Efficacy and safety analysis of bevacizumab combined with capecitabine in the maintenance treatment of RAS-mutant metastatic colorectal cancer

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Abstract
What is known and objectives: The optimal strategy for maintenance therapy in patients with metastatic colorectal cancer (mCRC) remains controversial. Considering that, beyond progression, co-therapy with bevacizumab and cytotoxic chemotherapy showed less toxicity and a significant disease control rate. We aimed to investigate the differences in efficacy and safety between bevacizumab combined with capecitabine maintenance therapy and capecitabine monotherapy for RAS-mutant mCRC (as defined by mutations in KRAS and NRAS exons 2–4) controlled by bevacizumab plus FOLFIRI chemotherapy for at least 12 weeks.

Methods: We retrospectively analysed patients with RAS-mutant mCRC admitted to the Department of Oncology, Huizhou Municipal Central Hospital from December, 2015 to December, 2020. All patients were first treated with bevacizumab combined with FOLFIRI for at least 12 weeks of induction therapy. 154 patients whose disease was brought under control then continued maintenance therapy. 78 patients were in the observation group (bevacizumab plus capecitabine) and 76 patients were in the control group (capecitabine alone). The efficacy and adverse effects of maintenance treatment were compared between the two groups. The clinicopathological characteristics such as sex, age, performance status (PS) score, primary tumour site, degree of pathological differentiation, baseline carcinoembryonic antigen (CEA) level, microsatellite instability (MSI) status, number of metastatic tumour sites and efficacy of induction treatment were compared in terms of prognosis.

Results and discussion: The median progression-free survival (mPFS) of patients was 9.0 months (95% CI 8.0–10.0) in the observation group and 7.2 months (95% CI 6.0–8.4) in the control group, with a statistically significant difference ($p < 0.05$). The baseline CEA level was an independent prognostic factor. Both groups tolerated the toxic side effects.
1 | WHAT IS KNOWN AND OBJECTIVE

Colorectal cancer (CRC) is the third most commonly diagnosed malignancy and the fourth leading cause of cancer-related deaths worldwide. The incidence of CRC and its associated mortality rates have been increasing. Recently, the International Agency for Research on Cancer of the World Health Organization released the updated global cancer data for 2020. More than 1.93 million new CRC cases and 940,000 deaths were estimated to occur in 2020, representing approximately one in 10 cancer cases and deaths. Overall, CRC ranks third in terms of incidence but second in terms of mortality. With the development of treatments, the disease control rate of metastatic colorectal cancer (mCRC) has significantly improved. Nearly half of the patients achieved stable disease (SD) after palliative chemotherapy. However, for patients whose disease is controlled after induction therapy, the choice of the follow-up treatment regimen remains unclear. The efficacies of maintenance and continuous treatments after induction therapy for mCRC were compared using the OPTIMOX-1 trial. The results showed that maintenance treatment, when compared with continuous treatment, did not reduce the overall survival (OS). Maintenance treatment can reduce toxic side effects and greatly reduce the economic burden of patients while improving the quality of life. The OPTIMOX-2 trial compared the efficacy of maintenance and intermittent treatments in patients with mCRC controlled by induction therapy. The results showed that maintenance therapy significantly prolonged progression-free survival (PFS) and OS without increasing the risk of adverse events. The optimal strategy for maintenance therapy in patients with mCRC remains controversial. In previous retrospective studies, capecitabine combined with bevacizumab as a first-line therapy for the mCRC patients with poor performance status (PS: 3) had a disease control rate of 83.3% and could provide favourable PFS and OS rates. For elderly mCRC patients (PS: 2) who were not suitable for irinotecan and oxaliplatin-containing chemotherapy regimens with an average age of over 75.5 years old, the combination of bevacizumab and capecitabine could significantly improve OS and PFS rates, without excessively serious toxic effects. A recent study also demonstrated that the co-therapy of bevacizumab and capecitabine showed curative effects on mCRC patients who had failed at least two chemotherapy regimens, with a disease control rate of 65% and an effective prolonged survival rate. Therefore, we speculated that bevacizumab plus capcitabine might be a useful option for maintenance treatment of patients with RAS-mutant mCRC. This study investigated the efficacy and safety of bevacizumab plus capcitabine versus capcitabine alone as maintenance therapy for patients with RAS-mutant mCRC after induction therapy remission.

2 | METHODS

2.1 | Clinical information

Among patients with mCRC treated with combination chemotherapy in Huizhou Municipal Central Hospital from 2015–12 to 2020–12, a total of 154 subjects met the inclusion criteria. The inclusion criteria were: (1) age 18–75 years; (2) PS score between 0 and 1; (3) life expectancy >3 months; (4) histologically confirmed colorectal adenocarcinoma; (5) imaging confirmed distant metastasis and non-surgical radical resection; (6) at least one measurable lesion; (7) RAS mutation type; (8) received bevacizumab plus FOLFIRI for at least 12 weeks and disease controlled after completion of induction therapy (efficacy evaluated as complete response [CR], partial response [PR] and SD); (9) hepatic, kidney and blood function within 1° of impairment before entering maintenance therapy. Exclusion criteria were: (1) resection of primary tumour or metastases during chemotherapy; (2) disease progression after induction therapy. The objective efficacy evaluation was based on RECIST1.1 as the reference standard. The results of peripheral blood tumour markers and other relevant tests were also collected from patients within 1 week before chemotherapy.

2.2 | Research methodology

The clinical data of patients in both groups were retrospectively analysed. The primary observational endpoint was PFS, defined as the time from maintenance therapy initiation to the last follow-up when the disease progressed, the disease led to death, or the disease had not progressed. The secondary observational endpoint was the occurrence and extent of adverse effects during treatment in both groups, with follow-up through March 2021. The population was also screened for prognostic heterogeneity stratification by analysing sex, age, PS score, primary tumour site, pathological differentiation,
baseline carcinoembryonic antigen (CEA) level, microsatellite instability (MSI) status, number of metastatic sites, induction therapy efficacy and other clinicopathological characteristics.

2.3 | Statistical analysis

Statistical analyses were performed using SPSS version 25.0 statistical software (SPSS). The baseline characteristics of patients and disease factors were summarized using descriptive statistics. Differences were analysed using Student's t-test. Categorical variables were analysed using the chi-square test or Fisher's exact probability test. Factors related to the prognosis of subjects were analysed using one-way Kaplan–Meier survival analysis and a multi-factor Cox proportional hazards regression model. Statistical significance was set at $p < 0.05$.

3 | RESULTS

3.1 | Baseline characteristics

A total of 154 patients were included in the study. 78 patients were in the observation group: (1) 43 men and 35 women; (2) mean age 58.28 ± 9.20 years; (3) tumour sites were colon (34 patients), rectum (42 patients), the colorectal junction (two patients); (4) 17 patients had a PS score of 0, and 61 patients had a PS score of 1; (5) 32 patients underwent resection of primary tumours and 46 patients did not undergo resection of primary tumours; (6) 52 patients had simultaneous metastasis and 26 patients had heterochronous metastasis; (7) 50 patients showed low differentiation, 28 patients showed intermediate differentiation, 0 patients showed high differentiation; (8) there were six MSI-H patients, 70 MSS/MSI-L patients and two unmeasured patients; (9) 30 patients had high baseline CEA levels and 48 patients had low baseline CEA levels; (10) regarding the efficacy of induction therapy, there were 46 patients with PR and 31 patients with SD; (11) 46 patients had one metastatic site, and 24 patients had two or more sites. 76 patients were in the control group: (1) 43 men and 35 women; (2) mean age 60.04 ± 8.87 years; (3) tumour sites were colon (37 patients), rectum (38 patients), the colorectal junction (one patient); (4) 22 patients had a PS score of 0, and 54 patients had a PS score of 1; (5) there were 31 patients with resected primary tumours and 45 patients with unresected primary tumours; (6) there were 49 patients with simultaneous metastasis and 27 patients with heterochronous metastasis; (7) 46 patients showed low differentiation, 29 patients showed intermediate differentiation, one patient showed high differentiation; (8) there were seven MSI-H patients, 66 MSS/MSI-L patients and three unmeasured patients; (9) 37 patients had high baseline CEA levels and 39 patients had low baseline CEA levels; (10) regarding the efficacy of induction therapy, there were 45 patients with PR and 31 patients with SD; (11) 46 patients had one metastatic site and 30 patients had two or more sites.

The independent sample t-test showed no statistically significant difference ($p > 0.05$) in general clinical information between the two groups (Table 1) and no further propensity score matching.

3.2 | Therapeutic efficacy analysis

The median progression-free survival (mPFS) was 9.0 months (95% CI 8.0–10.0) for patients in the observation group and 7.2 months (95% CI 6.0–8.4) for patients in the control group, ($p < 0.05$) (Figure 1).

3.3 | Toxic side effects

Toxic side effects observed in the two groups during the maintenance period were compared (Table 2). Hypertension, proteinuria and venous thromboembolism were toxic side effects in the observation group, and there were differences between the two groups. Grade III or higher hypertension occurred in 4 patients with a history of hypertension in the observation group. All patients with hypertension were able to resume bevacizumab therapy after a period of suspension of bevacizumab during antihypertensive therapy, and none of the patients permanently discontinued bevacizumab because of uncontrolled blood pressure or a hypertensive crisis. 12 patients who developed proteinuria that is above grade II proteinuria were able to recover to grade II after 2 weeks of delayed dosing, and could subsequently continue to receive reduced doses of bevacizumab treatment. In the control group, those in grade II or in grades above grade II were suspended until they recovered to grade 0–1, and all continued treatment with dose adjustment according to the capecitabine instructions. The remaining toxic side effects have been alleviated to varying degrees after drug suspension and symptomatic supportive treatment. No other treatment-related deaths occurred.

3.4 | Prognostic influencing factors

Univariate analysis showed that the differences in mPFS between gender, age, primary tumour site, PS score, primary tumour resection, tumour metastasis time, degree of differentiation, MSI status, induction therapy efficacy, metastatic sites were not statistically significant ($p > 0.05$). Whereas the mPFS between different baseline CEA levels were statistically significant ($p < 0.05$). The mPFS was 8.8 months (95% CI 7.9–9.7) for those with low CEA levels versus 7.6 months (95% CI 6.5–8.7) for those with high CEA levels (Table 3). The mPFS between different groups were also statistically significant ($p < 0.05$). The mPFS was 9.0 months (95% CI 8.0–10.0) for patients in the observation group and 7.2 months (95% CI 6.0–8.4) for patients in the control group ($p < 0.05$) (Table 3). Multiple factor Cox proportional hazards regression analysis showed that baseline CEA, metastasis time and different groups independently influenced the prognosis of patients with mCRC (Figure 2).
In the era of precision medicine, the US FDA has approved several targeted drugs for CRC, which can be divided into two main categories: drugs targeting vascular endothelial growth factor (VEGF) and its receptor (VEGFR), and drugs targeting the epidermal growth factor receptor (EGFR). The RAS (rat sarcoma) gene was the first human cancer gene to be identified and can be classified into K-RAS, N-RAS and H-RAS. Among the targets of various tumour-targeted therapies, the RAS gene is one of the most widely present oncogenes. Approximately 40% of CRCs harbour activating missense mutations in KRAS. The efficacy of anti-EGFR molecular targeted drugs such as cetuximab and pertuzumab is closely associated with the mutation status of the RAS gene, and only patients with wild-type (wt) gene

| Parameters | Bevacizumab + Capecitabine | Capecitabine | p-value |
|-----------|-----------------------------|--------------|---------|
| Gender    |                             |              |         |
| Men       | 43                          | 41           | 0.884   |
| Women     | 35                          | 35           |         |
| Age (years) |                           |              |         |
| ≥60       | 34                          | 36           | 0.640   |
| <60       | 44                          | 40           |         |
| Average age | 58.28 ± 9.20              | 60.04 ± 8.87 |         |
| Primary tumour site |                      |              |         |
| Colon     | 34                          | 37           | 0.465   |
| Rectum    | 42                          | 38           |         |
| Colorectal junction |                  | 1            |         |
| PS        |                             |              |         |
| 0         | 17                          | 22           | 0.311   |
| 1         | 61                          | 54           |         |
| Primary tumour resection |                     |              |         |
| Yes       | 32                          | 31           | 0.976   |
| No        | 46                          | 45           |         |
| Metastatic time |                     |              |         |
| Simultaneity | 52                         | 49           | 0.776   |
| Heterochronous | 26                       | 27           |         |
| Degree of differentiation |                    |              |         |
| Low       | 50                          | 46           | 0.546   |
| Medium    | 28                          | 29           |         |
| High      | 0                           | 1            |         |
| MSI status |                             |              |         |
| MSI-H     | 6                           | 7            | 0.547   |
| MSS/MSI-L | 70                          | 66           |         |
| Unmeasured | 2                         | 3            |         |
| Baseline CEA |                          |              |         |
| ≤5        | 48                          | 39           | 0.203   |
| >5        | 30                          | 37           |         |
| Induction therapy efficacy |                    |              |         |
| PR        | 47                          | 45           | 0.896   |
| SD        | 31                          | 31           |         |
| Metastatic sites |                      |              |         |
| 1         | 54                          | 46           | 0.261   |
| ≥2        | 24                          | 30           |         |

Abbreviations: CEA, carcinoembryonic antigen; MSI, microsatellite instability; PR, partial response; PS, performance status; SD, stable disease.

4 | DISCUSSION

In the era of precision medicine, the US FDA has approved several targeted drugs for CRC, which can be divided into two main categories: drugs targeting vascular endothelial growth factor (VEGF) and its receptor (VEGFR), and drugs targeting the epidermal growth factor receptor (EGFR). The RAS (rat sarcoma) gene was the first human cancer gene to be identified and can be classified into K-RAS, N-RAS and H-RAS. Among the targets of various tumour-targeted therapies, the RAS gene is one of the most widely present oncogenes. Approximately 40% of CRCs harbour activating missense mutations in KRAS. The efficacy of anti-EGFR molecular targeted drugs such as cetuximab and pertuzumab is closely associated with the mutation status of the RAS gene, and only patients with wild-type (wt) gene
can benefit from anti-EGFR therapy. For patients with RAS-mutant mCRC who cannot benefit from anti-EGFR therapy, anti-VEGF combined with chemotherapy is usually chosen as the first-line treatment for mCRC. Although the PFS and OS of maintenance therapy did not differ significantly from that of continuous therapy, exposure to drug toxicity associated with chemotherapy and targeted therapy decreased patient compliance with prolonged induction therapy which increases the risk of recurrence upon discontinuation. Therefore, with the increasing OS of mCRC, the concept of effective, low-toxicity and low-cost maintenance therapy has gradually gained acceptance. However, there is a lack of clinical evidence for low-intensity or low-toxicity maintenance therapy after fluorouracil-based chemotherapy combined with anti-VEGF induction therapy in patients with RAS-mutant mCRC.

The CAIRO3 trial included untreated patients with mCRC in 64 hospitals in the Netherlands. 558 patients with disease in remission or with SD after six cycles of induction therapy with capecitabine, oxaliplatin and bevacizumab (CAPOX-B) were randomly assigned (1:1) to receive either maintenance therapy with capecitabine and bevacizumab (maintenance group) or observation (observation group). On the first progression (defined as PFS1), patients in both groups were on the induction regimen of CAPOX-B until the second progression (PFS2). The primary endpoint of median PFS2 significantly improved in patients on maintenance treatment and was 8.5 months in the observation group and 11.7 months in the maintenance group (HR 0.67 [0.56–0.81], p < 0.0001). However, in the previous phase 3 CAIRO3 trial, the analysis of untreated mCRC patients with the characterized KRAS exon 2 wt was ignored. The study by Su et al. included 233 untreated female patients with characterized KRAS exon 2 wt mCRC. After six cycles of induction therapy (CAPOX-B), all patients received capecitabine plus bevacizumab (CAP-B) or capecitabine alone (CAP) as maintenance therapy. The mPFS of the CAP-B and the CAP treatment groups were 11.5 and 9.2 months (95% CI 5.6–17.4 vs. 95% CI 3.6–14.8; HR 0.54 [0.32–0.85], p = 0.013), respectively. The median OS of the CAP-B and CAP treatment groups were 16.2 months and 12.4 months (95% CI 11.4–18.7 vs. 95% CI 10.6–15.5; HR 0.72 [0.51–0.94], p = 0.022).

In summary, in these cases that have previously received six cycles of CAPOX-B induction therapy, the combination of bevacizumab and capecitabine often brings benefits. Therefore, the current research seems to support the treatment concept that bevacizumab combined with capecitabine is superior to capecitabine alone in maintenance therapy.

The MACRO trial evaluated the efficacy of bevacizumab alone and XELOX plus bevacizumab in mCRC patients receiving maintenance therapy after XELOX combined with bevacizumab induction therapy. The results showed that the differences in median PFS and OS between the two groups were not statistically significant, but the adverse events were significantly more common in the continuous treatment group than in the maintenance treatment group. Although our study was retrospective, the co-therapy of bevacizumab and capecitabine could be a tolerable treatment option.

Professor Xu Ruihua’s team initiated a randomized, open-label, multicenter, phase III trial. Patients with mCRC from 11 sites in

![FIGURE 1 Progression-free survival time curves of the two groups in maintenance treatment](image)

**TABLE 2** Toxic side effects during maintenance therapy in both groups

| Toxic side effects                          | Bevacizumab combined with capecitabine group [cases (%)] | Capecitabine monotherapy group [cases (%)] |
|---------------------------------------------|----------------------------------------------------------|--------------------------------------------|
| Hand–foot syndrome                          | Grade I 26 (33.3) Grade II 13 (16.7) Grade III 9 (11.5) Grade IV 0 (0.0) | Grade I 21 (27.6) Grade II 15 (19.7) Grade III 10 (13.2) Grade IV 0 (0.0) |
| Gastrointestinal reactions                  | Grade I 20 (25.6) Grade II 11 (14.1) Grade III 0 (0.0) Grade IV 0 (0.0) | Grade I 20 (26.3) Grade II 8 (10.5) Grade III 0 (0.0) Grade IV 0 (0.0) |
| Neutropenia                                 | Grade I 6 (7.7) Grade II 3 (3.8) Grade III 4 (5.1) Grade IV 0 (0.0) | Grade I 5 (6.6) Grade II 6 (7.9) Grade III 4 (5.3) Grade IV 0 (0.0) |
| Thrombocytopenia                            | Grade I 4 (5.1) Grade II 1 (1.3) Grade III 0 (0.0) Grade IV 0 (0.0) | Grade I 2 (2.6) Grade II 2 (2.6) Grade III 0 (0.0) Grade IV 0 (0.0) |
| Hepatic and kidney function impairment       | Grade I 4 (5.1) Grade II 0 (0.0) Grade III 0 (0.0) Grade IV 0 (0.0) | Grade I 3 (3.9) Grade II 0 (0.0) Grade III 0 (0.0) Grade IV 0 (0.0) |
| Hypertension                                | Grade I 20 (25.6) Grade II 7 (9.0) Grade III 4 (5.1) Grade IV 0 (0.0) | Grade I 9 (11.8) Grade II 0 (0.0) Grade III 0 (0.0) Grade IV 0 (0.0) |
| Proteinuria                                 | Grade I 10 (12.8) Grade II 6 (7.7) Grade III 6 (7.7) Grade IV 0 (0.0) | Grade I 0 (0.0) Grade II 0 (0.0) Grade III 0 (0.0) Grade IV 0 (0.0) |
| Fatigue                                     | Grade I 12 (15.4) Grade II 3 (3.8) Grade III 0 (0.0) Grade IV 0 (0.0) | Grade I 10 (13.2) Grade II 4 (5.3) Grade III 0 (0.0) Grade IV 0 (0.0) |
| Venous thromboembolism                      | Grade I 1 (1.3) Grade II 1 (1.3) Grade III 0 (0.0) Grade IV 0 (0.0) | Grade I 0 (0.0) Grade II 0 (0.0) Grade III 0 (0.0) Grade IV 0 (0.0) |
China enrolled in the study. A total of 274 patients who received 18–24 weeks of induction chemotherapy with XELOX or FOLFOX and achieved disease control were randomly assigned (1:1) to receive maintenance therapy with capecitabine or only observation until disease progression. The results showed that the primary observation endpoint of PFS was significantly longer in the maintenance group given capecitabine than in the observation group (6.43 [95% CI 5.26–7.71] vs. 3.43 [2.83–4.16] months, HR 0.54 [0.42–0.70], p < 0.001). The median OS was longer in the maintenance group given capecitabine than in the observation group (25.63 [22.46–27.80] months

| Parameters                      | N    | mPFS | 95% CI    | p-value |
|---------------------------------|------|------|-----------|---------|
| **Gender**                      |      |      |           |         |
| Men                             | 84   | 8.1  | 6.7–9.5   | 0.874   |
| Women                           | 70   | 8.1  | 7.0–9.2   |         |
| **Age (years)**                 |      |      |           |         |
| ≥60                             | 70   | 7.3  | 5.1–9.5   | 0.358   |
| <60                             | 84   | 8.1  | 7.4–8.8   |         |
| **Primary tumour site**         |      |      |           |         |
| Colon                           | 71   | 7.6  | 6.6–8.6   | 0.764   |
| Rectum                          | 80   | 8.5  | 7.6–9.4   |         |
| Colorectal junction             | 3    | 6.1  |           |         |
| **PS**                          |      |      |           |         |
| 0                               | 39   | 7.3  | 5.5–9.1   | 0.804   |
| 1                               | 115  | 8.1  | 7.4–8.9   |         |
| **Primary tumour resection**    |      |      |           |         |
| Yes                             | 63   | 8.1  | 7.6–8.6   | 0.992   |
| No                              | 91   | 8.6  | 7.2–10.0  |         |
| **Metastasis time**             |      |      |           |         |
| Simultaneity                    | 101  | 8.5  | 7.6–9.4   | 0.342   |
| Heterochronous                  | 53   | 7.8  | 7.0–8.6   |         |
| **Degree of differentiation**   |      |      |           |         |
| Low                             | 96   | 8.1  | 7.0–9.2   | 0.145   |
| Medium                          | 57   | 8.1  | 7.2–9.0   |         |
| High                            | 1    | 5.9  |           |         |
| **MSI status**                  |      |      |           |         |
| MSI-H                           | 13   | 8.1  | 7.3–8.9   | 0.444   |
| MSS/MSI-L                       | 136  | 7.2  | 6.0–8.4   |         |
| Unmeasured                      | 5    | 9.8  |           |         |
| **Baseline CEA**                |      |      |           |         |
| ≤5                              | 87   | 8.8  | 7.9–9.7   | 0.037   |
| >5                              | 67   | 7.6  | 6.5–8.7   |         |
| **Induction therapy efficacy**  |      |      |           |         |
| PR                              | 92   | 7.8  | 6.4–9.3   | 0.459   |
| SD                              | 62   | 8.1  | 7.2–9.0   |         |
| **Metastasis sites**            |      |      |           |         |
| 1                               | 100  | 8.1  | 7.1–9.1   | 0.573   |
| ≥2                              | 54   | 8.6  | 7.0–10.2  |         |
| **Groups**                      |      |      |           |         |
| Bevacizumab + Capecitabine      | 78   | 9.0  | 8.0–10.0  | 0.004   |
| Capecitabine                    | 76   | 7.2  | 6.0–8.4   |         |

Abbreviations: CEA, carcinoembryonic antigen; CI, confidence interval; mPFS, median progression-free survival; MSI, microsatellite instability; PR, partial response; PS, performance status; SD, stable disease.
Similar safety profiles were observed in both the clinical trial arms. This study led to the conclusion that maintenance therapy with a single agent of capecitabine can be considered an appropriate option following the induction of XELOX or FOLFOX in mCRC patients with acceptable toxicities.

Carcinoembryonic antigen is an acidic glycoprotein with human embryonic antigen properties that was first extracted from colon cancer and embryonic tissue by Gold and Freedman in 1965. CEA is present on the surface of cancer cells that are differentiated from endodermal cells. Clinical practice has revealed that CEA is a broad-spectrum tumour biomarker associated with colon, breast and lung cancers. In this study, multiple-factor Cox proportional hazards regression analysis showed that baseline CEA level independently influenced the prognosis of patients with mCRC. This result is consistent with a meta-analysis investigating the relationship between CEA and CA199 levels and prognosis in patients with advanced CRC in China.

WHAT IS NEW AND CONCLUSION

This study demonstrates that bevacizumab plus capecitabine can be used in the maintenance treatment of disease-controlled patients with mCRC after induction therapy. The regimen has significant efficacy, is well tolerated and can bring survival benefits to patients. However, since this study was a non-randomized retrospective study, it is necessary to expand the sample size and carry out a multicenter, prospective, randomized controlled study in the future, which can confirm the feasibility of bevacizumab combined with capecitabine maintenance therapy and promote its application. mCRC was controlled after induction therapy, including CR, PR and SD. At what kind of treatment response, the maximum survival benefit can be obtained by starting maintenance treatment remains to be further studied. In addition, the lack of monitoring of changes in RAS status after 12 weeks of induction therapy with bevacizumab plus the FOLFIRI, which makes it impossible to further analyse whether the effectiveness of bevacizumab in maintenance therapy is related to changes in RAS status.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest to report regarding the present study.

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REFERENCES

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209-249. doi:10.3322/caac.21660
2. Tournigand C, André T, Achille E, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J Clin Oncol. 2004;22(2):229-237. doi:10.1200/JCO.2004.05.113
3. Van Cutsem E, Köhne C-H, Hitre E, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. N Engl J Med. 2009;360(14):1408-1417. doi:10.1056/NEJMoa0805019
4. Tournigand C, Cervantes A, Figer A, et al. OPTIMOX1: a randomized study of FOLFOX4 or FOLFOX7 with oxaliplatin in a stop-and-go fashion in advanced colorectal cancer—a GERCOR study. J Clin Oncol. 2006;24(3):394-400. doi:10.1200/JCO.2005.03.0106
5. Chiabudel B, Mairnraut-Goebel F, Ledo G, et al. Can chemotherapy be discontinued in unresectable metastatic colorectal cancer? The GERCOR OPTIMOX2 Study. J Clin Oncol. 2009;27(34):5727-5733. doi:10.1200/JCO.2009.23.4344
6. Yamada Y, Yoshimatsu K, Yokomizo H, et al. Capecitabine plus bevacizumab as first-line therapy for metastatic colorectal cancer patients with poor performance status. J Nippon Med Sch. 2020;JNMS(2021):88-415. doi:10.1272/jnms.JNMS.2021_88-415
7. Ozcelik M, Odabas H, Ercelep O, et al. The efficacy and safety of capecitabine plus bevacizumab combination as first-line treatment in elderly metastatic colorectal cancer patients. Clin Transl Oncol. 2016;18(6):617-624. doi:10.1007/s12094-015-1408-6
8. Bang YH, Kim JE, Lee JS, et al. Bevacizumab plus capecitabine as later-line treatment for patients with metastatic colorectal cancer refractory to irinotecan, oxaliplatin, and fluoropyrimidines. Sci Rep UK. 2021;11(1):1-9. doi:10.1038/s41598-021-86482-x

9. Li W, Qiu T, Ling Y, Guo L, Li L, Ying J. Molecular pathological epidemiology of colorectal cancer in Chinese patients with KRAS and BRAF mutations. Oncotarget. 2015;6(37):39607-39613. doi:10.18632/oncotarget.5551

10. Ma H, Wu X, Tao M, et al. Efficacy and safety of bevacizumab-based maintenance therapy in metastatic colorectal cancer: a meta-analysis. Medicine (Baltimore). 2019;98(50):e18227. doi:10.1097/MD.0000000000018227

11. Simkens LHJ, van Tinteren H, May A, et al. Maintenance treatment with capecitabine and bevacizumab in metastatic colorectal cancer (CAIRO3): a phase 3 randomised controlled trial of the Dutch Colorectal Cancer Group. Lancet. 2015;385(9980):1843-1852. doi:10.1016/S0140-6736(14)62004-3

12. Su J, Lai J, Yang R, et al. Capecitabine plus bevacizumab versus capecitabine in maintenance treatment for untreated characterised KRAS exon 2 wild-type metastatic colorectal cancer: a retrospective analysis in Chinese postmenopausal women. BMC Gastroenterol. 2019;19(1):1-9. doi:10.1186/s12876-018-0916-6

13. Díaz-Rubio E, Gómez-España A, Massuti B, et al. First-line XELOX plus bevacizumab followed by XELOX plus bevacizumab or single-agent bevacizumab as maintenance therapy in patients with metastatic colorectal cancer: the phase III MACRO TTD study. Oncologist. 2012;17(1):15-25. doi:10.1634/theoncologist.2011-0249

14. Luo HY, Li YH, Wang W, et al. Single-agent capecitabine as maintenance therapy after induction of XELOX (or FOLFOX) in first-line treatment of metastatic colorectal cancer: randomized clinical trial of efficacy and safety. Ann Oncol. 2016;27(6):1074-1081. doi:10.1093/annonc/mdw101

15. Jin X, Xu X, Xu H, Lv L, Lu H. The diagnostic value of carcinoembryonic antigen and squamous cell carcinoma antigen in lung adenosquamous carcinoma. Clin Lab. 2017;63(4):801-808. doi:10.7754/Clin.Lab.2016.160921

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