Efficacy and safety of chemotherapy combined with bevacizumab in Chinese patients with metastatic colorectal cancer: A prospective, multicenter, observational, non-interventional phase IV trial

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Abstract

Objective: Bevacizumab has an important and evolving role in improving outcomes in patients with metastatic colorectal cancer (mCRC) worldwide and was approved in China in 2010. However, there are limited real-world data on the efficacy and safety of chemotherapy regimens combined with bevacizumab in Chinese patients with mCRC. This observational, phase IV trial study aimed to obtain more experience on the efficacy and safety of bevacizumab combined with chemotherapy in Chinese mCRC patients.

Methods: Between September 2013 and November 2016, patients with histologically confirmed mCRC were enrolled in a prospective, multicenter, observational, non-interventional phase IV trial at 26 centers across China. Eligible patients received different chemotherapeutic regimens combined with bevacizumab. The efficacy and safety data in the intention-to-treat study population were analyzed.

Results: A total of 611 patients were included in the efficacy analysis. The median overall survival and median progression-free survival was 18.00 and 10.05 months, respectively. The objective response rate was 21.00% and disease control rate was 89.40%. In subgroup analyses, the survival differences were observed according to metastatic status, duration of treatment and elevation in blood pressure. A total of 613 patients were evaluable for safety assessments. And 569 (92.82%) patients reported at least one adverse event (AE), and 151 (24.63%) experienced grade 3 or higher AEs. The incidence of bevacizumab-associated AEs of special interest was reported in 31 (5.06%) patients with hypertension (n=12), abscesses and fistulae (n=7), bleeding (n=6), proteinuria (n=3), gastrointestinal perforation (n=2) and venous thrombotic events (n=1).

Conclusions: This observational phase IV trial broadens our experience and knowledge of bevacizumab in the Chinese population and provides a good indication of its overall efficacy and safety. Bevacizumab in combination...
with chemotherapy offers clinical benefits to Chinese patients with mCRC and has an acceptable and manageable safety profile.

**Keywords:** Metastatic colorectal cancer; bevacizumab; chemotherapy; efficacy; safety

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**Introduction**

Colorectal cancer (CRC) is the most common gastrointestinal cancer worldwide and the second leading cause of cancer-related death (1,2). Despite improvements in screening, diagnosis, and treatment regimens, the 5-year mortality rate for patients with CRC remains high (approximately 40%–50%), and the disease represents a significant global health burden (3). The current standard of care for patients with localized CRC includes surgical resection followed by adjuvant chemotherapy in selected patients (4,5). However, many patients experience recurrence or metastasis (6,7).

Vascular endothelial growth factor (VEGF) is considered as a key mediator of angiogenesis signaling pathways involved in both physiological and pathological conditions (8,9). Bevacizumab, a humanized monoclonal antibody targeting VEGF, is the first anti-angiogenic agent to be approved for the metastatic CRC (mCRC) treatment in combination with 5 - fluorouracil - based chemotherapy regimens (10). Several pivotal randomized clinical studies had demonstrated that the addition of bevacizumab to chemotherapy conferred clinically significant improvements in overall survival (OS), progression-free survival (PFS), and objective response rate (ORR) (11-14). In addition, observational cohort studies have shown that bevacizumab in combination with chemotherapy was well tolerated and effective in broad western mCRC patient populations (15,16).

Bevacizumab was approved by the National Medical Products Administration (NMPA) in China in 2010. The ARTIST registration study showed that both OS and PFS were notably prolonged in Chinese mCRC patients treated with bevacizumab plus modified IFL regimen (irinotecan, leucovorin bolus, and 5-fluorouracil intravenous infusion) as first-line treatment (12). However, there are limited real-world data from large-scale phase IV clinical trials on the efficacy and safety of chemotherapy regimens combined with bevacizumab in Chinese patients with mCRC. In this prospective, multicenter, observational, non-interventional phase IV trial, we aimed to obtain more data on the efficacy and safety of bevacizumab and provide an insight into the treatment profile of this agent in Chinese unselected patients with mCRC.

**Materials and methods**

**Patient selection and study design**

This was a prospective, multicenter, observational, non-interventional phase IV clinical trial conducted between September 2013 and November 2016 at 26 participating centers across China. The study protocol was approved by the institutional review boards and ethical committees of the participating centers and registered on the website (Identifier: NCT01912443; Registered 31 July 2013 https://clinicaltrials.gov/ct2/show/). The study was conducted in compliance with Good Clinical Practice procedures set out in the Declaration of Helsinki and the requirements of China’s National Medical Products Administration (NMPA) and approval by the ethics committee of each participating institution [including Ethical Committees of Sun Yat-sen University Cancer Center (B2012-020-01), Ethical Committees of Chinese PLA General Hospital (C2013-061-01), Ethical Committees of the Sixth Affiliated Hospital of Sun Yat-sen University (2014ZSLYEC-007), Ethical Committees of Xinjiang Medical University Cancer Hospital (2013 010), Ethical Committees of Foshan First People’s Hospital (2013 26), Ethical Committees of Shandong Cancer Hospital (201405008), Ethical Committees of West China Hospital of Sichuan University (2014 12), Ethical Committees of Jiangsu Cancer Hospital (2014NL-007), Ethical Committees of Fujian Cancer Hospital (201409), Ethical Committees of Sichuan Cancer Hospital (SCCHEC2013013), Ethical Committees of Anhui Provincial Hospital (2014 11), Ethical Committees of the First Affiliated Hospital of Soochow University (2013 309),
The safety profile of regimens containing bevacizumab was assessed from data on the incidences of all adverse events (AEs), including serious AEs (SAEs) and non-SAEs. In addition, the incidence of bevacizumab-associated AEs of special interest (AESIs) was noted, including hypertension (grade ≥3), proteinuria (grade ≥3), bleeding (grade ≥3), gastrointestinal perforations, arterial and venous thromboembolic events, wound healing complications (grade ≥3), congestive heart failure (grade ≥3), posterior reversible encephalopathy syndrome, abscesses, fistulae (grade ≥2), elevated levels of alanine transaminase or aspartate transaminase, and elevated level of bilirubin or clinical jaundice.

The National Cancer Institute’s Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 was used to classify the severity of AEs. All AEs were recorded up to 28 d after the last infusion of bevacizumab, whereas AESIs were recorded up to 6 months after the last bevacizumab dose.

### Statistical analysis

The analysis of patient demographics and baseline characteristics was based on all enrolled patients. The analysis of safety was based on the safety set (SS), which included all patients who received at least one cycle of bevacizumab treatment and had at least one valid safety assessment. The analysis of efficacy was based on the full analysis set (FAS), which included all patients who received at least one cycle of bevacizumab and had at least one efficacy assessment. Subgroup analyses were conducted for patient age (<65 years vs. ≥65 years), KRAS status, primary tumor site (colon vs. rectum), primary tumor resection, peritoneal metastasis, metastatic status (synchronous vs. metachronous), duration of treatment (≤8 weeks vs. >8 weeks), blood pressure elevations (>10/5 mmHg) and treatment line (first-line vs. second-line).

Categorical variables were summarized in frequency tables and continuous variables were summarized with descriptive statistics. Differences in rates for qualitative factors were compared by Pearson’s χ² contingency table analysis. The Kaplan-Meier method was used to estimate the distribution of PFS and OS. Comparisons between several factors were assessed using the log-rank test. All tests were conducted at a two-sided alpha level of 0.05, and 95% confidence intervals (95% CIs) were given at a two-sided level. All clinical data were analyzed using SAS™ (Version 9.4; SAS Institute Inc., Cary, USA).
**Results**

**Patient characteristics and treatment**

A total of 613 patients were screened for inclusion in this study. The study design is illustrated in Figure 1. All patients were included in the safety population and 611 patients were included in the efficacy analysis because two patients were excluded due to the absence of efficacy data. The demographic and baseline characteristics of all enrolled patients are shown in Table 1. The median age was 55 (range, 16–85) years, and 384 (62.64%) patients were male. The Eastern Cooperative Oncology Group performance status (ECOG PS) was 0–1 in 426 (95.30%) of the 447 patients assessed, and KRAS mutation was found in 98 (57.99%) of the 169 patients tested.

Patients received bevacizumab at a median dose of 33.23 (range, 2.73–328.00) mg/kg for a median of 9 (range, 1–53) cycles. There were 343 (55.95%) patients received first-line bevacizumab-based therapy and 270 (44.05%) patients received second-line bevacizumab-based therapy. Main chemotherapeutic regimens included irinotecan-based regimens (62.32%), oxaliplatin-based regimens (60.85%) and capecitabine (28.38%) (Table 2).

**Efficacy**

Patients were followed up for a median time of 9.21 (range, 0.03–33.87) months, and 280 (45.83%) of 611 patients died at the end of follow-up. The median OS was 18.00 (95% CI, 16.99–20.07) months and median PFS was 10.05 (95% CI, 9.20–11.37) months (Figure 2). The ORR was 21.00% and DCR was 89.40%. The median PFS in patients who received first-line therapy was longer than in those who received second-line therapy (11.04 months vs. 8.74 months). Higher ORR were also seen in those who

![Figure 1 Flowchart of study design.](image-url)
In subgroup analyses of FAS population, no significant interactions were observed for age, KRAS mutation status, primary tumor site, or primary tumor resection and different chemotherapy regimens. However, survival differences were observed according to metastatic status, duration of treatment and elevation in blood pressure (Table 4). Patients with metachronous metastasis showed a shorter median PFS than those with synchronous metastasis (9.20 months vs. 10.97 months; P=0.044). The longer duration of treatment was significantly associated with better survival. With a cut-off of 8 weeks, patients receiving more than 8 weeks of treatment had a significantly improved median OS compared with those receiving ≤8 weeks of treatment (19.15 months vs. 17.81 months; P<0.001). Patients with elevated blood pressure had a longer median OS than those without elevated blood pressure (20.80 months vs. 16.66 months; P=0.002).

Safety

All patients (n=613) were evaluable for safety assessments, and observed AEs are summarized in Table 5. A total of 569 (92.82%) patients reported at least one AE, and 151 (24.63%) experienced grade 3 or higher AEs. The most common AEs were leukopenia (39.97%), nausea (39.31%), neutropenia (29.04%), vomiting (27.24%), loss of appetite (23.16%), hypertension (19.25%), diarrhea (18.76%), and anemia (17.78%). Incidences of SAEs were reported in 27 (4.40%) patients and included neutropenia, death, leukopenia, diarrhea, pulmonary infection, and stoma-related bleeding. And 288 (46.98%) patients had bevacizumab-related AEs. AESIs were reported in 31 (4.40%) patients and included neutropenia, death, leukopenia, diarrhea, pulmonary infection, stoma-related bleeding, and venous thrombotic events (n=1). AEs leading to treatment discontinuation occurred in 31 (5.06%) patients. Dose adjustments were done in 76 patients (12.40%).

Across age, KRAS status, chemotherapy regimen, tumor
Figure 2 Kaplan-Meier plots of OS [median OS: 18.00 (95% CI: 16.99–20.07) months] (A) and PFS [median PFS: 10.05 (95% CI: 9.20–11.37) months] (B) in FAS population. OS, overall survival; PFS, progression-free survival; 95% CI, 95% confidence interval; FAS, full analysis set.

Table 3 Efficacy according to administered treatment in evaluable patients

| Efficacy            | FAS population (N=611) | First-line therapy (N=342) | Second-line therapy (N=269) |
|---------------------|------------------------|-----------------------------|-----------------------------|
| Median OS (95% CI) (month) | 18.00 (16.99–20.07)    | 18.00 (17.08–21.82)         | 17.45 (14.72–20.07)         |
| Median PFS (95% CI) (month)   | 10.05 (9.20–11.37)     | 11.04 (9.66–13.34)          | 8.74 (7.49–10.58)           |
| ORR (%)              | 21.00                  | 27.08                       | 13.45                       |
| SD (%)               | 68.40                  | 65.70                       | 71.75                       |
| PD (%)               | 10.60                  | 7.22                        | 14.80                       |
| DCR (%)              | 89.40                  | 92.78                       | 85.20                       |

OS, overall survival; 95% CI, 95% confidence interval; PFS, progression-free survival; ORR, objective response rate; SD, stable disease; PD, progressive disease; DCR, disease control rate; FAS, full analysis set.

Table 4 Subgroup analysis of efficacy according to patients’ metastasis status, duration of treatment, blood pressure elevation, and peritoneal metastasis

| Population     | Subgroup analysis                  | Efficacy                                      | P     |
|----------------|------------------------------------|-----------------------------------------------|-------|
| FAS            | Metastasis status                  | Median PFS (95% CI) (month)                    | 0.044 |
|                | Synchronous metastatic lesions: 10.97 (9.59–13.01) |                                |       |
|                | Metachronous metastatic lesions: 9.20 (7.59–10.58) |                                |       |
|                | Duration of treatment              | Median OS (95% CI) (month)                    | <0.001|
|                | ≤8 weeks: 17.81 (15.77–19.48)      |                                |       |
|                | >8 weeks: 19.15 (17.02–23.92)      |                                |       |
|                | Elevated blood pressure*           | Median OS (95% CI) (month)                    | 0.002 |
|                | No: 16.66 (14.72–18.00)            |                                |       |
|                | Yes: 20.80 (17.74–23.92)           |                                |       |
| First-line     | Peritoneal metastasis              | Median OS (95% CI) (month)                    | 0.001 |
| therapy        | No: 19.48 (17.54–22.37)            |                                |       |
|                | Yes: 10.84 (8.05–25.82)            |                                |       |
|                | Median PFS (95% CI) (month)        |                                | 0.008 |
|                | No: 11.70 (9.99–14.95)             |                                |       |
|                | Yes: 6.90 (5.42–10.84)             |                                |       |
|                | Duration of treatment              | Median PFS (95% CI) (month)                    | 0.004 |
|                | ≤8 weeks: 12.32 (10.05–14.95)      |                                |       |
|                | >8 weeks: 8.87 (6.90–10.55)        |                                |       |
| Second-line    | Duration of treatment              | Median OS (95% CI) (month)                    | <0.001|
| therapy        | ≤8 weeks: 15.38 (11.86–18.99)      |                                |       |
|                | >8 weeks: 21.45 (16.49–not reached)|                                |       |

*, Defined as an elevation in systolic BP of 10 mmHg or diastolic BP of 5 mmHg within 60 d of starting bevacizumab treatment. FAS, full analysis set; PFS, progression-free survival; 95% CI, 95% confidence interval; OS, overall survival.
Table 5 Summary of adverse events (N=613)

| AEs                                      | n   | %   |
|------------------------------------------|-----|-----|
| Overall AEs                              | 569 | 92.82|
| Grade ≥3 AEs                             | 151 | 24.63|
| SAEs                                     | 27  | 4.40 |
| AESIs                                    | 31  | 5.06 |
| Proteinuria                              | 3   | 0.49 |
| Hypertension                             | 12  | 1.96 |
| Bleeding                                 | 6   | 0.98 |
| Abscesses and fistulae                   | 7   | 1.14 |
| Gastrointestinal perforation             | 2   | 0.33 |
| Venous thrombotic events                 | 1   | 0.16 |
| AEs leading to discontinuation of treatment | 31  | 5.06 |
| AEs leading to dose adjustment           | 76  | 12.40|
| AEs leading to death                     | 15  | 2.45 |
| AEs associated with bevacizumab          | 288 | 46.98|

AE, adverse event; SAE, serious adverse event; AESI, adverse event of special interest.

Discussion

In the prospective, multicenter, observational, non-interventional phase IV study, we reported the efficacy and safety profile of bevacizumab combined with chemotherapy in patients with mCRC and provides valuable information on bevacizumab that the safety profile of bevacizumab in Chinese patients is comparable with that observed in other patient populations.

In terms of the response of bevacizumab-containing regimens, the reported ORR of 21.00% in this study (first-line: 27.08% and second-line: 13.45%) was comparable to that of previous randomized phase III trials, such as E3200 trial (11) and ML18147 trial (17). The E3200 trial compared three different regimens (FOLFOX4 with bevacizumab vs. FOLFOX4 vs. bevacizumab) in previously treated mCRC. The ORRs were 22.7%, 8.6% and 3.3%, respectively (11). The ML18147 trial assessed the continued use of bevacizumab plus standard second-line chemotherapy in patients with mCRC progressing after standard first-line bevacizumab-based treatment, and the response rate was found to be 22% with bevacizumab-containing chemotherapy (17). However, it was lower than that of other previously reported phase II–IV trials (11-14, 17-22) (Table 6). One explanation to note is the different methods assessing ORR. For example, in the study of Saltz et al. (13), ORR with bevacizumab plus chemotherapy assessed by investigators was 47%, but 38% by the independent response committee review. Another explanation is that our trial is non-interventional and enrolls different patients with no strict selection.

In terms of survival, patients in this trial had a median OS of 18.00 months and a median PFS of 10.05 months. Median OS between patients with first-line therapy and second-line therapy was comparable (18.00 vs. 17.45 months), but median PFS of patients with first-line therapy was longer than those with second-line therapy (11.04 vs. 8.74 months). In both first- and second-line therapy settings, previous randomized trials have demonstrated improvements in OS or PFS in patients with mCRC treated with bevacizumab in combination with cytotoxic chemotherapy (11,14). The ML18147 trial showed that the benefits of bevacizumab continued beyond disease progression and that switching chemotherapy was beneficial for patients with mCRC who were previously treated with bevacizumab in the first-line setting. The continued use of bevacizumab beyond disease progression led to a significant improvement in OS and PFS compared with post-progression chemotherapy alone (17). Our observational study confirmed this result as the use of bevacizumab after disease progression was also associated with survival benefits. The findings from our subgroup analyses were generally consistent with those in the overall study population. The unfavorable prognostic impact of KRAS mutations in patients with mCRC has been reported previously (23). The exploratory analysis of the KRAS subgroup in our study showed that there was no evidence to suggest a difference between the overall population and subgroups based on the KRAS mutational status.

The safety profile of bevacizumab-based therapy in this trial was similar to that observed in previous clinical trials (15,16). We did not detect any new safety signals concerning the use of bevacizumab in mCRC, and all observed AEs in our patient population have a well-known association with either bevacizumab or chemotherapy. Our results showed that bevacizumab was well-tolerated and associated with a relatively low incidence of severe AEs (4.4%). In addition, the rates of treatment discontinuation and death were lower than those reported in other studies (11,17,19,20). Guan et al. (12) showed that compared with chemotherapy alone, the administration of a combination
of bevacizumab and chemotherapy in Chinese patients with mCRC resulted in a slightly higher incidence of AEs, especially chemotherapy-associated AEs, such as neutropenia, diarrhea, and nausea. According to previous reports, the most frequent AEs associated with bevacizumab are hypertension and proteinuria, with gastrointestinal perforation being the most serious (24-26). Hypertension and proteinuria are likely directly related to the inhibition of VEGF, which results in vasoconstriction and regulated glomerular vascular permeability (27,28). In our study, we noted relatively low rates of hypertension (1.96%) and proteinuria (0.94%), and only two patients experienced gastrointestinal perforation. Most cases of hypertension and proteinuria were asymptomatic. According to the summary of product characteristics for bevacizumab, minor bleeding events have been observed in approximately 30% of patients with mCRC who received bevacizumab (29). Only 6 (0.98%) patients experienced bleeding events in this study. The rates of thromboembolic events were also consistent with those findings from previous trials of bevacizumab in patients with mCRC, as providing further evidence of the safety of bevacizumab in Chinese patients.

Conclusions

The real-world data from the phase IV trial broaden our experience and knowledge of bevacizumab in the Chinese population and provide a good indication of its overall efficacy and safety. The study showed that bevacizumab in combination with chemotherapy has an acceptable and manageable safety profile, with no new safety signals reported, and it offers clinical benefits to patients with mCRC.
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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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