Postprint: Clinical Efficacy and Safety of PD-1 Inhibitor Plus Fruquintinib Versus Fruquintinib Monotherapy as Later-Line Treatment for Metastatic Colorectal Cancer

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Date: 2023-01-09T00:00:00+00:00

Abstract

Background: Colorectal cancer has a high incidence rate. Metastatic colorectal cancer (mCRC) has entered a new era of targeted and immunotherapy. Currently, studies on the efficacy and safety of PD-1 inhibitors combined with fruquintinib versus fruquintinib alone are rarely reported.

Objective: To observe the efficacy and adverse reactions of fruquintinib combined with PD-1 inhibitors in later-line treatment of third-line and beyond metastatic colorectal cancer.

Methods: Clinical data of 75 patients with metastatic colorectal cancer admitted to our hospital from June 2020 to March 2022 were collected for retrospective analysis. Patients were divided into a fruquintinib group (n=28) and a PD-1 inhibitor combined with fruquintinib group (n=47) based on different treatment regimens. The main study indicators were objective response rate (ORR), disease control rate (DCR), median progression-free survival (PFS), and adverse reactions.

Results: As of the last follow-up, the ORR of the monotherapy group and the combination group were 7.1% and 14.9%, respectively, with no statistically significant difference (P=0.528). The DCR were 67.9% and 89.4%, respectively, with a statistically significant difference between the two groups (P=0.021). The median PFS time was 4.5 months (95% CI: 3.0-6.0) in the monotherapy group and 6.4 months (95% CI: 5.3-7.5) in the combination group, with a statistically significant difference in PFS between the two groups (P=0.019). Additionally, the median survival time of different types of PD-1 inhibitors was analyzed, and the results suggested no significant difference in PFS between fruquintinib

combined with different types of PD-1 inhibitors (P=0.361). The adverse reactions in both groups were mainly grade 1-2. Compared with the monotherapy group, the incidence of hypothyroidism was significantly higher in the combination group (P=0.043). Besides, there was no statistically significant difference in the incidence of other adverse reactions between the two groups (P>0.05).

Conclusion: Compared with fruquintinib monotherapy, PD-1 inhibitors combined with fruquintinib prolongs the survival of patients with metastatic colorectal cancer and has a low incidence of severe adverse reactions, representing a treatment regimen with good efficacy and high safety.

Full Text

Efficacy and Safety of PD-1 Inhibitor Plus Fruquintinib Versus Fruquintinib Monotherapy as Third-Line and Above Treatment for Metastatic Colorectal Cancer

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Funding: Henan Provincial Medical Science and Technology Joint Project "DUSP2 Involvement in Cetuximab Resistance in Colon Cancer Through Regulation of the HSP27/IGF-2 Signaling Pathway" (Project No.: SBGJ2018008)

Abstract

Background: Colorectal cancer carries a high disease burden, and metastatic colorectal cancer (mCRC) has entered a new era of targeted immunotherapy. However, studies comparing the efficacy and safety of PD-1 inhibitors combined with fruquintinib versus fruquintinib monotherapy remain scarce.

Objective: To evaluate the clinical efficacy and adverse effects of fruquintinib combined with PD-1 inhibitors as third-line or later therapy for mCRC.

Methods: We retrospectively analyzed clinical data from 75 patients with metastatic colorectal cancer treated at our institution between June 2020 and March 2022. Patients were divided into two groups based on treatment regimen: a fruquintinib monotherapy group (n=28) and a PD-1 inhibitor plus fruquintinib combination group (n=47). The primary endpoints were objective response rate (ORR), disease control rate (DCR), median progression-free survival (mPFS), and adverse events.

Results: At the final follow-up, ORR was 7.1% in the monotherapy group versus 14.9% in the combination group, with no statistically significant difference (P=0.528). However, DCR was significantly higher in the combination group (89.4% vs. 67.9%, P=0.021). The median PFS was 4.5 months (95% CI: 3.0–6.0) for monotherapy and 6.4 months (95% CI: 5.3–7.5) for combination therapy, with the difference reaching statistical significance (P=0.019). Subgroup analysis revealed no significant difference in PFS among different PD-1 inhibitor types used in combination with fruquintinib (P=0.361). Adverse reactions in both groups were predominantly grade 1–2. Notably, the incidence of hypothyroidism was significantly higher in the combination group compared with the monotherapy group (P=0.043), while other adverse events showed no significant between-group differences (P>0.05).

Conclusion: Compared with fruquintinib monotherapy, the combination of PD-1 inhibitor and fruquintinib extends survival in patients with metastatic colorectal cancer while maintaining a favorable safety profile with low rates of severe adverse events. This represents an effective and well-tolerated treatment option for third-line and beyond therapy.

Keywords: fruquintinib; PD-1 inhibitor; metastatic colorectal cancer; efficacy; safety

Introduction

Colorectal cancer (CRC) ranks among the most common malignant tumors worldwide, representing the third most frequently diagnosed cancer and the second leading cause of cancer-related mortality [1]. In China, its incidence continues to rise annually. While surgical resection offers a curative option for early-stage disease, many patients present with metastases at initial diagnosis, precluding surgical intervention [2]. Currently, fluorouracil (5-FU) combined with oxaliplatin and irinotecan-based chemotherapy, plus cetuximab or bevacizumab targeted therapy, constitutes the standard first- and second-line regimen for metastatic colorectal cancer (mCRC) [3]. Although this approach improves clinical outcomes, many patients eventually develop intolerance to chemotherapy toxicity or tumor resistance, leading to recurrence and progression. Effective treatment options for later-line mCRC remain limited, and patients who have undergone three or more lines of therapy often experience substantial physical decline, necessitating exploration of less toxic yet effective therapeutic strategies. Current guidelines recommend regorafenib, fruquintinib, and TAS-102 as standard third-line treatments [4].

Malignant tumors require vascular support for continued growth [5]. Fruquintinib is an oral tyrosine kinase inhibitor that primarily targets vascular endothelial growth factor receptors 1, 2, and 3 (VEGFR1-3) on endothelial cells, effectively suppressing tumor angiogenesis as a small-molecule agent [6]. Multiple studies [7-9] have demonstrated that fruquintinib monotherapy significantly pro-

longs survival in advanced colorectal cancer patients. Beyond targeted therapy, immunotherapy has emerged as a promising approach for advanced CRC [10], exemplified by programmed death receptor-1 (PD-1)/programmed death ligand-1 (PD-L1) inhibitors. However, single-agent immunotherapy shows limited efficacy, particularly in microsatellite stable (MSS) mCRC patients who constitute approximately 95% of cases [11]. Recent research [12] suggests that combining fruquintinib with PD-1 inhibitors synergistically enhances tumor suppression by fostering a more robust anti-tumor immune microenvironment. Nevertheless, clinical data comparing PD-1 inhibitor plus fruquintinib versus fruquintinib alone remain scarce. This study investigates the efficacy and safety of this combination regimen to provide evidence for later-line mCRC treatment.

1.1 Study Subjects

We retrospectively collected clinical data from mCRC patients who received fruquintinib plus PD-1 inhibitor or fruquintinib monotherapy at The First Affiliated Hospital of Zhengzhou University between June 2020 and March 2022. Patients were stratified into two groups: a fruquintinib monotherapy group (n=28) and a combination therapy group (n=47).

Inclusion criteria (all required): (1) age 18–75 years; (2) histologically and cytologically confirmed CRC with radiologically documented metastases; (3) progression after prior standard chemotherapy and failure of second-line therapy; (4) ECOG performance status $ $1; (5) at least one measurable target lesion; (6) estimated life expectancy >3 months.

Exclusion criteria (any of the following): (1) concurrent other primary malignancies; (2) hypersensitivity to fruquintinib or PD-1 inhibitors; (3) uncontrolled hypertension or severe cardiac disease; (4) history of active autoimmune disease; (5) poor compliance.

1.2 Treatment Methods

Fruquintinib monotherapy group: Oral fruquintinib 5 mg once daily for 3 weeks, followed by a 1-week break, constituting a 28-day treatment cycle. Dose reduction to 3–4 mg was permitted for poor tolerance; treatment discontinuation if intolerance persisted.

Combination therapy group: Fruquintinib was administered identically to the monotherapy group. PD-1 inhibitors were given as intravenous infusions on day 1 of each 21-day cycle: camrelizumab, sintilimab, or pembrolizumab 200 mg, or toripalimab 240 mg. Both fruquintinib and PD-1 inhibitors were continued until disease progression, intolerable toxicity, or patient withdrawal.

1.3 Efficacy and Safety Evaluation

Treatment response was assessed by CT every two treatment cycles according to RECIST 1.1 criteria, categorized as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). Progression-free survival (PFS) was defined as the interval from treatment initiation to first documented tumor progression or death from any cause. Objective response rate (ORR) was calculated as (CR+PR)/total$×100×$100%. Toxicity was graded using the National Cancer Institute' s Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

1.5 Statistical Analysis

Data analysis was performed using SPSS 26.0 and GraphPad Prism 8.4. The chi-square test or Fisher' s exact test was used to compare ORR, DCR, and toxicity incidence. Kaplan-Meier survival analysis was employed for PFS, with survival curves generated and compared using the log-rank test. Statistical significance was set at $P<0.05$.

2.1 Baseline Characteristics

A total of 75 patients were enrolled, including 42 males (56.0%) and 33 females (44.0%). The combination group comprised 47 patients receiving fruquintinib plus PD-1 inhibitor (sintilimab n=19, camrelizumab n=17, toripalimab n=8, pembrolizumab n=3), while 28 patients received fruquintinib monotherapy. The median age was 53 years (range 30–70) in the combination group and 55 years (range 34–75) in the monotherapy group. Univariate chi-square analysis revealed no significant differences between groups in age, gender, ECOG performance status, primary tumor location, pathological differentiation, distant metastasis, or gene mutation status (all $P>0.05$). Baseline characteristics are summarized in .

2.2 Treatment Efficacy

No complete responses were observed in either group. In the combination group (n=47), 7 patients (14.9%) achieved partial response, 35 (74.5%) had stable disease, and 5 (10.6%) experienced progressive disease, yielding an ORR of 14.9% and DCR of 89.4%. In the monotherapy group (n=28), 2 patients (7.1%) achieved partial response, 17 (60.7%) had stable disease, and 9 (32.1%) experienced progressive disease, yielding an ORR of 7.1% and DCR of 67.9%. The between-group difference in ORR was not statistically significant (^{2}=0.399, P=0.528), whereas DCR differed significantly (^{2}=5.345, P=0.021). Detailed efficacy data are presented in .

2.3 Survival Analysis

Follow-up data were censored on May 31, 2022. The median follow-up duration was 10.5 months (range 8.23–10.37) in the combination group and 8.5 months in the monotherapy group. The median PFS was 6.4 months (95% CI: 5.3–7.5) for the combination group versus 4.5 months (95% CI: 3.0–6.0) for the monotherapy group, with the difference being statistically significant (P=0.019) [Figure 1: see original paper]A. Additionally, we analyzed PFS across different PD-1 inhibitor types in the combination group and found no significant differences (P=0.361) [Figure 1: see original paper]B.

2.4 Adverse Events

All adverse events during treatment were collected and graded for both groups . Toxicities were predominantly grade 1-2, with the most common being hypertension, fatigue, leukopenia, thrombocytopenia, anemia, hepatic dysfunction, proteinuria, and hand-foot syndrome. Grade $ $3 adverse events were uncommon. Compared with monotherapy, the combination group showed a significantly higher incidence of hypothyroidism (P=0.043), which was manageable with supportive care and did not compromise treatment continuation. No significant differences were observed in other adverse events (P>0.05). In the combination group, 2 patients (4.3%) discontinued therapy due to immune-related pneumonitis, while no treatment discontinuations due to adverse events occurred in the monotherapy group. No treatment-related deaths were reported in either group.

Discussion

Recent advances in multidisciplinary treatment have improved colorectal cancer outcomes. However, CRC remains highly prevalent and often insidious, with approximately 50% of patients developing distant metastases—the primary cause of mortality [13]. The advent of genetic testing has accelerated precision medicine in CRC, making targeted therapy and immunotherapy promising options for patients failing standard chemotherapy. While anti-angiogenic agents improve survival, resistance inevitably develops after prolonged effective treatment. Immunotherapy has achieved remarkable success in various malignancies including lung and liver cancers, emerging as a major research focus. In advanced CRC, single-agent immunotherapy provides durable clinical benefit only in the approximately 5% of patients with dMMR/MSI-H status, whereas the remaining 95% with MSS/pMMR disease show poor response [14-15]. Consequently, multiple trials investigating anti-angiogenic drugs combined with immunotherapy for mCRC have demonstrated significant survival prolongation [16-18].

Our retrospective analysis of 47 patients receiving immunotherapy plus fruquintinib versus 28 receiving fruquintinib alone as third-line or later therapy for mCRC revealed median PFS of 4.5 months and DCR of 67.9% with monotherapy, compared with 6.4 months and 89.4% with combination therapy, respectively—both favoring the combination approach. These findings likely reflect dual mechanisms: anti-angiogenic therapy increases the ratio of anti-tumor to pro-tumor immune cells while hypoxia upregulates immunosuppressive signals (e.g., IL-6, IL-10) that facilitate immune evasion; conversely, activated T cells secrete interferon-γ (IFN-γ), promoting tumor vascular normalization and regression through IFN-γ receptors on tumor endothelial cells [19].

Adverse events in both cohorts were predominantly grade 1–2, with hypertension, fatigue, nausea/vomiting, myelosuppression, and hyperlipidemia being most common in the monotherapy group. In the combination group, no treatment-related fatalities occurred, and common toxicities included hypertension, constipation, fatigue, proteinuria, hepatic injury, and hand-foot syndrome —all manageable with supportive care. Notably, grade 1–2 hypothyroidism was significantly more frequent with combination therapy (P=0.042). Two patients (4.3%) in the combination group developed grade 1–2 immune-related pneumonitis, which resolved after corticosteroid treatment following drug discontinuation. Grade $ $3 toxicities, including hypertension, leukopenia, thrombocytopenia, hepatic dysfunction, and hand-foot syndrome, were alleviated through dose adjustment or supportive measures, with no uncontrollable adverse events reported in either group.

In summary, compared with fruquintinib monotherapy, the combination of PD-1 inhibitor and fruquintinib demonstrates superior efficacy for third-line and beyond treatment of mCRC, substantially improving patient survival while optimizing anti-cancer activity. The addition of PD-1 inhibitors did not increase severe adverse events, maintaining an acceptable safety profile. However, several limitations warrant consideration: first, this is a single-center retrospective study; second, the use of four different PD-1 inhibitors in the combination group introduced heterogeneity; third, the relatively small sample size necessitates validation through larger randomized clinical trials. Further exploratory studies are anticipated to confirm these findings and establish the broader therapeutic potential of this combination for advanced colorectal cancer, offering new hope for affected patients.

Author Contributions: CHEN Lulu conceptualized and designed the study, drafted the manuscript, and performed statistical analysis. CHEN Lulu, ZHANG Liping, and LI Jingwen collected and organized case data and revised the manuscript. DONG Wenjie and WU Xinai conducted feasibility analysis, quality control, and critical revision of the article, assuming overall responsibility for the work.

Conflict of Interest: The authors declare no conflicts of interest.

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Note: Figure translations are in progress. See original paper for figures.