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REVIEW ARTICLE

New Directions in Anti-angiogenesis Therapy in Metastatic Colorectal Cancer

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ABSTRACT

Mortality from metastatic colorectal cancer has declined over the past decade, partly due to improvement in survival secondary to incorporation of targeted biologics in the treatment paradigm. We are now witnessing a new wave of new therapeutic options that may further improve survival outcomes for patients with metastatic colorectal cancer. This review will discuss recently matured data on the treatment outcomes of new anti-angiogenic targeted therapies in metastatic colorectal cancer and how they may affect the practice of oncology.

Key Words: *Angiogenesis inhibitors; Chemotherapy, adjuvant; Colorectal neoplasms; Receptors, vascular endothelial growth factor*

中文摘要

抗血管生成治療轉移性結直腸癌的新方向

龍浩鋒、馬碧如

轉移性結直腸癌的死亡率在過去十年有下降的趨勢，部份原因是因為採納了生物製劑的標靶治療，改善了存活率。我們現在見證了可以進一步改善轉移性結直腸癌患者的新一代治療。本文將會討論抗血管生成治療轉移性結直腸癌結果的最新成熟數據，並探討這些數據如何影響腫瘤學的實踐。

INTRODUCTION

Vascular endothelial growth factor (VEGF) is a critical regulator of angiogenesis, which is crucial for tumour growth and metastasis.[1,2] Several mechanisms of action of anti-VEGF drugs have been postulated, one of which is improvement in the delivery of chemotherapy via both normalisation of stromal vasculature and disruption of tumour vasculature.[3] Another possible mechanism is control of the repopulation of tumour cells during the chemotherapy-free intervals in between treatment cycles. It has also been hypothesised that anti-VEGF therapies may inhibit the mobilisation of bone marrow–derived circulating endothelial cells and their progenitors, therefore slowing tumour growth and improving the efficacy of cell cycle–specific cytotoxic chemotherapy. Bevacizumab, a monoclonal antibody that binds to circulating VEGF, is the first anti-VEGF drug approved by the regulatory authorities for the treatment of metastatic colorectal cancer (mCRC). Bevacizumab has been shown in randomised clinical trials and meta-analyses to improve treatment outcomes when combined with cytotoxic chemotherapy as first- and second-line treatment of mCRC.[1,4-7]

These studies have also shown that bevacizumab can be safely combined with many commonly used cytotoxic

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agents, such as 5-fluorouracil (5-FU), leucovorin plus oxaliplatin (FOLFOX), capecitabine plus oxaliplatin (XELOX; CAPOX), or irinotecan-based regimens without exacerbating chemotherapy-related toxicities. Since the approval of bevacizumab in 2004, researchers have turned their attention to elucidating other potential applications of anti-angiogenesis therapy in mCRC. These applications include whether it is beneficial to continue bevacizumab beyond disease progression after first-line therapy, the role of bevacizumab as 'maintenance' therapy for patients who have responded to chemotherapy and the utility of combining bevacizumab with anti-epidermal growth factor receptor (EGFR) agents. This review summarises some of the latest reports of randomised studies that have addressed these issues, and examine the implications of these new data on clinical practice.

CONTINUING BEVACIZUMAB BEYOND DISEASE PROGRESSION FOLLOWING FIRST-LINE CHEMOTHERAPY FOR METASTATIC COLORECTAL CANCER

Preclinical data have shown that prolonged exposure to anti-VEGF antibodies beyond the stoppage of cytotoxic agents may improve tumour control by delaying tumour progression in xenograft models of CRC.[8] The Bevacizumab Regimens: Investigation of Treatment Effects and Safety (BRiTE) registry project provided the first clinical hint that the continuation of bevacizumab beyond first disease progression may extend survival.[9] More than 1400 patients with mCRC were entered into this study after receiving treatment with bevacizumab in combination with first-line chemotherapy. The median overall survival (OS) was 25.1 months and the median progression-free survival (PFS) was 10.0 months in the entire population enrolled in the study. In the subgroup of 640 patients who continued to receive bevacizumab beyond progression (BBP) together with their next line of chemotherapy, a median OS rate of 31.8 months was reported. This was longer than the median OS rates observed with other subgroups that did not receive bevacizumab with subsequent lines of therapy (OS, 19.9 months), or subgroups that did not receive any subsequent therapy at all (OS, 12.6 months). Compared with no BBP, BBP was strongly and independently associated with improved survival (hazard ratio [HR] = 0.48; $p < 0.001$). This finding was supported by the Avastin Regimens: Investigation of treatment Effects and Safety (ARIES) study, which is another population-based observational study that enrolled over 2000 patients.[10] BBP was independently associated with improved survival beyond progression, with a similar HR (HR = 0.41; 95% confidence interval [CI], 0.34-0.49; $p < 0.001$) as reported in the BRiTE study.

The Treatment across Multiple Lines (TML; ML18741) study is the first reported phase III study that tested the hypothesis that continuing BBP in patients with mCRC may extend survival.[11] This study was presented at the 2012 American Society of Clinical Oncology (ASCO) Annual Meeting. A total of 820 patients who were previously treated with bevacizumab plus standard first-line chemotherapy (either oxaliplatin- or irinotecan-based), were randomised in a 1:1 fashion to either second-line chemotherapy alone, or chemotherapy plus bevacizumab at 2.5 mg/kg/week on confirmation of disease progression. The primary endpoint was OS from the date of randomisation and secondary endpoints included PFS, overall response rate, and safety parameters. Patients were stratified according to the following characteristics: the type of chemotherapeutic regimen received as first-line therapy (oxaliplatin- or irinotecan-based); first-line PFS ≤9 months or >9 months; time interval from the last date of administration of bevacizumab; and performance status at baseline. Notably, it appears that only patients who had benefited from prior bevacizumab-containing treatment were selected for the study, as only patients who progressed within 3 months after the last administration of bevacizumab were eligible. Also, those who had received <3 months of bevacizumab in the first-line setting were excluded. Statistically significant improvements in OS (11.2 months vs. 9.8 months; HR = 0.81; 95% CI, 0.69-0.94; $p = 0.0062$) and PFS (5.7 months vs. 4.1 months; HR = 0.68; 95% CI, 0.59-0.78); $p < 0.0001$) were reported in the intent-to-treat population for the BBP arm, with an absolute improvement in OS of around 1.4 months. This magnitude of benefit was relatively modest compared with that suggested by the BRiTE and ARIES studies as described above, thereby underscoring the pitfalls of registry-derived data. The TML study is important scientifically as a proof-of-concept in the benefit of continual blockade of VEGF-mediated signalling in mCRC. This strategy provided an added therapeutic option for patients with good performance status, metastatic disease that was not rapidly progressing following first-line chemotherapy, and in whom the aim of treatment is to slow progression. Further investigations are needed to clarify how this strategy

should be optimally incorporated into existing clinical algorithms, such as in the *KRAS* wild-type populations.

NEWER APPROACHES TO TARGETING THE VEGF PATHWAY — VEGF-TRAP

Aflibercept is a fully human recombinant protein constructed by fusing the second extracellular domain of vascular endothelial growth factor receptors 2 (VEGFR-2) to the fragment crystallisable segment of immunoglobulin G1.[12,13] Otherwise known as the VEGF-trap, aflibercept binds to all isomers of circulating VEGF-A and VEGF-B, as well as to placental growth factor. In preclinical studies, aflibercept can bind to VEGF with higher affinity than other anti-VEGF agents,[14] decrease vascular growth and density, and suppress tumour growth in vivo. In a phase I study of aflibercept, the recommended dose was determined to be 4 mg/kg every two weeks, and activity against glioblastoma multiforme, renal cell carcinoma, melanoma, ovarian cancer, and lung adenocarcinoma were reported.[15,16]

The VELOUR study is a randomised phase 3 trial evaluating aflibercept in combination with 5-FU, leucovorin, and irinotecan (FOLFIRI) as second-line treatment for mCRC.[17] A total of 1226 patients who had previously received oxaliplatin-based chemotherapy were randomised to either FOLFIRI plus aflibercept or FOLFIRI plus placebo. The primary endpoint was OS. More than 30% of recruited patients had prior bevacizumab use. At the time of presentation of this study's result at the ASCO Annual Meeting in 2012, the median OS was 13.5 months for the aflibercept arm versus 12.1 months for the placebo arm (HR = 0.92; p = 0.003) and PFS was 6.9 months versus 4.7 months (HR = 0.76; p < 0.001). There was a significant improvement in overall response rate in the aflibercept arm (19.8% vs. 11.1%) regardless of prior exposure to bevacizumab in the first-line setting. However, bevacizumab-naïve patients seemed to have a larger incremental OS benefit than bevacizumab-treated patients: 11.7% versus 8.4% in the bevacizumab-pretreated group compared with 23.3% versus 12.4% in bevacizumab-naïve patients. Treatment-related discontinuation due to adverse events (i.e. grade 3/4 toxicities) was more common in the aflibercept arm than in the placebo arm (26.6% vs. 12.1%), with asthenia, infections, diarrhoea, hypertension, and venous thromboembolic events being the most commonly encountered toxicities. Aflibercept has since been approved by the United States Food & Drug Administration (US FDA) in combination with FOLFIRI in second-line treatment of mCRC after failure of oxaliplatin-based first-line chemotherapy. This agent is being evaluated in the first-line setting in combination with modified FOLFOX6 (mFOLFOX6) in the phase 2 Aflibercept And Modified FOLFOX6 As First-Line Treatment In Patients With Metastatic Colorectal Cancer (AFFIRM) trial (NCT00851084).[18] This trial has completed enrolment and the results are eagerly awaited.

TARGETING VEGF AND THE EGFR AS MAINTENANCE TREATMENT

EGFR and VEGFR signalling have shown extensive cross-talk in pre-clinical studies, thus providing a rationale for dual targeting of the two signalling pathways.[19] The combination of bevacizumab, chemotherapy, and EGFR antibodies such as cetuximab or panitumumab have produced unanticipated adverse effects on survival and, in some cases, added toxicities in randomised studies.[20,21] In contrast, a preclinical study in CRC models suggested that the combination of small molecules against the VEGFR and EGFR may exert a more effective inhibitory effect on downstream oncogenic signalling after failure from treatment with antibodies.[22] Erlotinib has been evaluated either as monotherapy or in combination with oxaliplatin- or irinotecan-based regimens in phase II studies in mCRC.[23,24] These studies have shown that erlotinib has a very modest disease-stabilising effect in patients with multiply-treated mCRC, and may have overlapping gastrointestinal and cutaneous toxicities with irinotecan and capecitabine. However, the clinical effect of combining erlotinib with non-cytotoxic–targeted agents remains unclear, although there is preclinical evidence to suggest that erlotinib and bevacizumab in combination may be synergistic in preclinical models of mCRC. The Double Reintroduction with Erlotinib and Avastin in Metastatic CRC (DREAM) study is a phase III randomised study designed to test the hypothesis that bevacizumab and erlotinib in combination may be a feasible and more effective 'maintenance' therapy than bevacizumab alone in mCRC.[25] Of the 700 patients who were enrolled before starting first-line chemotherapy, 446 patients were deemed eligible for subsequent randomisation. These 446 patients who did not progress after six months of initial treatment with bevacizumab chemotherapy were randomised to 'maintenance' with either bevacizumab alone, or bevacizumab in combination with erlotinib until disease progression. The primary endpoint was PFS while on

maintenance treatment, and patients were stratified by performance status, *KRAS* status, and the quality of initial response (either partial response or stable disease as per the Response Evaluation Criteria in Solid Tumors criteria). In the initial results presented at the ASCO Annual Meeting in 2012, a 1.2-month improvement in PFS favouring the combination arm (PFS from randomisation) was observed — the median PFS was 5.75 months for the combination arm and 4.57 months for the bevacizumab alone arm (HR = 0.73; 95% CI, 0.59-0.91; p = 0.005). OS data are not yet mature and *KRAS* analysis is ongoing. Toxicities were acceptable with an expected increase in grade 3/4 diarrhoea and skin toxicities in the combination arm. The DREAM study is important scientifically as it has provided further support to the maintenance strategy in mCRC, which was first evaluated by the French Groupe Coopérateur Multidisciplinaire en Oncologie study group in the Optimized Leucovorin-Fluorouracil-Oxaliplatin (OPTIMOX) studies.[26,27] However, the clinical applicability of the DREAM study has been questioned because of the use of erlotinib in partnership with bevacizumab. Unlike 5-FU, which was used in the OPTIMOX study as maintenance, erlotinib has uncertain single-agent activity in mCRC and is not approved for the treatment of mCRC. Other studies that evaluate capecitabine and / or bevacizumab as maintenance are ongoing.

REGORAFENIB — A VEGFR AND MULTI-TARGETED KINASE INHIBITOR

Regorafenib is a novel oral diphenylurea-based multikinase inhibitor of pathways that are associated with proliferation, tumour microenvironment, and neo-angiogenesis.[28] In pre-clinical studies, regorafenib has been shown to be a potent inhibitor of several angiogenic and stromal receptor tyrosine kinases, including the VEGFR-1, VEGFR-2, VEGFR-3, platelet-derived growth factor receptor–β, fibroblast growth factor receptor–1, and TIE2. Regorafenib can also inhibit c-KIT, RET, and BRAF. In phase 1 trials, the recommended dose of regorafenib is 160 mg/day on a three-week on, 1-week off schedule.[29,30] Pharmacokinetics studies have shown that there are two active metabolites of regorafenib — M2 and M5; M2 has a similar half-life to the parent compound of 24 hours, while M5 has a half-life of over 90 hours.

The Colorectal Cancer Treated with Regorafenib or Placebo (CORRECT) trial is a pivotal phase III study in which 760 patients from 16 countries who were refractory to all standard systemic options for mCRC were randomised in a 2:1 ratio to either regorafenib or placebo without any crossover at progression. This study showed that regorafenib could significantly improve OS (HR = 0.77; 2-sided p = 0.0102) and PFS (HR = 0.49; 2-sided p < 0.0001) compared with placebo.[31] The median OS and PFS were 6.4 and 2.0 months in the regorafenib arm, versus 5.0 and 1.7 months in the placebo arm, respectively. Five patients (1%) in the regorafenib arm and one patient (0.4%) in the placebo arm had partial responses. The most frequently observed severe adverse drug reactions (i.e. grade 3 or above) in patients who received regorafenib were palmar-plantar erythrodysesthesia (16.6%), asthenia (9.6%), decreased appetite and food intake, diarrhoea (7.2%), and hypertension (7.2%). There was no significant difference in health-related quality of life with regorafenib versus placebo.

The mechanism of action of regorafenib in mCRC remains unclear, and thus predictive biomarkers are not yet available for optimal patient selection. Whether the positive effects seen with single-agent regorafenib is predominantly due to VEGF inhibition or to its ability to suppress other pathways beside VEGF is uncertain. The pharmacokinetic properties of regorafenib with the long half-life of some of its metabolites might have also contributed to better drug exposure and thus better outcome. Regorafenib is now approved by the US FDA as third-line treatment in patients with mCRC who have progressed during or after oxaliplatin- and irinotecan-based chemotherapy.

CONCLUSIONS

The recently reported positive results of the DREAM and TML studies are good examples of the successful translation of preclinical 'proof-of-mechanism' studies on the use of continual angiogenesis blockage in mCRC. The use of bevacizumab beyond disease progression or as a maintenance treatment following induction chemotherapy in mCRC has expanded our therapeutic armamentarium against mCRC. The next step is to investigate how we should optimally select patients for these strategies and incorporate them into existing clinical algorithms. The pivotal studies on aflibercept and regorafenib provide further proof of the relevance of anti-angiogenesis in mCRC. With the increased availability and application of high-throughput molecular platforms around the world, it is hoped that newer biomarkers will be discovered soon to

better individualise the myriad of options available to our patients.

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