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REVIEW ARTICLE

Optimising Systemic Therapy in Metastatic Colorectal Cancer

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ABSTRACT

The last 30 years have witnessed numerous advances in the management of metastatic colorectal cancer leading to an expansion in treatment options and improvement in treatment outcomes. The management of metastatic colorectal cancer involves an individualised treatment strategy based on evaluation of treatment goals for different patient subgroups, taking into account a variety of tumour-, host-, and treatment-related factors. Available systemic therapy includes chemotherapy regimens that can be combined with targeted agents such as anti–vascular endothelial growth factor antibodies (e.g. bevacizumab) and anti–epidermal growth factor receptor antibodies (e.g. cetuximab, panitumumab) to yield improved clinical outcomes. This article discusses recent clinical data on systemic therapy for metastatic colorectal cancer using different treatment combinations in various clinical settings.

Key Words: *Chemotherapy; Colorectal cancer; Targeted therapy; Bevacizumab; Maintenance*

中文摘要

優化轉移性結直腸癌的全身性治療

許斌

過去30年間轉移性結直腸癌治療的進展帶來了更多的治療選擇，並改善了治療結果。轉移性結直腸癌的治療，涉及根據病人亞組評估而定的個人化治療目標，需要考慮多個腫瘤、宿主及治療相關的因素。現有的全身性治療包括：可與標靶藥物例如抗血管內皮生長因子抗體（如貝伐株單抗bevacizumab）及抗上皮生長因子受體抗體（如西妥昔單抗cetuximab、帕尼單抗panitumumab）合併使用的化療方案，以達致更好的臨床結果。本文討論了在各種臨床情況下，採用不同治療組合對轉移性結直腸癌進行全身性治療的近期臨床數據。

INTRODUCTION

For more than 40 years, 5-fluorouracil (5-FU) has been the mainstay of treatment for patients with metastatic colorectal cancer (mCRC). As single-agent therapy, the response rate to 5-FU is usually less than 20%. Since the 1990s, many advances have been made in the management of mCRC resulting in an increase in treatment options and improved clinical outcomes. In addition to 5-FU, the available treatment modalities now include other cytotoxic agents (irinotecan, oxaliplatin, capecitabine), anti–vascular endothelial growth factor (VEGF) monoclonal antibodies (e.g. bevacizumab), anti–epidermal growth factor receptor (EGFR) monoclonal antibodies (e.g. cetuximab, panitumumab), as well as newer targeted agents such as aflibercept and regorafenib. Survival of patients with mCRC has improved substantially from less than 1 year with 5-FU alone to now reaching more than 2 years.

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PERSONALISED APPROACH FOR METASTATIC COLORECTAL CANCER: DOES ONE SIZE FIT ALL?

A variety of treatment combinations is now available, integrating cytotoxic agents and targeted agents with the aim of improving response rates and survival compared with single agent alone. It has been shown that exposure to all three active cytotoxic agents (5-FU/leucovorin, irinotecan, and oxaliplatin) confers a survival benefit in patients with mCRC. A meta-analysis of 21 arms of 11 phase III trials showed that improved median overall survival (OS) was strongly associated with treatment with all three agents during the course of disease ($R^2 = 0.85$, $p = 0.0001$).[1] This suggested that combination therapy is important in first-line treatment of mCRC as it allows patients to have an improved chance of receiving all three active agents in the course of therapy.

In clinical practice, every patient is different and treatment decisions should take individual clinical situations into consideration. The European Society for Medical Oncology guidelines suggest that patients with initially unresectable mCRC can be individually divided into three clinical groups, for which treatment goals and strategies differ.[2] The first category includes patients with liver or lung metastases that might become resectable; treatment in these patients should aim at conversion to resectability and R0 resection. The second category includes patients with rapid progression of multiple metastases, presence of tumour-related symptoms and risk of rapid deterioration; in these patients, treatment should aim at maximum tumour shrinkage and control of progressive disease. The third category includes patients with multiple metastases where resection is not an option, and patients with asymptomatic disease or severe comorbidity that does not permit surgery and / or intensive systemic therapy; treatment goals in these patients should focus on minimising treatment toxicity, improving quality of life, and controlling further progression.[2] For all patients, the ultimate goal is to prolong progression-free survival (PFS) and OS.

Other important factors that influence treatment selection include tumour biology (e.g. dynamics of progression, biomarkers, mutation status), patient's psychological capacity and willingness to undergo more intensive treatment, drug toxicity profile, and treatment cost.[2] These factors should be considered along with patient preferences and individual treatment goals when selecting appropriate treatment for patients with mCRC.

TREATMENT COMBINATIONS: DO BAD TREATMENT PARTNERS EXIST?

Different combinations of cytotoxic and targeted agents may generate regimens that are more effective or less favourable than others. It is important that treatment combinations avoid overlapping toxicities or antagonistic effects that may have a detrimental impact on survival. Two phase III randomised studies, CAIRO2 and PACCE, suggested that chemotherapy should not be combined with dual blockade with both anti-VEGF and anti-EGFR antibodies.[3,4] Both studies showed that adding cetuximab or panitumumab to a combination of bevacizumab and chemotherapy resulted in significantly shorter PFS. Furthermore, the combination of panitumumab, bevacizumab, and chemotherapy was associated with increased frequency of high-grade adverse events.[4]

Randomised studies using anti-EGFR monoclonal antibodies in combination with chemotherapy in first- and second-line mCRC showed mixed outcomes. Improved response rates with anti-EGFR antibodies were almost exclusively observed in patients with *KRAS* wild-type tumours.[5] The choice of chemotherapy backbone matters in *KRAS* wild-type tumours as it affects the response rate and survival. FOLFIRI (5-FU, folinic acid, irinotecan) appeared to be the most optimal backbone for the addition of cetuximab, and was associated with significantly improved objective response rate and prolonged PFS and OS. Conversely, the addition of anti-EGFR antibodies to bolus 5-FU– or capecitabine-based regimens was not associated with improved response or survival in patients with *KRAS* wild-type tumours, and may even be detrimental when combined with oxaliplatin-based regimens in *KRAS* mutant tumours.[5]

Results from recent randomised trials — New EPOC, FIRE-3 and CAIRO3 — provided new insight into the role of targeted agents in different treatment strategies and clinical settings.

ANTI–EPIDERMAL GROWTH FACTOR RECEPTOR WITH PERIOPERATIVE CHEMOTHERAPY: THE NEW EPOC STUDY

Although the PFS benefits of perioperative chemotherapy and surgery were previously demonstrated in the EPOC study,[6] recent extension of the study — the New EPOC — failed to show any benefit of

adding cetuximab to perioperative and postoperative chemotherapy.[7] The study randomised 272 patients with *KRAS* wild-type CRC and resectable liver metastases to FOLFOX (5-FU, folinic acid, oxaliplatin) / FOLFIRI regimen with or without cetuximab for 12 weeks before, and 12 weeks following surgery.[7] Results were unexpected in that the cetuximab arm demonstrated a significantly worse PFS than the chemotherapy arm (14.8 vs. 24.2 months; hazard ration [HR] = 1.50; $p < 0.048$). The study was terminated early on the recommendation of the Independent Data Monitoring Safety Board. Reasons for the negative results are currently unknown; an imbalance of biomarkers in the two study arms has been speculated to have contributed to the outcome.

ANTI–VASCULAR ENDOTHELIAL GROWTH FACTOR VERSUS ANTI–EPIDERMAL GROWTH FACTOR RECEPTOR: IS THERE A CLEAR WINNER?

FIRE-3 is the first study with head-to-head comparison between first-line bevacizumab/FOLFIRI and cetuximab/FOLFIRI in *KRAS* wild-type mCRC to determine which targeted therapy is optimal as part of the first-line chemotherapy regimen.[8] This phase III study involved 592 patients with confirmed *KRAS* wild-type tumours, who were randomised to receive either bevacizumab or cetuximab with first-line FOLFIRI chemotherapy. While the mean treatment duration was comparable between the two arms, patients who took bevacizumab with chemotherapy received significantly more treatment cycles ($p = 0.014$). The study's primary endpoint was overall response rate (ORR), which was not significantly different between the two arms (62% with FOLFIRI plus cetuximab vs. 58% with FOLFIRI plus bevacizumab; odds ratio = 1.18; $p = 0.183$). The main reason for not reaching the primary endpoint was the higher-than-expected ORR in the bevacizumab arm. In a subgroup of patients assessable for response (i.e. those who completed three cycles of treatment and had one computed tomography scan), there was a statistically significant superiority in ORR in favour of cetuximab (72.2% vs. 63.1%; $p = 0.017$).

Regarding survival outcomes, median PFS was nearly identical in both arms (10.0 months with FOLFIRI plus cetuximab vs. 10.3 months with FOLFIRI plus bevacizumab). Interestingly, OS was significantly longer in patients receiving FOLFIRI plus cetuximab compared with those receiving FOLFIRI plus bevacizumab (28.7 months vs. 25.0 months, $p = 0.017$). The survival curves in the two study arms began to separate about 24 months after the start of treatment, well after the 10-month median PFS. This suggested that second or subsequent lines of treatment may have influenced the OS outcome.

In this study, approximately 25% of patients did not receive any second-line therapy. Selecting appropriate first-line treatment is thus important in clinical practice as a substantial proportion of patients are unlikely to receive second-line therapy. Of those who received second-line therapy, the majority of patients in the FOLFIRI plus cetuximab arm received second-line bevacizumab and oxaliplatin-based therapy, and most patients in the FOLFIRI plus bevacizumab arm received second-line anti-EGFR and oxaliplatin-based therapy. The unfavourable combination of anti-EGFR antibodies with oxaliplatin may play a role in the OS outcome.

Safety data revealed no significant difference in the haematological or non-haematological toxicity between the two study arms. FOLFIRI plus bevacizumab did not lead to any significant difference in grade ≥3 adverse events of special interest versus anti-VEGF treatment. It is hoped that results of the ongoing CALGB 80405 study, which has a very similar design to FIRE-3 and compares bevacizumab with cetuximab in combination with FOLFOX or FOLFIRI, will serve to provide further survival data in this patient population.

MAINTENANCE THERAPY: NEW OPTION TO EXTEND SURVIVAL

Various treatment strategies can be employed for disease control, such as multi-line strategy with fixed sequence of continuous treatment, stop-and-go strategy, and intermittent therapy.[9] In daily practice, many patients prefer taking a chemotherapy break after achieving initial disease control to reduce treatment toxicities and improve their quality of life. The OPTIMOX1 study showed that oxaliplatin can be safely stopped after six cycles in a FOLFOX regimen to achieve the same efficacy and survival as continuous FOLFOX treatment.[10] However, the subsequent OPTIMOX2 showed that complete stoppage of chemotherapy was associated with a shorter duration of disease control.[11] Maintenance therapy incorporating well-tolerated targeted agent is thus an attractive option to ensure long-term response and disease control.

The recent phase III CAIRO3 study investigated the role of bevacizumab and capecitabine as maintenance

therapy after disease control with induction therapy. In this study, patients were randomised to receive bevacizumab plus capecitabine or observation after six cycles of induction therapy with capecitabine and oxaliplatin (XELOX) plus bevacizumab.[12] Upon the first episode of disease progression, patients in both arms were treated with XELOX plus bevacizumab until second progression, which was the study's primary endpoint.

It was observed that maintenance treatment with bevacizumab and capecitabine significantly prolonged the time to first and second episodes of disease progression. The median first progression occurred at 8.5 months in the maintenance arm versus at 4 months in the observation arm (adjusted HR = 0.41; $p < 0.001$).[12] After XELOX plus bevacizumab treatment, the median time to second progression was 11.8 months in the maintenance arm and 10.5 months in the observation arm, giving a 23% reduction in risk of second progression (adjusted HR = 0.77; $p = 0.007$). Maintenance therapy also led to an OS benefit (21.7 months with maintenance vs. 18.2 months with observation; adjusted HR = 0.80; $p = 0.035$). Grade 3 or 4 toxicity in both arms was manageable. The most clinically relevant adverse events were hand-foot syndrome (22% with maintenance vs. 0% with observation) and neurotoxicity (10% with maintenance vs. 5% with observation).

Among four randomised trials comparing maintenance therapy with chemotherapy-free interval in advanced CRC, prolonged PFS was observed in all maintenance arms but a significant OS benefit was only reported in the CAIRO3 study.[11-14] Since OS remains the key endpoint for patients and for changing practice, data from CAIRO3 support the use of bevacizumab plus capecitabine maintenance therapy in routine practice.

BIOMARKERS BEYOND *KRAS* EXON 2

KRAS mutations are a well-recognised negative predictive biomarker for anti-EGFR therapy in CRC in clinical practice. In addition to *KRAS*, mutations in other signal transducer components of the RAS/RAF pathway — such as *BRAF*, NRAS, PIK3CA, Akt, PTEN and TP53 — may also affect response to anti-EGFR therapy. A European consortium study analysed 773 primary tumour samples for mutation frequency from chemotherapy-refractory mCRC treated with cetuximab.[15] Results showed that 40% of the tumours harboured a *KRAS* mutation, 14.5% harboured a *PIK3CA* mutation, 4.7% harboured a *BRAF* mutation, and 2.6% harboured an *NRAS* mutation. *BRAF*, *NRAS*, and *PIK3CA* exon 20 mutations were significantly associated with a low response rate. In the unselected patient population, ORRs were only 24%, but extended up to 41% by additional genotyping of *BRAF*, *NRAS*, and *PIK3CA* exon 20 mutations in the *KRAS* wild-type population.

KRAS mutations in CRC commonly refer to mutations detected in codons 12 and 13 of exon 2. The recent phase III PRIME study on the efficacy of panitumumab plus FOLFOX in *KRAS* wild-type mCRC revealed that other *RAS* mutations beyond *KRAS* may be predictive of negative outcomes in patients receiving anti-EGFR therapy. In this analysis, patient tumour samples with wild-type *KRAS* status were assessed for additional *RAS* mutations and for *BRAF* mutations. Results showed that 17% of the *KRAS* exon 2 wild-type tumours had other mutations, most commonly *BRAF* exon 15 codon 600 (8%), followed by *KRAS* exon 4 (6%), *KRAS* exon 3 (4%), *NRAS* exon 3 (4%), and *NRAS* exon 2 (3%).[16,17] Patients with any *RAS* mutation had worse PFS and worse OS with panitumumab. In contrast, wild-type *RAS* tumours were associated with a 5.8-month improvement in OS among patients who received panitumumab in addition to FOLFOX (HR = 0.78; $p = 0.043$). Since this analysis, the European Medicines Agency has changed the indication and contraindication of panitumumab; panitumumab is now indicated for the treatment of adult patients with *RAS* wild-type mCRC, and contraindicated in those with *RAS* mutant mCRC or with unknown *RAS* mCRC status.[18]

RESISTANCE TO TARGETED THERAPY

Many patients with CRC who receive anti-EGFR therapy are prone to develop secondary resistance within several months of initiating therapy. Recent reports proposed that resistance could be caused by the proliferation of rare tumour cells with mutations in the *KRAS* gene that allow them to survive anti-EGFR therapy.[19-21] These mutations can now be detected and quantified by a new system testing for the presence of *KRAS* mutations in circulating tumour DNA derived from a patient's blood. This 'liquid biopsy' may allow detection of the onset of drug resistance well before that with standard imaging techniques, allowing more time for planning and executing subsequent treatment.

Bevacizumab targets VEGF overexpressed throughout the tumour's life cycle. The mechanism of bevacizumab resistance is likely due to tumours acquiring the means to use alternative proangiogenic proteins. A strategy to overcome resistance is changing the chemotherapy partner of anti-VEGF therapy.[22] Anti-VEGF agents are likely to remain a valid treatment even in the late stage of disease.

CONCLUSION

The optimal systemic therapy for patients with mCRC should be individualised according to the treatment goals for different patient subgroups, taking into account tumour biology factors, mutation status, patient characteristics and preferences, treatment efficacy, toxicity profile, and cost. Certain treatment partners may have unfavourable effects and should be avoided; these may include combination of both bevacizumab and anti-EGFR antibodies with chemotherapy. Cetuximab is best partnered with a FOLFIRI or irinotecan-based chemotherapy backbone, while the combination with bolus 5-FU– or capecitabine-based regimen is not recommended. Panitumumab can be partnered with FOLFIRI or FOLFOX, while bevacizumab partners well with most available regimens (except with oxaliplatin alone, which has no single-agent activity). The optimal choice of targeted agent (bevacizumab vs. cetuximab) with first-line chemotherapy remains a subject of debate and findings from the FIRE-3 study await validation with results from the CALGB 80405 study. In CAIRO3 study, bevacizumab plus capecitabine maintenance therapy significantly prolonged PFS, OS and time to progression, making it an attractive strategy to maintain disease control after induction therapy. Apart from *KRAS* exon 2 mutations, other *RAS* mutations may also be predictive of negative outcomes in patients receiving anti-EGFR therapy, while *BRAF* mutation is a marker of poor prognosis. In the future, new mutation detection technology using circulating tumour DNA may help to direct therapeutic decisions and biomarker development. Improved understanding of the interaction between different treatment combinations would help further optimise systemic treatment of mCRC.

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