of advanced colorectal cancer, could not benefit from this approach^[11].

Recent data suggest a possible synergic effect between regorafenib and immune checkpoint inhibitors, as has been shown in REGONIVO trial, which reported a response rate of 33% and median progression-free survival of up to 7.9 months in a cohort of 24 Japanese patients with MSS treatment-refractory metastatic colorectal cancers^[12]. In REGOTORI trial, which produced the similar results, the objective response rate (ORR) was 15.2% and median overall survival was 15.5 months in patients with refractory pMMR/MSS mCRC^[13]. However, further research should be conducted to address this therapeutic strategy applying on elderly Chinese patients. This study aimed to investigate the treatment patterns, clinical outcomes and prognostic factors of regorafenib plus PD-1 inhibitors therapy to Chinese elderly patients with advanced colorectal cancer.

Materials And Methods

Study population

We retrospectively reviewed the patients treated with regorafenib plus PD-1 inhibitors for unresectable mCRC in Henan Cancer Hospital (China) from January 2019 to January 2021.

Patients were eligible for participation if they were 60 years of age or older and had histologically or cytologically confirmed mCRC. Patients were required to have failed to respond to all the available systemic agents, including fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab, and cetuximab when applicable; and received at least one cycle of regorafenib plus PD-1 inhibitors. Besides, the medical record should be complete and legible. Patients who met any of the following criteria at the time of screening will be excluded: other histological types instead of adenocarcinoma of the colon or rectum; at stage $\geq$ III according to TNM staging system; Eastern Cooperative Oncology Group (ECOG) performance status of 3 or more. This work was approved by the ethics committee of Henan Cancer Hospital (Approval number: 2020103005). Patients were followed up by telephone questionnaires every three months until death or trial data cutoff date (July 31, 2021).

Treatment and evaluation of therapeutic efficacy

Regorafenib was prescribed at 40, 80, 120 or 160 mg daily from day 1 to day 21 of each 28-day cycle. Depending on the patient's tolerability, the daily dose was allowed at the discretion of treating physicians. All patients received immune checkpoint inhibitors at the first day of regorafenib treatment, according to recommended dose: nivolumab 240 mg every 2 weeks, camrelizumab 200 mg every 2 weeks, sintilimab 200 mg every 3 weeks, toripalimab 240 mg every 3 weeks, pembrolizumab 200 mg every 3 weeks, tislelizumab 200 mg every 3 weeks.

Demographics, disease features and therapy information of patients were documented at baseline examinations. Tumour response was evaluated every 2 or 3-cycle treatment of PD-1 inhibitors, according to the Response Evaluation Criteria in Solid Tumour (RECIST) Version 1.1.

The primary endpoint was overall survival (OS), which was defined as the duration from treatment to death as a result of any cause. Other endpoints included progression-free survival (PFS), disease-control rate (DCR), objective response rate (ORR). Progression-free survival (PFS) was defined as the duration from treatment to first documented disease progression, or death. The objective response rate (ORR) was defined as complete response (CR) + partial response (PR) and the disease-control rate (DCR) was defined as CR + PR + stable disease (SD). Adverse Events were graded and analysed according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03.

Statistical analysis

All statistical analysis was performed using IBM SPSS Statistics for Windows Version 25.0 (IBM Corp., Armonk, New York, USA). Quantitative data were displayed as mean with standard deviation (SD), and qualitative data were expressed as number with percentage [No. (%)]. Survival data were analysed using the Kaplan–Meier method and compared by log-rank test. *P* value < 0.05 was considered as statistically significant.

Results

Study participants' clinical characteristics

At a median follow-up of 16.2 months, a total of 24 patients were enrolled. 9 of these patients (37.5%) were male; Median age was 68.0 years. The primary tumour site was the right-side colon in 33.3% (n = 8) of patients, the left-side colon in 29.2% (n = 7) and the rectum in 37.5% (n = 9). The main metastatic sites were the liver and/or lung (91.7%), only lung (25.0%), only liver (29.2%), distal lymph nodes (45.8%) and peritoneum (16.7%). Other baseline characteristics of the patients are presented in Table 1.

Table 1
Baseline demographic and clinical characteristics of 24 mCRC patients.

Characteristics	N = 24 patients n (%)
Age (year)	
Median (range)	68
Gender	
Male	9 (37.5%)
Female	15 (62.5%)
ECOG performance status	
0	5 (20.8%)
1	16 (66.7%)
2	3 (12.5%)
Primary tumor location	
Colon	15 (62.5%)
Right-side	8 (33.3%)
Left-side	7 (29.2%)
Rectum	9 (37.5%)
Whether the primary tumor is resected	
Resected	21 (87.5%)
Not resected	3 (12.5%)
Type of metastasis	
With liver or lung metastasis	22 (91.7%)
With only liver metastasis	6(25.0%)
With only lung metastasis	7(29.2%)
With liver and lung metastasis	9(37.5%)
With bone metastasis	3(12.5%)
With brain metastasis	1 (4.2%)
With distant lymph nodes metastasis	11 (45.8%)

Note: Abbreviations: mCRC, metastatic colorectal cancer; pMMR, mismatch repair-proficient; MSS, microsatellite stable; dMMR, mismatch repair-deficiency; MSI-H, microsatellite instability-high.

Characteristics	N = 24 patients n (%)
With peritoneum metastasis	4 (16.7%)
With other organs metastasis	2 (8.3%)
Previous lines of chemotherapy	
Two lines	13 (54.2%)
Three or more lines	11 (45.8%)
Previous targeted therapy	
Bevacizumab	15 (62.5%)
Cetuximab	3 (12.5%)
With Bevacizumab and Cetuximab	3 (12.5%)
Without previous targeted therapy	6 (25.0%)
Combination immunization agents	
Sintilimab	12 (50.0%)
Carrelizumab	6 (25.0%)
Nivolumab	2 (8.3%)
Toripalimab	2 (8.3%)
Pembrolizumab	1 (4.2%)
Tislelizumab	1 (4.2%)
Whether previous exposure to regorafenib	
Exposure to regorafenib	8 (33.3%)
No exposure to regorafenib	16 (66.7%)
Whether with the local treatment	
With the local treatment	3 (12.5%)
Without the local treatment	21 (87.5%)
Gene mutation status	
RAS and BRAF wild-type	5 (20.8%)
K-RAS mutant	16 (66.7%)

Note: Abbreviations: mCRC, metastatic colorectal cancer; pMMR, mismatch repair-proficient; MSS, microsatellite stable; dMMR, mismatch repair-deficiency; MSI-H, microsatellite instability-high.

Characteristics	N = 24 patients n (%)
BRAF mutant	1 (4.2%)
Unknow	2 (8.3%)
MMR or MSI status	
pMMR or MSS	19 (79.2%)
dMMR or MSI-H	1 (4.2%)
Unknown	4 (16.7%)
Note: Abbreviations: mCRC, metastatic colorectal cancer; pMMR, mismatch repair-proficient; MSS, microsatellite stable; dMMR, mismatch repair-deficiency; MSI-H, microsatellite instability-high.	

Regorafenib plus PD-1 inhibitors were given to 13 patients (54.2%) in third-line treatment, and 11 patients (45.8%) in fourth-line treatment and beyond. The most common PD-1 inhibitors was Sintilimab (50.0%), followed by carrelizumab (25.0%), nivolumab (8.3%), toripalimab 2 (8.3%), pembrolizumab (4.2%) and tislelizumab (4.2%). There were 8 patients (33.3%) previously received regorafenib therapy and no one having taken PD-1 inhibitors before entering this trial. MSI/MMR status data were available from 20 patients (83.3%). Of these, only one patient (4.2%) had an MSI-high tumor, and the remaining 19 patients (79.2%) were MSS or MMR proficient.

Primary efficacy

The median OS and median PFS were 15.0 months(95% CI, 7.0–23.0) and 4.0 months (95% CI, 1.8–6.2), respectively (Fig. 1A&B). Overall, the ORR and DCR were 8.3% and 70.8%, respectively. CR, PR, SD, PD and patients without tumor response assessment were observed in 0, 2(8.3%), 15 (62.5%), 4 (16.7%), 3 (12.5%) patients, respectively.

Specifically, patients with previous treated with regorafenib had longer median PFS than those without it. Median PFS was 6.3 months (95% CI, 5.6-7.0) in the former and 2.8 months (95% CI, 1.9–3.7) in the latter ($P = 0.445$, Fig. 1C). No significant associations for PFS could be seen in whether previously treated with bevacizumab ($P = 0.874$), K-RAS status ($P = 0.150$), tumor sites ($P = 0.321$) and any kind of PD-1 inhibitors ($P = 0.477$).

16.6% of patients (n = 4) started regorafenib at daily doses of 120 mg, 79.2% of patients (n = 19) started at 80 mg and 4.2% of patients (n = 1) started at 40 mg. There were 12.5%, 70.8%, 4.2% and 12.5% of patients received the final daily doses of 40, 80, 120 and 160 mg, respectively. Dose modifications were performed in overall 9 patients (37.5%), including dose reduction in 5 patients (20.8%) and dose escalation in 4 patients (16.7%). When compared with PFS and OS in high initial daily doses group (120 and 160 mg) and low initial daily doses group (40 and 80 mg), we concluded that there were no significantly difference between the two groups (median PFS, $P = 0.643$; median OS, $P = 0.279$). However, median PFS and OS in final high daily doses group (> 80 mg) had better trends than those in final low

daily doses group (≤ 80 mg). Median PFS was increased in final high daily doses group (10.0 months) vs (3.5 months) with final low daily doses group (Fig. 1D). Median OS was also increased in final > 80 mg group (NR) versus in final ≤ 80 mg group (15.0 months).

Safety

5 patients had a dose reduction due to adverse events, hand-foot skin reaction in 3 patients, hypertension in 1 patient, proteinuria in 1 patient. The most common adverse events were hand-foot skin reaction, fatigue, hypertension, diarrhea. The grade 3 to 4 adverse events occurred in 5 patients (20.8%). The most common grade 3 to 4 events were hand-foot skin reaction, hypertension and oral mucositis.

Discussion

As the majority of CRC cases display a molecular MSS/pMMR profile, it is particularly meaningful to investigate the clinical applications of adaptive immune or combination regimens in MSS CRC patients. Several studies have shown that the combination regimen using regorafenib combined with PD-1 inhibitors has promising efficacy for those patients^[12–18]. The highest ORR which can be seen in REGONIVO study, was 33%; and the median OS from REGOTORI was up to 15.5 months. However, there is a lack of clear evidence regarding real world effects of this therapeutic strategy, especially in elderly Chinese patients.

In this single-center, retrospective study involving Chinese elderly patients with refractory advanced colorectal cancer, the median age of patients enrolled in our study is 68 years, which is older than that in most trials conducting with regorafenib or regorafenib plus PD-1 inhibitors (53.0 to 61.3 years)^[4, 5, 12, 14, 15]. Notably, the reported median OS of 15.03 months was comparable to those reported in REGOTORI (15.5 months)^[13]. The combination using regorafenib plus PD-1 inhibitors seemed to achieve a better OS and ORR (8.3%) than regorafenib alone (ORR 1–4%; OS 6.4–8.8 months) for patients with mCRC^[4, 5]. Although the combination regimen yields a response rate of less than 10%, which lower than those reported in REGOTORI (15.2%)^[13] and REGONIVO (36.0%)^[12], more than 70% of patients (70.8%) in our study achieved disease control, which was superior to the results of single-agent regorafenib, and similar to those from another China trial^[4, 5, 14]. Hence, there is a possible reason that patients achieved higher DCR resulted in better OS in our trial. Overall, these results showed that it was worth to be recommended for regorafenib plus PD-1 inhibitors for elderly patients with mCRC, especially in patients with a molecular MSS/pMMR profile.

Further analyses of effectiveness in our study showed that there were no obvious correlation for survival between patients only had liver metastasis and lung metastasis ($P > 0.05$). In addition, PFS were similar for patients with KRAS wild-type versus mutant, left- versus right-sided tumours, and among various types of PD-1 inhibitors. However, patients with previous treated with regorafenib had longer PFS than those without it (6.30 months versus 2.80 months, $P > 0.05$). Several reports showed that regorafenib modulated immuno-suppressive tumor microenvironment by blocking VEGFRs, TIE2, and CSF-1R,

RET/Src axis signal pathways, and increased intratumoral CD45⁺ leukocytes, CD8⁺ T cells, which would enhance anti-tumor immunity when using regorafenib alone and plus various immunotherapies^[19–21]. This could be why patients who had previously received regorafenib obtained longer PFS. Further resources and research should be conducted to address time of administration for regorafenib plus PD-1 inhibitors.

We noticed that most patients in our cohort started at the lower dose of regorafenib. All were at the doses of less than 120mg and patients started at the dose of ≤ 80 mg accounted for 83.4%. During follow-up, 4 patients received higher dose and 5 patients had dose reduction. Consequently, the number of patients received less than 80 mg doses stayed the same with those in baseline; whereas 4 patients (16.7%) raised the doses up to 120mg or 160mg. When compared with PFS and OS in different initial daily doses group of regorafenib (≤ 80 versus > 80 mg), we concluded that there were no significant difference between these groups. And similar results were found in final daily doses groups. However, it showed a trend toward better PFS in patients with final daily doses > 80 mg group compared to ≤ 80 mg group (median PFS was 10.0 months in > 80 mg group versus 3.5 months in ≤ 80 mg). Considering the safety and tolerability profile of regorafenib, we argue that it should be started with a lower dose for regorafenib and adjusted it until the maximum tolerable dose was reached, by periodic follow-up and communication in time between nurse and patients. This strategy could contribute to enhance the tolerability and improve adherence, and reduce the risk of adverse events from regorafenib and/or PD-1 inhibitors.

The limitations of our study include its retrospective nature, the inadequate data on toxicity evaluation, the small sample size, and the short median follow-up. Besides, there were 4 PD-1 inhibitors just approved in China but no other countries, which means these therapeutic drugs not available to other countries. However, the results may provide a clearer picture of the efficacy and safety of regorafenib plus PD-1 inhibitors in elderly Chinese patients with mCRC.

To our knowledge, this is the first paper describing the detailed information of regorafenib plus PD-1 inhibitors in elderly Chinese patients with mCRC in real-world settings. This real-world evidence confirms that Chinese elderly patients with advanced colorectal cancer can benefit from treatment of regorafenib combined with PD-1 inhibitors, similarly with this combination therapy strategies in all age patients. However, further larger cohorts research should investigate whether the PFS advantage in high dose group could eventually lead to improved OS outcomes. Besides, considering the quality of life, closely monitoring and management for adverse drug events are needed.

Declarations

Ethics approval and consent to participate

This work was approved by the ethical committee of Henan Cancer Hospital (Approval number: 2020103005). All subjects signed their informed consents before treatments. All methods were performed in accordance with the relevant guidelines and regulations.

Consent for publication

Not applicable

Availability of data and materials

The datasets presented in this article are not readily available because of Chinese regulations and conditions for informed consent. Requests to access the dataset should be directed to Beibei Chan, zlyyichenbb1429@zzu.edu.cn.

Competing interests

Conflicts of Interest: The authors declare no conflict of interest.

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Authors' contributions

Beibei Chen is expected to have made substantial contributions to the conception and designed of the work, together drafted it. Huichen Zhao, Jinxi Huang, Huifang Lv, Weifeng Xu were responsible for data collection. Jing Zhao, Yunduan He, Saiqi Wang were responsible for statistical analysis and making tables and figures. Caiyun Nie, Jianzheng Wang revised the manuscript. Xiaobing Chen was in charge of the protocol and approved the submitted version. All authors had reviewed the manuscript.

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Figures

Figure 1

Kaplan–Meier survival curves. PFS of 21 evaluable patients (A). OS of the whole cohort (B). PFS for patients with or without previous exposure to regorafenib (C). PFS for patients with various final dose level (D).