The Efficacy and Safety of Fruquintinib Plus PD-1 Inhibitor in ≥3 line MSS Metastatic Colorectal Cancer Patients

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Research Article

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The efficacy and safety of fruquintinib plus PD-1 inhibitor in ≥3 line MSS metastatic colorectal cancer patients

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Abstract
Purpose: Based on the suggestion of REGONIVO study, we reviewed the data of 26 MSS mCRC patientsto elaborate the efficacy and safety of fruquintinib (a VEGFR inhibitor) plus PD-1 inhibitor and explore the potential predictors for survival in 3+ line microsatellite stable (MSS) metastatic colorectal cancer (mCRC) patients.

Patients and methods: This retrospective study enrolled 26 MSS mCRC patients who progressed after at least 2 lines of systematic chemotherapy but didn't receive PD-1 inhibitors. Fruquintinib of 3mg was administered once daily with 21 days on/7 days off plus PD-1 inhibitor 200mg every 3 weeks until intolerable toxicity or disease progression.

Results: Median overall survival (mOS) was 6.1m (ranged 1.8m-NR 95%CI: 2.60-9.60); median progression free survival (mPFS) was 2.3m (ranged 1.5m-NR 95%CI: 0.93-3.67). There was one complete response (CR) and no partial response (PR). Stable disease was observed in 11 patients (42%) and progression disease (PD) was observed in 14 patients (54%). The object response rate (ORR) was 4% (1/26) and disease control rate (DCR) was 46 %(12/26). Grade ≥3 AEs were observed in 5 patients (19.2%). Grade 5 AEs (immune related encephalitis and cardiotoxicity) were observed in 2 patients. Additionally, there was a significant correlation between NLR < 3.06 and longer survival (P=0.000) for MSS mCRC patients treated with fruquintinib plus PD-1 inhibitor.
Conclusions: Fruquintinib plus PD-1 inhibitor may be a choice for 3+ line MSS mCRC patients，especially with pretreatment NLR<3.06.

Keywords: metastatic colorectal cancer, microsatellite stable, fruquintinib, PD-1 inhibitor, neutrophil-to-lymphocyte

Introduction

It has been proven MSI-H advanced or metastasis CRC patients were benefited from PD-1 blockade, which led to longer survival and fewer treatment-related adverse events [1-3]. However, the use of PD-1 inhibitor has shown little or no clinical benefit in the majority of patients with mCRC[4]. Therefore, it is necessary to explore an amenable interventions for effective immunotherapy.

In the REGONIVO study, the combination of regorafenib plus nivolumab had a manageable safety profile and encouraging antitumor activity in MSS mCRC patients. The objective response rates (ORR) of MSS mCRC and mPFS were 36% and 7.9m, respectively [5].

Fruquintinib is a VEGFR inhibitor that blocks new blood vessel growth associated with tumor proliferation, which is effective among Chinese patients with mCRC who had tumor progression following at least 2 prior chemotherapy regimens [6]. Based on efficacy and safety, there is a tendency that fruquintinib is superior to regorafenib[7].

Based on these findings, we retrospectively analyzed the data of fruquintinib plus PD-1 inhibitors (including 3 kinds of drugs: camrelizumab, sintilimab and tislelizumab) , to provide more evidences and experiences for the strategy setting for ≥3 lines MSS mCRC patients.

Patients and methods

Patients enrolled in this study were diagnosed with mCRC histologically at Peking University International Hospital from March 2019 to January 2021 and had received at least two previous standard treatment lines. All patients with ECOG 0~1 haven't got contraindication for PD-1 inhibitor and VEGFR inhibitor. All patients have signed the informed consent for participation.

Data were collected from the clinical medical records, including gender, age, time of progression or death, adverse events, pathological type, quality of life, laboratory test reports, MSS and driver gene status. All patients were followed up, including telephone follow-up or review of medical records, to determine the patient's survival and calculate the survival time.

Data analysis

The survival curves were analyzed using the Kaplan–Meier method. The optimal cutoff value of NLR was determined by time-dependent receiver operating characteristic (ROC) curve analysis. The ROC analysis was performed by Matlab statistics toolbox [25]. The relationship between pretreatment (within 7 days) NLR (granulocyte to lymphocyte ratio) level and survival was analyzed.

Treatment

Fruquintinib of 3mg was administered once daily with 21 days on/7 days off plus PD-1 inhibitor 200mg every 3 weeks. Tumors were evaluated every 6 weeks according to RECIST v1.1. Adverse events (AEs) were recorded according to CTCAE

v5.0.

Results

Characteristics of patients

Totally, 26 patients were enrolled in this study. All the patients were followed up. The last follow-up was March 25, 2021. Patient's baseline characteristics were summarized in Table 1. Of the 26 MSS mCRC patients, the median age is 63 years and there were 10 (38%) men. All patients had multiple metastases, with liver metastases present in 22 (85%) patients and lung metastases present in 11 (42%) patients. 19 (73%) patients received 2 lines of standard systematic chemotherapy plus targeted therapy and 7 (27%) received more lines. 24 (92%) patients received bevacizumab and 5 (18%) regorafenib in the course. 15 (58%) patients had KRAS mutations and 11 patients received cetuximab. All patients were MSS which was confirmed by next generation sequencing (NGS) .

Adverse events

In the safety analysis set, 5 (19.2%) patients experienced a treatment-emergent adverse event of grade 3 or higher severity. Serious adverse events were reported in 3 (11.6%) patients. Among those, there were two cases of treatment-related deaths including immune-related encephalitis and cardiotoxicity. The adverse event data were summarized in Table 2. The grade 1 to 2 immune-related adverse events most frequently reported were rash (3/26), hypothyroidism(2/26) and the most common grade 1 to 2 adverse events of fruquintinib were hypertension (4/26), hand-foot skin reaction (3/26) and proteinuria (3/26) .

Efficacy

All the patients were evaluated every 6 weeks through imaging examination. There was one complete response (CR) and no partial response (PR). Stable disease was observed in 11 patients (42%) and progression disease (PD) was observed in 14 patients (54%). The object response rate (ORR) was 4% (1/26) and disease control rate (DCR) was 46 % (12/26). The median overall survival (mOS) was 6.1m (ranged 1.8m-NR 95%CI: 2.60-9.60) (Figure 1A). The median progression free survival (mPFS) was 2.3m (ranged 1.5m-NR 95%CI: 0.93-3.67)(Figure 1B). The further efficacy data according to the biological characteristics were presented in Table 3.

Potential predictors for survival

Baseline NLR ≥5 was associated with shorter OS and TTF in melanoma patients treated with PD-1 Inhibitor monotherapy[8]. The similar conclusions were drawn in the studies about non small cell lung cancer[9] and hepatocellular carcinoma patients[10] treated with anti-pd-1 therapy. However there is no agreement on the cutoff value of NLR.

In our cohort, the ROC analysis is performed by Matlab statistic toolbox [25]. The distribution over overall survival and NLR values are shown in Figure 2. The optimal cut-off value is defined as the NLR value at which the absolute value of the difference

between sensitivity and specificity is minimum in the ROC curve. The AUCs for the prediction of 3-month, 6-month and 12-month survival time are 0.790, 0.869 and 0.795 respectively. The cut-off values of NLR for 3-month, 6-month and 12-month survival are 3.79, 3.06 and 2.88 respectively. Its sensitivity is 71.4% and specificity is 73.7% for 3-month, 83.3% and 85.7% for 6-month, 61.9% and 60.0% for 12-month. The preferred cut-off value of NLR is defined as 3.06 for the survival time of 6-month.

Therefore, the patients were divided into two groups, low NLR group (NLR <3.06) and high NLR group (NLR ≥3.06). There were 14 patients in the low NLR group and 12 patients in the high NLR group.The mOS in the high NLR group was 2.7m (range, 1.8–8.4months, [95%CI: 1.68-3.72]) compared with 8.6m (range 2.7–18.0 months, [95%CI: 5.30-11.9]) in the low NLR group, P=0.000 (Figure 3).

There were two cases of treatment-related deaths including immune-related encephalitis and cardiotoxicity. The NLR values were 10.7 and 12.5 respectively.

Discussions

Checkpoint inhibitors (ICIs) including antibodies against PD-1 and CTLA-4 have been approved in patients with dMMR/MSI-H mCRC[1-3]. For the pMMR/MSS mCRC with progression after the two lines of standard systematic therapies, although some agents such as regorafenib[11], fruquintinib[6] and trifluridine/tipiracil (TAS-102)[12] have been approved in previous studies, survival benefits are limited. The REGONIVO study, regorafenib plus PD-1inhibitor,has brought new sight for 3+ line MSS mCRC patients.

Based on efficacy and safety, there was a tendency that fruquintinib was superior to regorafenib[7]. Recent research [13] shows the cotreatment of fruquintinib plus PD-1 inhibitor can significantly inhibit tumor growth and promote survival time for tumor-bearing mice compared with the single drug alone. Meanwhile, the cotreatment is proved to decrease angiogenesis, enhance normalization of the vascular structure and improve tumor immuno microenviroment. In our studies, some MSS mCRC patients who were progressive to at least the second-line treatment were administered fruquintinib plus PD-1 inhibitor. This study aims to summarize the data in the real world and provided evidence for the further research.

In this study, fruquintinib of 3mg was administered once daily with 21 days on/7 days off plus PD-1 inhibitor 200mg every 3 weeks. There were 3 kinds of PD-1 inhibitor involved, including camrelizumab, sintilimab and tislelizumab. The median PD-1 inhibitor exposure was 3 cycles. ORR was 4% (1/26) and DCR was 46 %(12/26). mOS was 6.1m and mPFS was 2.3m. Compared to single agent regimen non head to head, just like TAS102 and regorafenib, mOS was not significantly prolonged in fruquintinib plus PD-1 inhibitor. The survival data was similar with the data reported by Ren, et al [14]. Until the last follow-up date, 2 patients harbored sustained tumor response with more than 1year-PFS.

Meanwhile, the survival data in different subgroups were compared respectively(Table 3). DCR in left-sided group was higher than in right-sided (53% vs

36%). The study[15] has shown that the immunosurveillance pattern differed between right-sided and left-sided CRC, even in pMMR CRC. Maybe the difference of DCR was associated with immuno microenvironment. Patients with third line therapy got higher DCR than patients with forth and fifth line(57% vs 25% and 0). Maybe the difference was associated with performance status and immuno microenvironment. It was reported[16] PD-1 inhibitor as first line treatment in non small cell lung cancer can reduce 30% risk of death, compared to later lines. In terms of molecular markers, there was no correlation between KRAS status and efficacy. KRAS mutation patients showed remarkable clinical benefit to PD-1 inhibitor[17]. However, no evidence was for mCRC patients. PD-L1 expression was associated with MSI-H, increased CD8+ TILs, mucinous and poor cell differentiation, and right-sided tumor location[18]. PD-L1 was not routinely detected in our study.

As for adverse events, grade ≥3 was experienced in 19.2% patients and there were two cases of treatment-related deaths including immune-related encephalitis and cardiotoxicity. Compared with previous studies, there was no new adverse events happened.

NLR has prognostic relevance in patients with a variety of cancers, even in mCRC[19]. In the meantime, several studies have illustrated NLR is a predictive marker for patients treated by PD-1 inhibitors and it is generally believed that higher NLR was associated with worse outcomes [20-23]. However, there is no conclusion about the cutoff value. In our study, we concluded that the NLR of 3.06 was the optimal cutoff value for the OS of 6-month. It was verified that mOS in NLR ≥ 3.06 group was shorter than in NLR<3.06 group (2.7m vs 8.6m P=0.000). Higher NLR was significantly associated with an increased risk of immune-related adverse events (irAE)[24]. In our research, the NLR values of patients who experienced immune-related encephalitis and cardiotoxicity were 12.5 and 10.7 respectively, obviously higher than the cutoff value.

In conclusion, the efficacy of fruquintinib plus PD-1 inhibitor as ≥3 line in MSS mCRC patients requires further verification. We need to do more studies to identify predictive markers. NLR<3.06 may be an ideal predictive marker for the dominant population who may benefit from this treatment model.

Acknowledgement

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Declarations of interest: none

Ethical approval and consent to participate:

All patients have signed the informed consent to participate in the study.

All procedures performed in studies involving human participants were in accordance

with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Availability of data and materials:

All data generated or analyzed during this study are included in this published article.

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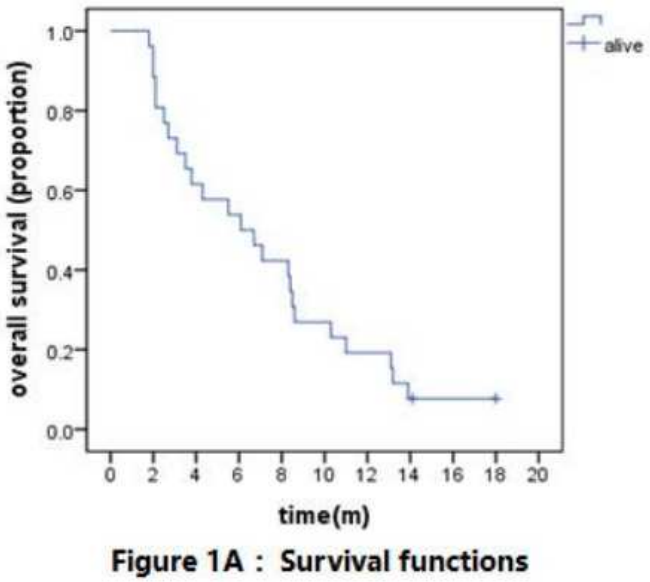
Figures



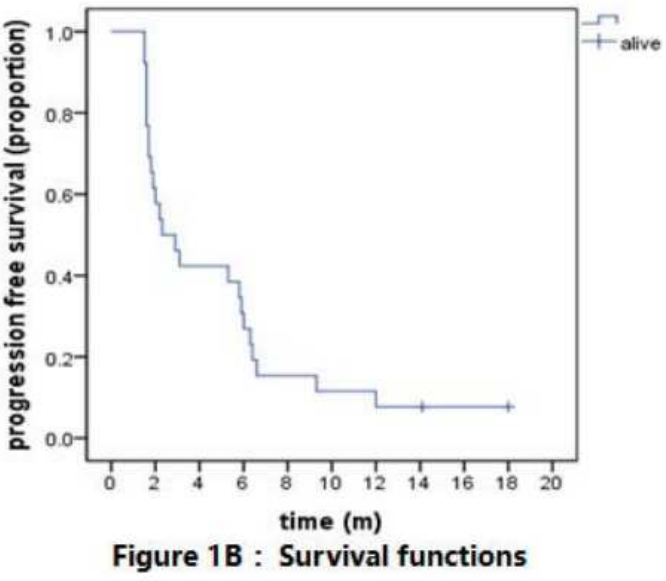


Figure 1

The median overall survival (mOS) was 6.1m (ranged 1.8m-NR 95%CI: 2.60-9.60) (Figure 1A). The median progression free survival (mPFS) was 2.3m (ranged 1.5m-NR 95%CI: 0.93-3.67)(Figure 1B).

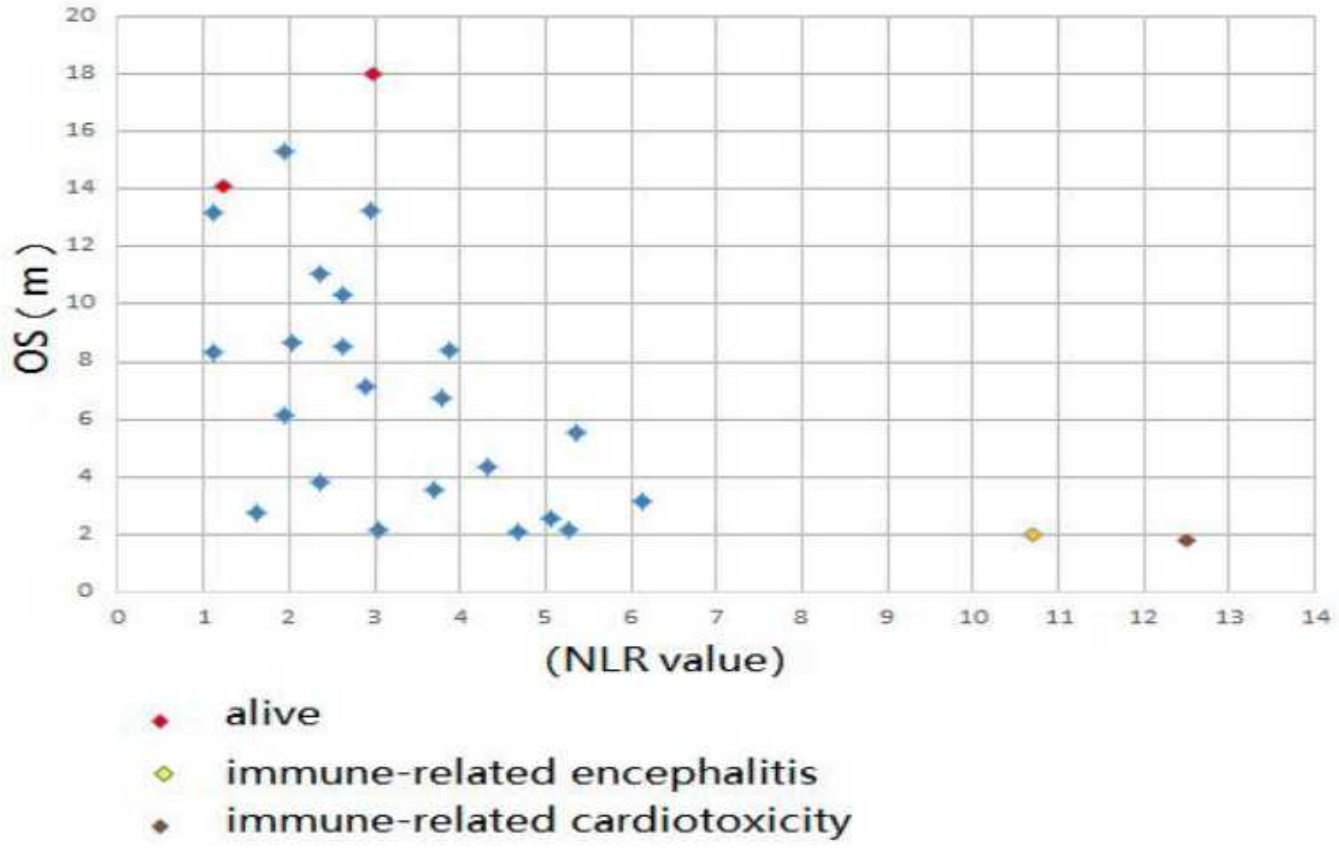


Figure 2

Data distribution over OS and NLR values

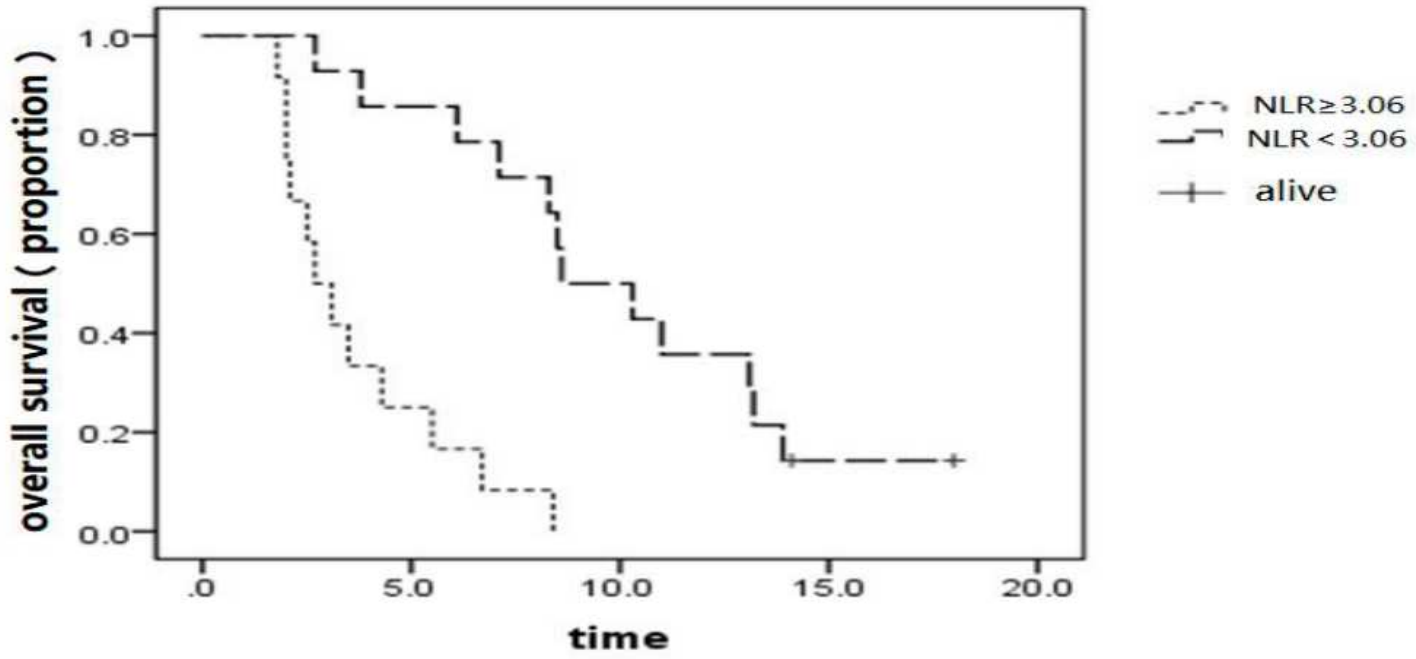


Figure 3

Comparison of overall survival rates in the low NLR (<3.06) group and high NLR (≥3.06) group

Supplementary Files

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- table.pdf