Chemotherapy plus bevacizumab as an optimal first-line therapeutic treatment for patients with right-sided metastatic colon cancer: a meta-analysis of first-line clinical trials

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ABSTRACT

Background Monoclonal antibodies of anti-epidermal growth factor receptor (EGFR) have been recommended as first-line therapy for patients with left-sided metastatic colorectal cancer (mCRC) with wild-type RAS. The effect of tumour laterality on antivascular endothelial growth factor antibody and how to optimise targeted therapies for the right-sided cases remain controversial.

Patients and methods A comprehensive meta-analysis enrolling 16 first-line clinical trials was performed to evaluate the efficacy of chemotherapy alone and chemotherapy plus targeted therapies for patients with mCRC with right primary tumour site, and we validated the results in metastatic setting (14 trials containing 4306 patients with unresectable mCRC).

Results Here, we found that progression-free survival (PFS) (combined HR 1.30, 95% CI 1.17 to 1.44) and overall survival (OS) (combined HR 1.46, 95% CI 1.32 to 1.62) of the right-sided patients were significantly inferior to the left-sided individuals receiving chemotherapy alone in overall population, regardless of race. Similar results were also observed in metastatic setting. OS of patients with left-sided mCRC receiving chemotherapy plus bevacizumab was superior to the right-sided individuals (combined median survival ratio (MSR)=1.23, 95% CI 1.05 to 1.45 for metastatic setting), especially for wild-type RAS and mixed population. Moreover, the right-sided patients benefited more from chemotherapy plus bevacizumab comparing with chemotherapy alone in both overall population and metastatic setting. Importantly, the RAS-wild right-sided patients achieved longer PFS (combined HR 0.67, 95% CI 0.52 to 0.88) and OS (combined HR 0.74, 95% CI 0.56 to 0.98) from chemotherapy plus bevacizumab comparing with chemotherapy associated with anti-EGFR agents.

Conclusions Patients with right-sided mCRC show impaired chemosensitivity, and chemotherapy plus bevacizumab can be an optimal first-line therapeutic regimen for the RAS-wild patients with right-sided mCRC.

INTRODUCTION

Metastatic colorectal cancer (mCRC) is a refractory malignancy with remarkable heterogeneity,1 and it accounts for approximately 40% of the newly diagnosed disease in clinic settings.2 Although patients with the early-stage disease can receive radical resection and adjuvant chemotherapy, the majority of them frequently experience recurrence or distal metastasis after surgery. In regard to mCRC, palliative resection, radiochemotherapy, targeted therapy and immune checkpoint therapy are some of the clinical managements for these patients.3 4 However,
responses of the patients to these treatments are variable. Moreover, inconsistent clinical benefits are also frequently dictated by their primary tumour sidedness.4–6

Studies suggest that patients with left-sided mCRC can benefit more from anti-epithelial growth factor receptor (EGFR) monoclonal antibodies (mAbs) compared with the right-sided cases.7 Consequently, the targeted drugs such as cetuximab and panitumumab have been proposed as first-line therapeutic defenses for the wild-type RAS patients with left-sided disease.8–9 Meanwhile, several clinical trials investigated the prognostic role of bevacizumab, the most commonly used antivascular endothelial growth factor (VEGF) mAb, in the treatment of patients with right-sided and left-sided mCRC.10–11 Specifically, AGITG MAX and CALGB 80405 trials revealed no effect of tumour laterality on prognosis of the patients undergoing first-line chemotherapy plus bevacizumab.7,12

In contrast, PROVETTA, AVP2107g and NO16966 trials identified improved outcome within bevacizumab-treated patients with left-sided mCRC compared with the right-sided cases.5,13 Compared with the left-sided patients, favourable efficacy and prognosis were also observed in the right-sided patients with the treatment of first-line chemotherapy plus bevacizumab as reported in ITACA trial.13 Overall, these trials highlighted an undergoing controversy regarding the efficacy and precise use of bevacizumab combined with chemotherapy. Importantly, there is no meta-analysis reported yet to evaluate the prognostic difference in patients with right-sided mCRC with first-line chemotherapy plus anti-EGFR mAbs or bevacizumab-based treatment.

Hence, a comprehensive meta-analysis with 16 first-line clinical trials was performed to investigate the effect of chemotherapy alone and chemotherapy plus either anti-EGFR mAbs or bevacizumab on prognosis of patients with right-sided mCRC, and to define which was more suitable as a first-line regimen for the patients.

PATIENTS AND METHODS

In the present study, we comprehensively screened and identified eligible studies to perform this meta-analysis in accordance with PRISMA guideline.14 First of all, medical subject heading terms including “rectal, colon, colorectal”; “cancer, tumour, neoplasms or carcinoma”; “sided, sidedness, side, location, localization, site, right and left-side, laterality”; “prognosis, survival, outcome”; and “bevacizumab, cetuximab, panitumumab, EGFR, VEGF, anti-VEGF or EGFR” were selected as the common measurements to assess the robust result by stratified analysis and different pooled model. Publication bias within the included studies was evaluated by Egger’s and Begg’s test.15 16 SPSS V.17.0 and Stata V.11.0 (Stata, College Station, TX, USA) software were used in all statistical analyses and p value <0.05 was considered as statistically significant.

RESULTS

The detailed search and selection procedure are depicted in figure 1. A total of 16 first-line trials,5 7 17–24 including 4574 patients with mCRC, were ultimately fulfilled the inclusion criteria. The baseline characteristics within each eligible study are summarised in table 1. As shown in table 1, 4306 patients within 14 included trials were confirmed as unresectable mCRC cases, which composed the metastatic setting in our study. Eight trials with 3154 patients with mCRC5 7 18 19 23 24 and 10 trials including 3247 patients with mCRC5 7 17 20 22 25 reported the survival difference between the right-sided and left-sided patients receiving first-line chemotherapy alone and chemotherapy plus bevacizumab, respectively. Effects of bevacizumab within the left-sided and right-sided patients were examined in three trials.5 17 Moreover, we also evaluated data of 273 patients with mCRC within three clinical
The combined survival of patients with mCRC receiving first-line chemotherapy is described in figure 2 and online supplementary table 1. Prognosis of chemotherapy-treated right-sided patients was significantly worse than the left-sided cases ($p_{LH}=0.280$, combined HR 1.30, 95% CI 1.17 to 1.44 for PFS; $p_{LH}=0.827$, combined HR 1.46, 95% CI 1.32 to 1.62 for OS), regardless of race. A similar result was also observed in metastatic setting ($p_{LH}=0.567$, combined HR 1.40, 95% CI 1.23 to 1.59 for PFS; $p_{LH}=0.661$, combined HR 1.43, 95% CI 1.24 to 1.64 for OS). Stratifying according to RAS status, the right tumour origin was only significantly associated with poor OS ($p_{LH}=0.756$, combined HR 1.32, 95% CI 1.02 to 1.72) in wild-type RAS subgroup.

In analysis of patients with mCRC treated with first-line chemotherapy plus bevacizumab, combined OS ($p_{LH}<0.001$, combined MSR=1.23, 95% CI 1.08 to 1.39 for overall population; $p_{LH}<0.001$, combined MSR=1.23, 95% CI 1.05 to 1.45 for metastatic setting) of the left-sided patients was obviously longer than the right-sided cases (figure 3), particularly in the RAS-wild individuals ($p_{LH}=0.169$, combined MSR=1.11, 95% CI 1.01 to 1.21 for PFS; $p_{LH}=0.045$, combined MSR=1.29, 95% CI 1.12 to 1.48 for OS) and mixed population ($p_{LH}=0.189$, combined MSR=1.18, 95% CI 1.13 to 1.22 for PFS; $p_{LH}<0.001$, combined MSR=1.29, 95% CI 1.10 to 1.51 for OS) (online supplementary table 2).

Next, we investigated the efficacy of the addition of bevacizumab to chemotherapy as compared with chemotherapy only or chemotherapy treatment plus anti-EGFR mAbs in patients with right-sided mCRC. In first-line chemotherapy plus bevacizumab-treated subgroup, PFS within the right-sided patients was obviously longer than those undergoing chemotherapy only ($p_{LH}=0.009$, combined MSR=1.40, 95% CI 1.15 to 1.71 for overall population; $p_{LH}=0.569$, combined MSR=1.57, 95% CI 1.39 to 1.77 for metastatic setting). Moreover, significantly improved OS was also observed in the right-sided patients ($p_{LH}=0.658$, combined MSR=1.21, 95% CI 1.11 to 1.31 for overall population; $p_{LH}=0.963$, combined MSR=1.20, 95% CI 1.06 to 1.36 for metastatic setting) (figure 4A and online supplementary table 3). Interestingly, the prognosis of RAS-wild right-sided patients receiving first-line chemotherapy plus bevacizumab was obviously superior to the patients undergoing chemotherapy plus anti-EGFR mAbs ($p_{LH}=0.552$, combined HR 0.67, 95% CI 0.52 to 0.88 for PFS; $p_{LH}=0.966$, combined HR 0.74, 95% CI 0.56 to 0.98 for OS) (figure 4B and online supplementary table 4).

In our study, the relative symmetric funnel plots were observed in prognostic comparisons of the right-sided and left-sided patients receiving chemotherapy or chemotherapy combined with bevacizumab; $p$ values of Egger’s and Begg’s tests were greater than 0.05 in each comparison (online supplementary figure 1).

**DISCUSSION**

Studies demonstrate a lack of consensus regarding to which kind of biological antibody is more effective to improve prognosis of patients with right-sided mCRC.22 26 In the present study, we specifically observed that survival of the right-sided patients was inferior to the left-sided individuals with first-line chemotherapy alone or chemotherapy plus bevacizumab, respectively. Whereas, the right-sided patients could benefit significantly from first-line chemotherapy plus bevacizumab, and also achieved strikingly improved prognosis from first-line chemotherapy plus bevacizumab in comparison with combined therapeutic regimen of chemotherapy and anti-EGFR mAbs.

Over the recent decade, targeted therapy has been emerging as an optimal therapeutic option for the treatment of patients with refractory mCRC.27 28 Notably, clinical responses to treatments with anti-EGFR and VEGF mAbs are inconsistent across patients with different primary tumour locations.29 30 In the current study, we found that the outcome of patients with left-sided mCRC was superior to the right-sided patients who received first-line chemotherapy with or without bevacizumab. The results revealed that primary tumour sidedness was linked to the efficacy of chemotherapy. Right-sided mCRC might induce impaired sensitivity to common chemotherapy, leading to different benefits from first-line chemotherapy between the right-sided and left-sided cases. The finding was consistent with our previous study.31 A recent study by Loupakis and his coworkers reported that the right-sided and left-sided patients could significantly benefit from the treatment of chemotherapy plus bevacizumab, especially in the left-sided cases.32 In our study, remarkable PFS and OS improvements were also observed in the
| Clinical trials | Design | Phase | Race | Recruitment time | RAS status | Palliative resection | Therapeutic regimen | Total | Left | Right | Outcome |
|----------------|--------|-------|------|-----------------|------------|---------------------|---------------------|-------|------|-------|---------|
| Negri et al.⁴   | RCT    | III   | Caucasian | 1992–1998     | NA         | No                  | 5-FU*†               | 135   | 96   | 39    | OS      |
| ITACA³          | RCT    | III   | Caucasian | 1997–2001     | NA         | No                  | LV5FU2†              | 172   | 110  | 62    | OS, PFS |
| FCD²            | RCT    | III   | Caucasian | 2001–2003     | NA         | No                  | FOLOX4, mFOLFOX6†    | 122   | 71   | 51    | OS      |
| PROVETTA⁵       | RCT    | III   | Mixed    | 2000–2005     | RAS WT     | No                  | CT+BEV                | 559   | 353  | 206   | OS      |
| AP2107g⁶        | RCT    | III   | Caucasian | 2007–2013     | RAS WT     | No                  | FU/FIRI/mIROX†       | 423   | 341  | 82    | OS      |
| CRESCENT²⁶      | RCT    | II    | Caucasian | 2009–2011     | RAS WT     | No                  | mFOLFOX6+BEV†        | 68    | 54   | 14    | OS      |
| NCT01311050     | Prospective trial | NA     | Asian    | 2009–2011     | No         | No                  | XELOXIRI+BEV†        | 53    | 42   | 11    | OS      |

*Enrolled into the subgroup analysis (right-sided vs left-sided) in patients with mCRC with chemotherapy treatment.
†Enrolled into the subgroup analysis (right-sided vs left-sided) in patients with mCRC with chemotherapy plus bevacizumab treatment.
‡Enrolled into the subgroup analysis (right-sided vs left-sided) in patients with mCRC with chemotherapy plus anti-EGFR treatment.
§Enrolled into the subgroup analysis (CT+BEV vs CT) in patients with right-sided mCRC.
¶Enrolled into the subgroup analysis (CT+BEV vs CT+anti-EGFR) in patients with right-sided mCRC.

BEV, bevacizumab; CET, cetuximab; CT, chemotherapy; FuFIRI, fluorouracil, leucovorin, irinotecan; FFCD, fluorouracil, leucovorin, oxaliplatin, and oxaliplatin; FU, fluorouracil; IV, intravenous; mCRC, metastatic colorectal cancer; mFOLFOX6, fluorouracil, oxaliplatin, and irinotecan; mFOLFOX6+BEV, fluorouracil, oxaliplatin, and irinotecan plus bevacizumab; NA, not available; OS, overall survival; PFS, progression-free survival; RCT, randomised controlled trial; RAS/BRAF WT, RAS/BRAF wild-type; XELOXIRI, capecitabine, oxaliplatin, and irinotecan.
right-sided patients with treatment of first-line chemotherapy plus bevacizumab compared with chemotherapy only. Moreover, we found that prognosis of patients with left-sided mCRC was superior to the right-sided patients receiving chemotherapy plus bevacizumab. These results suggest that bevacizumab improves the prognosis of patients with mCRC; however, impaired chemosensitivity restricts the survival benefit from bevacizumab plus chemotherapy, resulting in poor prognosis in the right-sided mCRC cases. The latest meta-analysis performed by Holch and his coworkers identified significant survival benefit from anti-EGFR mAbs compared with bevacizumab when added to standard chemotherapy in RAS-wild patients with left-sided mCRC.32 Interestingly, the drastically improved prognosis was examined in patients with right-sided mCRC receiving first-line chemotherapy plus bevacizumab comparing with the patients undergoing chemotherapy plus anti-EGFR mAbs in our study.

It indicates that first-line chemotherapy combined with bevacizumab is an optimal clinical treatment of patients with right-sided mCRC to achieve a satisfactory prognosis.

Tumour laterality is one of the most debated topics in treatment of CRC.6 33 34 There is significant heterogeneity in genetic alteration and tumour microecology in right-sided and left-sided cancer.35 36 High CpG island methylator phenotype and microsatellite instability as well as hypermutation within DNA mismatch repair (MMR), MAPK, TGF-β and insulin signalling pathways are prevalent in the right-sided disease compared with its counterpart.22 37–39 The MMR-deficient status impairs genomic stability, leading to carcinogenesis, chemoresistance and progression of the disease.40 41 Meanwhile, chromosome instability, mutations of APC, SMAD4 and P53 as well as EGFR amplification are frequently detected within the left-sided CRC,42 43 while the low instability of genome-wide copy number alterations within right-sided mCRC confers no additional benefit from bevacizumab, resulting in drug resistance.44 Moreover, relatively abundant Prevotella, Pyramido-bacterium, Selenomonas and Peptostreptococcus with low infiltration of activated CD8+ T cell and T helper type 1 cell as well as high infiltration of neutrophils and regulatory T cells are commonly observed in the right-sided disease.45 46 Combination of the environmental factors cross-talk with the cancer cell to release various cytokines such as IL-6, CXCL8 and MIP-1α, creating excessive inflammatory microenvironment in the right-sided disease.47 Our previous study also
identified severe inflammation in the right-sided mCRC, and severe inflammation was also linked with resistance to chemotherapy, leading to poor clinical response and prognosis.\textsuperscript{31} In addition, VEGF expression is relatively high in the left-sided cancer comparing with the right-sided disease.\textsuperscript{48, 49} The right-sided patients often present with inactive EGFR pathway and low expressions of EGFR endogenous ligands such as epiregulin and amphiregulin,\textsuperscript{42} resulting in resistance to EGFR inhibition in these patients.\textsuperscript{50} These differences can likely explain the survival differences between the right-sided and left-sided patient receiving the same therapeutic regimen. Specifically, we come closer to understanding why the prognosis of the bevacizumab-treated right-sided patients is superior to the patients receiving anti-EGFR mAbs-based therapy. This work, to the best of our knowledge, is the first comprehensively designed study examining clinical responses and survival differences in the right-sided patients treated with chemotherapy or chemotherapy plus biological antibodies. Moreover, our work first provides the evidence illustrating first-line bevacizumab-based treatment, instead of chemotherapy plus anti-EGFR mAbs, is likely more suitable for patients with right-sided mCRC. Only the first-line clinical trials were examined in our study, so as to arrive at accurate and robust conclusions.

The following limitations should be addressed to fully understand the findings in our study. The sample size of enrolled studies relating to comparison of the two kinds of biological therapies was small; our findings should be validated by large sample size and multicentre clinical trials. It is also important to emphasise that the majority of examined studies are from Caucasian population, and we do not know the role of primary tumour sidedness in Asian population, especially in Chinese. Finally, there was only one eligible study concerning \textit{RAS}-mutated population, so we could not specifically examine the prognostic difference in \textit{RAS}-mutated patients with right-sided and left-sided mCRC.

In summary, right tumour sidedness confers impaired sensitivity to chemotherapy, and chemotherapy plus bevacizumab can be selected as an optimal first-line therapeutic regimen for the treatment of \textit{RAS} wild patients with right-sided mCRC. The results provide new evidence for clinical practice to precisely select optimal targeted therapeutic regimens for patients with right-sided mCRC and also help to reduce medical costs and prolong the survival of those patients. Further studies are warranted to validate the findings in Asian population and to explore effective biomarkers to predict the prognosis of the patients.

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Contributors X-HY screened and selected the eligible study in the meta-analysis, and performed all the statistics. Y-HJ and ZF contributed to select and identify the eligible study, and extract the data of enrolled studies. FS, YL and Z-JX contributed to data extraction. X-ZW contributed to examining the data. H-QY provided the idea, established the study design, and revised and approved the manuscript.

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