
ORIGINAL ARTICLE

Current Role of Biological Agents in Colorectal Cancer

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ABSTRACT

Colorectal cancer is one of the most frequently diagnosed malignancies in the world. In spite of recent advances in chemotherapy, the prognosis for patients with metastatic colorectal cancer remains poor. The last decade of ground-breaking research on molecular pathways involved in tumour growth has paved the way for targeted therapies, such as bevacizumab and cetuximab. Emerging data contribute to our understanding of the clinical application of these novel therapies in the pharmaceutical armamentarium for colorectal cancer. The identification of biomarkers associated with disease control, including K-ras and B-raf mutations, is changing the colorectal cancer treatment paradigm. Clinical and molecular predictive markers of response are being evaluated. Recent clinical studies may help us better select patients who could benefit from targeted therapies, and thus optimise patient outcomes and minimise unnecessary toxicities.

Key Words: Bevacizumab; Capecitabine; Cetuximab; Colorectal neoplasms

中文摘要

治療結直腸癌的最新生物製劑發展

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結直腸癌是最常見的癌症之一。儘管化療技術有最新發展，轉移性結直腸癌的預後仍然很差。過去十年，對腫瘤生長的分子路徑的研究有突破性進展，為標靶治療（如阿瓦斯汀bevacizumab及西妥昔單抗cetuximab）打下了基礎。最新的數據更有助我們了解這些在治療結直腸癌藥物庫中的嶄新療法於臨床上的使用。辨析與病情控制有關的生物標記，包括K-ras及B-raf基因突變，正在改變結直腸癌的治療模式。研究人員現正評估可預測療效的臨床及分子指標。最新的臨床研究有助我們更好的篩選那些可受惠於標靶治療的病人，從而確保病人得到最佳的臨床效果及減少不必要的治療毒性。

INTRODUCTION

Colorectal cancer (CRC) is the second most common cancer in Hong Kong. In 2007, there were 4084 new cases of CRC accounting for about 17% of all newly diagnosed cancers in the Hong Kong SAR region.¹ CRC is also the most rapidly increasing, in terms of numbers, among all cancers in Hong Kong over the last 20 years.²

As one of the leading causes of cancer mortality

worldwide,³ CRC claimed the lives of 1686 Hong Kong patients in 2008 alone. This translates to about 14% of all cancer deaths in Hong Kong.¹

The management of CRC is largely dependent on staging, and therefore driven by patient assessment. While surgery remains the mainstay of CRC treatment,⁴ chemotherapy also has an important role in management. The administration of chemotherapy to CRC patients with initially unresectable metastases

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can increase the number of patients who can undergo potentially curative resections later.⁵

FIRST-LINE CHEMOTHERAPY

FOLFOX4 — oxaliplatin in combination with infusional 5-fluorouracil (5-FU) — has been one of the standard regimens for first-line chemotherapy of advanced CRC.^{6,7}

GERCOR,⁸ a phase III study, investigated 2 chemotherapy sequences in previously untreated CRC patients with assessable disease:

- (1) irinotecan-based therapy (FOLFIRI) followed by oxaliplatin-based therapy (FOLFOX6); and
- (2) oxaliplatin-based therapy (FOLFOX6) followed by irinotecan-based therapy (FOLFIRI).

GERCOR data showed those randomised to either sequence achieved prolonged survival and similar efficacy.⁸ An interesting finding in this trial was that patients who received FOLFOX6 first-line had significantly more resectable tumours ($p = 0.02$).⁸

One of the newer approaches to CRC treatment is a return to the oral route of administration. The oral approach is preferred by patients as it is more convenient (involving fewer medical office visits) and more comfortable (requiring no intravenous access).⁹ Clinicians also prefer this approach as it reduces the risk of complications, such as infection and clotting, that are associated with venous access devices and infusion pumps.⁹

Capecitabine is an oral antimetabolite that is metabolised to 5-FU. It is converted to 5-FU preferentially in tumour tissues, where it inhibits DNA synthesis and slows tumour growth. Capecitabine mimics continuous-infusion 5-FU. Its oral route of administration, coupled with evidence of efficacy from recent clinical trials, places capecitabine firmly in the therapeutic armamentarium for CRC.

A large, open-label, phase II study of XELOX (capecitabine + oxaliplatin) as first-line therapy for metastatic CRC (mCRC) was conducted in 13 centres in Europe and North America.¹⁰ Half of the patients in this study had multiple metastases. A preclinical study confirmed that capecitabine had supra-additive activity with oxaliplatin.¹⁰ In the clinical study, XELOX was found to be a highly effective first-line treatment for mCRC. Response rates, time to progression, and overall

survival (OS) were similar to those observed with fluorouracil, leucovorin and oxaliplatin combinations. Based on such efficacy data, capecitabine can replace fluorouracil and leucovorin in a combination regimen with oxaliplatin for mCRC. To that end, the authors concluded that XELOX was a convenient regimen and likely to be preferred by both patients and health care providers.¹⁰

A phase III non-inferiority study compared XELOX to FOLFOX4 (fluorouracil, folinic acid and oxaliplatin) as first-line therapy in mCRC. Progression-free survival (PFS) was the primary endpoint for the non-inferiority. Median PFS and median OS were similar in both the XELOX and FOLFOX4 study arms. While the FOLFOX4 regimen was associated with more grade 3/4 neutropenia, granulocytopenia and febrile neutropenia, patients on XELOX were more prone to diarrhoea and grade-3 hand-foot syndrome. This study showed that XELOX was non-inferior to FOLFOX4 as first-line treatment for mCRC.¹¹

Given the evidence from clinical trials to date, we can reasonably conclude that XELOX and FOLFOX are both effective first-line treatment options for the management of mCRC. Clinicians can now choose the appropriate treatment regimen taking into account different toxicity profiles and patient preferences.

ADJUVANT CHEMOTHERAPY

Analysis of the ACCENT database concluded that in patients aged 70 years and above, newer adjuvant regimens are not associated with significant efficacy benefits compared to 5-FU/leucovorin.¹² A post-hoc analysis of the XELOXA trial compared adjuvant treatment with XELOX versus 5-FU/leucovorin in patients with lymph node-positive colon cancer to investigate if age affected the results.

According to a sub-analysis of the XELOXA trial presented at the 2010 American Society of Clinical Oncology Gastrointestinal Cancers Symposium (ASCO-GI), XELOX was associated with improved disease-free survival over bolus 5-FU/leucovorin regimens in stage III colon cancer, regardless of age.¹³

Based on these results, the European Medicines Agency has approved capecitabine in combination with oxaliplatin for the treatment of patients with early colon cancer.¹⁴ The National Comprehensive Cancer Network (NCCN) also updated the NCCN Colon

Cancer Guidelines to include CapeOX (capecitabine + oxaliplatin) as an alternative option to FOLFOX.¹⁵

TARGETED THERAPY IN COLORECTAL CANCER

Advances in the therapy of CRC are expanding the therapeutic options available for patients who once had limited treatment choices. Targeted therapies block the growth of cancer cells by interfering with specific molecules involved in carcinogenesis.¹⁶ By focusing on molecular and cellular changes that are specific to cancer, targeted cancer therapies may be less harmful to normal cells and may therefore minimise the risk of complications and drug-induced reactions without sacrificing therapeutic benefit.¹⁶

Some targeted therapies interfere with angiogenesis to block tumour growth. Bevacizumab inhibits vascular endothelial growth factor (VEGF) to control, or slow, cancer progression.

Mutations affecting epidermal growth factor receptor (EGFR) expression or activity result in cancer.¹⁷ Cetuximab and panitumumab are monoclonal antibody inhibitors that target EGFR. There is more market experience with cetuximab, as it has been available in most countries for several years. Panitumumab has only just entered the market.

PRIME was a randomised, phase III trial of panitumumab plus FOLFOX4 versus FOLFOX4 alone, used as first-line treatment in patients with mCRC. This study demonstrated that panitumumab plus FOLFOX4 was well tolerated and significantly improved PFS when used first-line in mCRC patients with wild-type *K-ras* tumours.¹⁸

Cediranib is an anti-angiogenic that inhibits all three VEGF receptors.¹⁹ The cediranib HORIZON III study was designed to evaluate the activity and clinical benefit of cediranib in combination with FOLFOX chemotherapy in patients with first-line mCRC.²⁰ However, cediranib's efficacy did not meet the pre-specified criteria for the primary endpoint of non-inferiority when compared with bevacizumab for PFS.²¹ HORIZON II assessed the efficacy of cediranib combined with chemotherapy compared with chemotherapy alone.²¹ Data from HORIZON II are expected in the coming months.

This article overviews the emerging evidence for

bevacizumab and cetuximab in this patient group.

BEVACIZUMAB

VEGF is an important signalling protein involved in vasculogenesis and angiogenesis. Cancers that express VEGF are able to grow and metastasise.¹⁶ In animal studies, anti-VEGF antibodies used as a single agent and in combination therapy have shown significant activity.²²

Bevacizumab, a recombinant monoclonal antibody which is administered intravenously, is a VEGF receptor inhibitor.

Bevacizumab as First-line Treatment

A phase III clinical study conducted by Hurwitz et al²³ presented data that enabled the licensing of bevacizumab as first-line treatment for mCRC in many countries. The study involved 813 patients with previously untreated mCRC. Patients were randomised to one of 2 treatment arms: (a) irinotecan, fluorouracil and leucovorin (IFL) plus bevacizumab; or (b) IFL plus placebo.²³

PFS was significantly increased by 71% in the IFL plus bevacizumab arm (10.6 [95% confidence interval, 9.0-11.0] vs 6.2 [5.6-7.7] months, $p < 0.001$).²³ The stratified hazard ratio for disease progression or death during first-line therapy in the IFL plus bevacizumab arm relative to the IFL plus placebo arm was 0.54 (95% confidence interval, 0.45-0.66).²³

It was interesting that the differences in OS and PFS between the 2 treatment arms were relatively constant at 4.7 and 4.4 months, respectively. Together with the study design, in which the treatment arms differed only with respect to the addition of bevacizumab to IFL, this finding suggests that the increase in survival was due to the addition of the former. This study showed that the addition of bevacizumab to fluorouracil-based combination chemotherapy as first-line treatment resulted in significantly superior, and clinically meaningful improvements in both PFS and OS among patients with mCRC.²³

The NO16966 trial evaluated the efficacy and safety of bevacizumab when added to first-line XELOX or FOLFOX4 in patients with mCRC.²⁴ The quantum of benefit from this trial seemed to be less than that in the Hurwitz et al's study,²³ which may be because the NO16966 trial used 'on-treatment' analysis; patients who were off chemotherapy for reasons other than toxicity

and progression were excluded. NO16966 showed that the addition of bevacizumab to chemotherapy (XELOX or FOLFOX) significantly improved median PFS compared to chemotherapy alone (10.4 vs 7.9 months).²⁴ These data clearly demonstrate that bevacizumab should be given until progression.

Bevacizumab as Second-line Treatment

First-line use of bevacizumab in combination with chemotherapy improves survival of mCRC patients.

The E3200 study was conducted to determine the effects of bevacizumab on survival for oxaliplatin-based chemotherapy in patients with previously treated mCRC. The study involved 829 mCRC patients who were previously treated with a fluoropyrimidine or irinotecan. The 3 treatment arms were: (a) FOLFOX4 plus bevacizumab; (b) FOLFOX4 only; and (c) bevacizumab only.²⁵

The E3200 study showed that the addition of bevacizumab to the FOLFOX4 chemotherapy regimen as second-line treatment improved survival duration for mCRC patients.²⁵

Bevacizumab Use after Progression on First-line Treatment

There is strong evidence for the use of bevacizumab until progression. However, the potential value of continuing bevacizumab after patients experience progression on first-line therapy with bevacizumab plus chemotherapy continues to be debated.²⁶

ARIES was a prospective, non-randomised, observational cohort study involving mCRC patients receiving first- or second-line bevacizumab. Results suggested that continued suppression of VEGF with bevacizumab post-progression might contribute to improved outcomes for mCRC patients.²⁷

The ML18147 (TML) trial is ongoing. This study randomises patients to second-line chemotherapy with, or without, bevacizumab after progression on a first-line regimen with bevacizumab.²⁶

Current data appear to support the use of bevacizumab post-progression in CRC patients. Nevertheless, changes in clinical practice should not be made in the absence of evidence from prospective, randomised clinical trials.

Bevacizumab and Biological Predictive Markers

K-ras mutations in codon 12 and 13 can predict primary resistance to targeted therapies. This predictive potential of *K-ras* mutations was originally described in retrospective evaluations.^{28,29}

The serine-threonine kinase *B-raf* is a direct downstream effector of *K-ras*. It has been identified as an additional biomarker of resistance.³⁰ *B-raf* mutations have been detected in approximately 5 to 10% of CRC tumours.³¹

Defects in apoptosis, caused by the inactivation of the p53 tumour suppressor gene, can produce treatment-resistant tumours. Therefore, the p53 status may be a determinant of response to therapy.³²

Ince et al³³ conducted a retrospective analysis of patients in the Hurwitz trial to evaluate whether *K-ras*, *B-raf* or p53 mutations, or p53 expression could predict which patients were more likely to respond to bevacizumab. No statistically significant relationships between mutations of *K-ras*, *B-raf* or p53 and the increase in median survival associated with the addition of bevacizumab to IFL in mCRC were found.³³

In view of this, it appears that the survival benefit from the addition of bevacizumab to first-line IFL was independent of *K-ras*, *B-raf* or p53 mutation status, or p53 expression.

CETUXIMAB

It is believed that EGFR, which is commonly found on CRC cells, participates in signalling pathways that are deregulated in cancer cells. Cetuximab is a chimeric monoclonal antibody that inhibits EGFR. It is administered as an intravenous infusion for the treatment of mCRC.

Cunningham et al³⁴ compared the efficacy of cetuximab in combination with irinotecan with that of cetuximab alone in mCRC patients refractory to treatment with irinotecan. They found that cetuximab had clinically significant activity both as monotherapy, and in combination therapy with irinotecan in patients with irinotecan-refractory CRC.³⁴ Cetuximab has also shown improvements in OS and PFS, when used as third-line therapy in patients with CRC.³⁵

Cetuximab is indicated for the treatment of patients with EGFR-expressing, *K-ras* wild-type mCRC, in

combination with chemotherapy, and as a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan.³⁶

Cetuximab as First-line Treatment for Epidermal Growth Factor Receptor-detectable Metastatic Colorectal Cancer

The benefits of cetuximab as second- or third-line therapy in mCRC are well known. Emerging evidence from the Cetuximab Combined with Irinotecan in First-Line Therapy for Metastatic Colorectal Cancer (CRYSTAL) study shows that the addition of cetuximab to FOLFIRI (irinotecan/5-FU/leucovorin) in the first-line therapy of mCRC significantly improves overall response rates and PFS, and an enhanced treatment effect in patients with *K-ras* wild-type tumours is evident.^{37,38}

The Oxaliplatin and Cetuximab in First-Line Treatment of mCRC (OPUS) study showed that cetuximab plus FOLFOX4 was superior to FOLFOX4 alone as first-line treatment of mCRC. In this study, the influence of the *K-ras* mutation was also assessed in a subset of patients with assessable tumour samples. OPUS showed that the overall response rate for cetuximab plus FOLFOX4 was higher than with FOLFOX4 alone. In patients with *K-ras* wild-type tumours, the addition of cetuximab to FOLFOX4 was associated with a clinically significant increased chance of response and lower risk of disease progression than in those receiving FOLFOX4 only.³⁹

A recent meta-analysis of the pooled CRYSTAL and OPUS in *K-ras* wild-type patients⁴⁰ showed that adding cetuximab to first-line chemotherapy of mCRC significantly improved OS, PFS and overall response (OR).^{38,41}

The results of the NORDIC VII study showed that adding cetuximab to the FLOX regimen (fluorouracil, folinate, and oxaliplatin) did not improve response rate, PFS or OS. This lack of benefit was irrespective of *K-ras* mutations.⁴²

One of the questions addressed by the COIN study was whether the addition of cetuximab to oxaliplatin-based chemotherapy improved OS when given as first-line therapy.⁴³ Its results indicated that such an addition made no difference to OS. Interestingly, OS for patients in this study was relatively low, and nor did cetuximab seem to benefit patients with *K-ras* wild-type tumours.⁴⁴

Cetuximab and Biological Predictive Markers

Patients with *K-ras* and *B-raf* wild-type tumours appeared to enjoy the best outcomes from cetuximab therapy.⁴¹

In the OPUS study, the *K-ras* mutation status was predictive for PFS and OR in mCRC patients treated with cetuximab plus FOLFOX4. Patients with *K-ras* wild-type tumours benefited from cetuximab in terms of OR and PFS. In this group of patients, addition of cetuximab to FOLFOX4 treatment was associated with a 43% reduction in the risk of progression and a 2.5-fold increased chance for response compared to therapy with FOLFOX4 only, though OS was not significantly longer.³¹

However, the addition of cetuximab to oxaliplatin-based therapy in patients with *K-ras* mutant tumours showed a decrease in activity when compared to chemotherapy alone.³⁹ Subsequently, this effect was also shown in the CAIRO⁴⁵ and COIN³⁷ studies, which seemed to suggest a negative interaction between cetuximab and oxaliplatin-based therapy in patients with *K-ras* mutant tumours.

Data on the influence of *B-raf* mutational status in the same setting should be available shortly.

SUMMARY

Based on available evidence, it appears that bevacizumab has poor activity as a single agent, though it confers significant improvements in PFS and OS when added to both fluorouracil- and oxaliplatin-based first-line chemotherapy.^{23,24} As second-line therapy, the addition of bevacizumab to the FOLFOX4 chemotherapy regimen improved survival duration for patients with mCRC.²⁵ The survival benefit conferred by adding bevacizumab to standard first-line chemotherapy appeared to be independent of *K-ras*, *B-raf* or p53 mutation status, or p53 expression.³³

It is clear that bevacizumab should be used at least until disease progression.²⁴ Some data support the use of bevacizumab post-progression in CRC patients.²⁷ Future results on ongoing clinical studies may provide more clinical guidance on this matter.

Currently available data from efficacy and safety clinical studies have contributed to our knowledge of the optimal use of targeted therapies in the management

of CRC patients. Even though our understanding of biological agents has extended significantly in recent years, many questions have yet to be answered.

Unlike bevacizumab, cetuximab can be used as monotherapy for the treatment of mCRC,³⁴ and can also be used in second- and third-line combination therapy.^{34,35}

Results of recent clinical trials suggest that cetuximab may have some activity as first-line therapy in mCRC.³⁷⁻³⁹ However, these benefits were not reproduced in the NORDIC VII⁴² and COIN studies.^{43,44} Further investigations are needed to clarify the potential benefits of cetuximab in this patient population.

Clinicians should be cautious when using cetuximab with oxaliplatin-based chemotherapy as this regimen may result in a negative interaction.³⁹

Patients with *K-ras* and *B-raf* wild type tumours appeared to derive the best outcomes from cetuximab therapy.⁴¹

CONCLUSIONS

CRC is a complex disease, with many variants and subtypes. As we develop greater sophistication in understanding the molecular biology of each individual's cancer, it is likely that more rational selection of targeted therapies, and combinations of targeted therapies, will lead to greater therapeutic success.

XELOX (capecitabine and oxaliplatin) therapy appears to be a good chemotherapy backbone for combination regimens with biological agents. Emerging evidence supports the use of bevacizumab with first-line chemotherapy regimens for mCRC. Conversely, the value of cetuximab appears to be in second-line and subsequent lines of treatment.

It is unlikely that any one biological agent, or even any one combination of biological agents, will be active in all patients with CRC. Yet these novel agents provide clinicians with more choices for targeted therapy. The most promising aspect of combination therapy may be to combine the right patient with the right drug or regimen.

There are many ongoing clinical trials that aim to evaluate the role of biological combinations in CRC.

Participation in these trials should be encouraged with a view to achieving progress in CRC treatment.

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