REVIEW ARTICLE

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Optimal Management of Metastatic Colorectal Cancer

Current Status

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Abstract

Colorectal cancer remains one of the most common causes of cancer death in the US, with approximately a quarter of patients presenting with metastatic disease at the time of diagnosis. Recent advances over the past 2 decades have increased the repertoire of chemotherapeutic agents for this disease and extended median overall survival to more than 20 months. An increasing body of evidence also supports the addition of targeted agents, those directed towards vascular endothelial growth factor and epidermal growth factor receptors, to expand treatment options for patients with metastatic disease. Ongoing trials are exploring the optimal combinations of these drugs as well as promising new investigational agents that take advantage of the genetic aberrations that drive tumour biology. This review aims to summarize the pertinent data on available cytotoxic and biological agents used to extend survival in metastatic colorectal cancer patients and provide a modern approach to treatment strategies while acknowledging the areas of controversy on which future clinical trials should be based.

Colon cancer is the third most common malignancy worldwide, with an estimated 1.24 million new diagnoses in 2008.[1,2] About 20% of patients present with metastatic disease at the time of their initial diagnosis and without treatment have a median overall survival (OS) of about 6 months.[3]

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Additionally, a significant portion of patients initially diagnosed with localized disease will eventually recur in the metastatic setting, with about 75 000 patients undergoing treatment for metastatic colorectal cancer (mCRC) in the US each year.[4]

Fortunately, the advances made in the treatment of mCRC over the past 40 years have dramatically improved outcomes. Single-agent 5-fluorouracil (5-FU) delivered alone affords an OS of 12–15 months. The anti-cancer armamentarium has been bolstered with the approval of six additional agents since 1996, including irinotecan, capecitabine, oxaliplatin, bevacizumab, cetuximab and panitumumab. By carefully combining agents, oncologists are extending the median survival for a majority of patients with mCRC to almost 2 years. These results have stemmed from clinical trials that identified more effective combinations of these drugs as well as advancing our understanding of the molecular pathways that lead to tumourigenesis and tumour progression in these patients. More recent trials have focused on how best to incorporate these agents, such as the monoclonal vascular endothelial growth factor (VEGF) antibody bevacizumab and the epidermal growth factor receptor (EGFR) inhibitors cetuximab and panitumumab, into standard chemotherapeutic regimens. In this review, we examine the evolution of treatment paradigms for patients with mCRC and focus on the importance of further advancing drug development in this arena, but more clearly delineating the key downstream effectors leading to malignant phenotypes.

1. Fluoropyrimidines

5-FU has been the backbone of treatment regimens for colorectal cancer for over 40 years. It functions as a nucleoside analogue, inhibiting thymidylate synthase (TS) and preventing production of the pyrimidine thymidine, which is required for DNA replication. Because TS converts deoxyuridine monophosphate into thymidine monophosphate via methylation, rapidly dividing cancer cells are left with a paucity of thymidine monophosphate and undergo cell death.[5] When 5-FU is administered with leucovorin, a folinic acid derivative, the inhibition of TS is potentiated because of the ability of leucovorin to stabilize the interaction between TS and 5-FU. The benefits of this synergy were suggested in early phase I/II studies of colorectal patients and then confirmed in a meta-analysis of nine randomized trials in which over 1300 colorectal cancer patients were enrolled to receive bolus 5-FU alone versus 5-FU with leucovorin, with an improved response rate (RR) of 23% reported with the addition of leucovorin compared with 11% in the 5-FU alone group.[6-9]

How to most effectively deliver 5-FU has been much debated. The French group led by de Gramont compared the traditional Mayo Clinic regimen, in which leucovorin 20 mg/m^2 is administered prior to a 5-FU bolus (425 mg/m^2) daily for 5 days, with a bimonthly regimen consisting of intravenous leucovorin 200 mg/m^2 as a 2-hour infusion followed by a bolus of 5-FU (400 mg/m^2) and a 22-hour infusion of 5-FU (600 mg/m^2) for 2 consecutive days every 2 weeks.[10] Not only was the de Gramont method more effective in terms of RRs and progression-free survival (PFS), but the incidence of grade 3/4 toxicities were fewer with less myelosuppression, diarrhoea and mucositis. Subsequently, a meta-analysis of six randomized trials involving over 1200 patients comparing the efficacy of the two delivery methods reiterated that infusional 5-FU resulted in an improved RR of 22% compared with 14% in those receiving bolus 5-FU.[11] There was no significant difference in OS. Additionally, in the Intergroup Trial N9741, which evaluated 5-FU/leucovorin in combination with either irinotecan or oxaliplatin in patients with untreated mCRC, the three arms containing bolus 5-FU had to be modified or closed due to toxicity or early death.[12] Five patients receiving bolus 5-FU with irinotecan (8.2%) and four patients receiving bolus 5-FU with oxaliplatin died within 2 months of entering the study. Therefore, it was felt that combination chemotherapeutic regimens containing bolus 5-FU carried an increased risk of severe gastrointestinal (GI) toxicity and early mortality and should instead include infusional 5-FU in the metastatic setting.

Capecitabine is the oral pro-drug of 5-FU that mimics the infusional properties of the agent with

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twice-daily administration. After being absorbed in the intestine, it is converted to the active metabolite of 5-FU via a pathway of three enzymes, the last of which is thymidine phosphorylase that acts as the rate-limiting step in converting 5′-deoxy-5-fluorouridine to the active drug fluorouracil.[13] Because this enzyme is found in higher concentrations within tumours themselves, higher concentrations of active drug can accumulate within areas of tumour involvement, sparing toxicity to neighbouring normal tissue.[14] Capecitabine is approved for use in mCRC patients as a single agent at a dose of 1250 mg/m^2 twice a day on days 1–14 of a 21-day cycle; however, for American patients whose diets are enriched with folate, a dose of 1000 mg/m^2 has been more widely adopted and better tolerated.

Several studies have compared different 5-FU regimens, both infusional and oral, against the traditional Mayo Clinic regimen, in which leucovorin 20 mg/m^2 is administered prior to a 5-FU bolus (425 mg/m^2) daily for 5 days.[15-18] In each study, OS was not significantly different when compared with control. Two large phase III trials were reported in 2001 that randomized patients with mCRC to receive capecitabine (1250 mg/m^2 twice a day on days 1–14) versus bolus 5-FU in the first-line setting.[18,19] The overall tumour RRs in the capecitabine group were at least equivalent to, if not higher than, those in the 5-FU/leucovorin group with the oral formulation having significantly less diarrhoea, stomatitis, neutropenia, nausea and hair loss. While about 40% of patients in the capecitabine group from both trials required a dose reduction as a result of toxicity, a safety analysis revealed that efficacy was not compromised in the group receiving lower doses of drug.[20] A direct comparison between capecitabine and the preferred infusional 5-FU regimen described by de Gramont et al. has not been performed; therefore, while the oral formation is often thought of as more convenient for some patients and at least equally efficacious, we have no direct comparison data to support substituting capecitabine for infusional 5-FU as the standard of care.

The conversion of 5-FU to its inactive metabolite 5, 6-dihydro-5-fluorouracil by dihydopyrimidine dehydrogenase (DPD) is the first and rate-limiting step of 5-FU catabolism in the liver. In fact, only about 1–3% of the original dose of 5-FU is responsible for the cytotoxic effects on tumour cells via anabolic inhibition of DNA synthesis.[21] Individuals with reduced activity of DPD due to missense mutations or polymorphisms within the DPD gene are more susceptible to 5-FU toxicity, some cases of which can be lethal. The most frequent of these mutations involves a G to A point mutation within the 5′-splicing site of intron 14, resulting in loss of exon 14 and a truncated, inactive protein product.[22] A study of 149 healthy African American and 109 Caucasian volunteers revealed that the prevalence of DPD deficiency was 3-fold higher in African Americans with African American women having the highest prevalence compared with African American men, Caucasian women and Caucasian men (12.3%, 4.0%, 3.5% and 1.9%, respectively).[23] Among a group of 25 patients reported to have severe 5-FU toxicity by their physicians, 20% were found to be heterozygous and 4% were homozygous for the exon 14 mutation.[22] All six patients with DPD deficiency developed grade 4 myelosuppression during treatment, with lethal outcomes reported in three patients (two heterozygous and one homozygous). Whether to screen all patients undergoing treatment with 5-FU in an effort to avoid such extreme effects is not clear; however, patients experiencing undue toxicity, especially myelosuppression, should have their dose reduced and be considered for mutational analysis.

2. Irinotecan

Until irinotecan was approved in 1996 as both a single agent and also in combination with 5-FU, there had been no significant therapeutic breakthroughs for patients with mCRC. By undergoing hydrolysis, irinotecan is converted to its active metabolite, SN38, which acts as a topoisomerase 1 inhibitor, preventing DNA replication and transcription. SN38 is further metabolized and hence inactivated via glucuronidation by uridine diphospho-glucuronosyltransferase 1A1 (UGTA1A1). First described as the underlying aetiology for patients with Gilbert's syndrome, polymorphisms

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in the TATA sequence of the promoter region of UGTA1A1 (deemed UGTA1A1*28) lead to decreased hepatic clearance of SN38 and are found in about 10% of the North American population.[24] When exposed to irinotecan, these patients exhibit increased susceptibility to severe neutropenia and sepsis when compared with those without the polymorphism.[25,26] Therefore, it is recommended that patients known to be homozygous for the UGTA1A1*28 polymorphism initially receive a reduced dose of irinotecan and be closely observed for bone marrow toxicity.

While irinotecan plays no role in the adjuvant setting for colorectal cancer, several non-randomized phase II trials have reported on the clinical efficacy of irinotecan as a single agent in patients with metastatic disease, with an average RR of approximately 20%.[27-29] The earliest of these studies led by Rothenberg et al.[28] enrolled 48 patients with mCRC who had progressed on 5-FU and found that at a dose of 150 mg/m^2 weekly for 4 weeks followed by a 2-week break, 44% of patients developed grade 4 diarrhoea. The toxicity incidence decreased to 23% with a weekly dose of 125 mg/m^2, which was the more commonly used regimen in subsequent studies. Furthermore, in a randomized trial reported by Cunningham et al.,[30] a group of 198 mCRC patients who had documented disease progression after treatment with 5-FU were randomized to receive irinotecan versus best supportive care (BSC). There was a significant survival advantage for patients in the treatment group with an increased 1-year survival of 36.2% compared with 13.8%.

Two large, randomized, phase III trials have investigated the role of first-line irinotecan in combination with 5-FU compared with 5-FU alone in the metastatic setting.[31,32] In both studies, the combination of irinotecan with 5-FU resulted in a significant improvement in RR, time to progression and OS. In general, the addition of irinotecan to either bolus or infusional 5-FU regimens increased the RR from approximately 20% to 35%. Douillard et al. employed an infusional 5-FU regimen for their study with an increase in grade 3/4 diarrhoea from 25.6% in the 5-FU/leucovorin-alone group to 44.4% in the combination arms containing irinotecan.[31] Alternatively, the trial reported by Saltz et al. randomized 683 patients using bolus 5-FU regimens administered either weekly or daily for 5 days every 4 weeks.[32] The overall incidence of grade 3/4 diarrhoea was lower in this trial with 22.7% in the irinotecan plus 5-FU/leucovorin arm versus 13.2% for the 5-FU/leucovorin-alone arm. Regardless, there were no toxicity-related deaths and this regimen emerged as the first-line standard of care for colorectal cancer patients in the metastatic setting.

It was not until the latter part of 2000 that the superiority of the modern day FOLFIRI regimen (irinotecan in combination with infusional 5-FU/leucovorin) was demonstrated in the randomized BICC-C trial (see table I for definitions of trial acronyms) reported by Fuchs et al. in which 430 previously untreated mCRC patients were randomly assigned to three arms: (i) FOLFIRI; (ii) a modified form of IFL (irinotecan plus bolus 5-FU/leucovorin) [mIFL]; or (iii) the combination of capecitabine with irinotecan (CapeIRI).[33] The trial reported a significant improvement in PFS when irinotecan was combined with infusional 5-FU compared with the bolus or oral formulation (7.6 months vs 5.9 months vs 5.8 months, respectively). Of critical importance, CapeIRI was associated with much higher rates of severe vomiting, diarrhoea and dehydration, and in an amended protocol in which patients were randomized to receive FOLFIRI or mIFL with or without bevacizumab, the CapeIRI arm was discontinued. A similar toxicity profile for this combination was reported in the non-inferiority EORTC 40015 trial in which mCRC patients were randomized to receive FOLFIRI versus CapeIRI in the second-line setting.[34] The trial was closed to accrual early after eight deaths unrelated to disease progression were reported, six in the CAPIRI arm and two in the FOLFIRI arm. Although the sample size was small with only 85 reportable patients, the median PFS and OS were shorter for CapeIRI versus FOLFIRI (5.9 months vs 9.6 months and 14.8 months vs 19.9 months, respectively). Therefore, while it is preferred that patients being treated with irinotecan receive combination therapy with infusional 5-FU, those that remain on capecitabine

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Table I. Definition of trial acronyms

Acronym	Trial
BICC-C	Randomized, controlled trial of irinotecan plus infusional, bolus, or oral fluoropyrimidines in first-line treatment of metastatic colorectal cancer
BOND	Randomized phase II trial of cetuximab, bevacizumab, and irinotecan compared with cetuximab and bevacizumab alone in irinotecan-refractory colorectal cancer
CAIRO	Sequential versus combination chemotherapy with capecitabine, irinotecan, and oxaliplatin in advanced colorectal cancer study
COIN	A three-arm randomized controlled trial comparing either continuous chemotherapy plus cetuximab or intermittent chemotherapy with standard continuous palliative combination chemotherapy with oxaliplatin and a fluoropyrimidine in first-line treatment of metastatic colorectal cancer
CRYSTAL	Cetuximab combined with irinotecan in first-line therapy for metastatic colorectal cancer
EORTC 40015	European Organisation for Research and Treatment of Cancer 40015 trial
EPIC	Phase III trial of cetuximab plus irinotecan after fluoropyrimidine and oxaliplatin failure in patients with metastatic colorectal cancer
GERCOR	Groupe Cooperateur Multidisciplinaire en Oncologie
MACRO	Phase III study of first-line XELOX plus bevacizumab (BEV) for 6 cycles followed by XELOX plus BEV or single-agent (s/a) BEV as maintenance therapy in patients (pts) with metastatic colorectal cancer (mCRC)
MOSAIC	Multicenter international study of oxaliplatin/5-fluorouracil/leucovorin in the adjuvant treatment of colon cancer
NORDIC VII	FLOX in combination with cetuximab in first-line treatment of colorectal cancer
OPTIMOX1	A randomized study of FOLFOX4 or FOLFOX7 with oxaliplatin in a stop-and-go fashion in advanced colorectal cancer
OPUS	Oxaliplatin and cetuximab in first-line treatment of metastatic colorectal cancer
PACCE	Panitumumab advanced colorectal cancer evaluation
PRIME	The panitumumab randomized trial in combination with chemotherapy for metastatic colorectal cancer to determine efficacy
TREE	Three regimens of eloxatin evaluation

should be monitored carefully for GI and haematological toxicity.

It should be noted, however, that in the group of 389 patients enrolled on the CAIRO study who received CapeIRI in the setting of a trial that was designed to investigate sequential versus concurrent administration of 5-FU, irinotecan and oxaliplatin, no significant difference was noted in the frequency of grade 3/4 toxicity when compared with patients receiving capecitabine alone or capecitabine plus oxaliplatin (CAPOX).[35] A total of 820 patients were randomly assigned to receive either first-line capecitabine followed by second-line irinotecan followed by third-line CAPOX versus CapeIRI in the first-line setting followed by CAPOX in the second-line setting. The trial concluded that no difference in OS was noted between the sequential versus combination arms (16.3 months vs 17.4 months, $p = 0.3281$).

3. Oxaliplatin

The addition of oxaliplatin to the list of approved therapies for patients with colorectal cancer provided yet another option for those in both the adjuvant and metastatic setting. Similar to other platinum agents, oxaliplatin acts as an alkylator, cross-linking DNA strands and thus preventing effective DNA replication and transcription. Oxaliplatin has been shown to have no significant activity as a single agent in colorectal cancer, but instead significantly improves RRs and PFS when combined with 5-FU. This was demonstrated in a group of 420 untreated advanced colorectal cancer patients who were randomized to receive treatment with 5-FU/leucovorin (per the de Gramont regimen) versus 5-FU/leucovorin combined with oxaliplatin.[36] The patients who received oxaliplatin had a median PFS of 9.0 months compared with 6.2 months in the 5-FU/leucovorin-alone group, with a markedly improved RR of 50.7% versus 22.3%. OS was not significantly different between the two groups but survival without a compromise on patients' quality of life (QOL) was longer in patients receiving oxaliplatin ($p = 0.004$).

These earlier studies led the way for later trials, specifically the MOSAIC trial, to solidify FOLFOX (oxaliplatin plus infusional 5-FU/leucovorin) as the standard of care for colorectal cancer patients in the adjuvant setting and to obtain US FDA approval of the drug in this setting.[37]

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The convenience that comes with delivering 5-FU in an oral formation makes capecitabine plus oxaliplatin (XELOX) an attractive regimen for patients with metastatic disease. Cassidy et al. reported in a large, randomized, phase III trial of over 2000 patients designed for non-inferiority that administering XELOX in the metastatic setting was essentially equivalent to FOLFOX-4.[38] The median OS rates for each regimen were 19.8 months with XELOX versus 19.6 months with FOLFOX-4 with a hazard ratio (HR) of 0.99. The use of capecitabine was associated with more diarrhoea and hand/foot syndrome but had less neutropenia than infusional 5-FU.

N9741, an Intergroup Trial led by Goldberg et al., investigated both the safety and efficacy of three different two-drug combinations, including IFL, FOLFOX and IROX (oxaliplatin and irinotecan), in untreated patients with mCRC.[39] A total of 795 patients were enrolled with a significantly superior RR of 45% and median survival time of 19.5 months for patients receiving FOLFOX.

While sensory neuropathy and myelosuppression were more common in this arm, the FOLFOX regimen had significantly lower rates of GI toxicity (including nausea, vomiting and diarrhoea), febrile neutropenia and volume depletion. As noted previously, three arms in the original N9741 protocol used bolus 5-FU, including the IFL arm, all of which required modifications and, in some cases, discontinuation due to toxicity and early patient deaths. It is therefore preferred to deliver FOLFIRI, a regimen that was compared head-to-head against FOLFOX in the randomized GERCOR study reported by Tournigand et al.[40] A total of 200 untreated patients were randomized to receive FOLFIRI followed by FOLFOX at the time of progression (Arm A) versus the reverse sequence of FOLFOX followed by FOLFIRI (Arm B). There was no difference in median survival (21.5 months vs 20.6 months, $p = 0.99$), PFS (14.2 months vs 10.9 months, $p = 0.64$) or RRs in the first-line setting (56% vs 54%, $p = 0.26$) between the two sequences. These findings were confirmed in an Italian trial led by Colucci et al. in which 360 mCRC patients were randomized to receive either FOLFIRI or FOLFOX in the first-line setting with no significant difference in RRs, time to progression, duration of response or OS.[41] There was a difference in toxicity profiles between the two treatments, with FOLFOX having more neuropathy and FOLFIRI having more GI toxicity. It is generally accepted that patients treated with FOLFOX in the adjuvant setting who experience a recurrence at least 12 months after completing therapy likely have oxaliplatin-sensitive disease and, therefore, can be retreated with FOLFOX in the first-line metastatic setting.

The neuropathy associated with oxaliplatin often results in discontinuation of the drug, even in the setting of responsive disease. Therefore, several large trials utilizing maintenance regimens have been conducted to explore how best to limit the degree of toxicity without compromising efficacy. The OPTIMOX1 trial enrolled over 600 previously untreated mCRC patients to receive either FOLFOX4 until progression (Arm A) or FOLFOX7 for six cycles followed by maintenance 5-FU/leucovorin for twelve cycles at which point FOLFOX7 was re-introduced for six additional cycles (Arm B).[42] Overall, the medical PFS and survival times were not significantly different between the two groups, with an average of 9 months and 10 months for the PFS and OS, respectively. Therefore, this trial suggested that discontinuing oxaliplatin after six cycles followed by 5-FU/leucovorin maintenance did not result in compromised RRs or survival, but did lower the incidence of grade 3 and 4 toxicities. This decrease was most apparent for cycles 7–12, which corresponds to the time period during which oxaliplatin was stopped in Arm B. Only about 40% of patients in this arm were retreated later with oxaliplatin, with the majority not restarting due to early progression, death or treatment-related toxicity. Of the approximately 125 patients who were able to receive additional FOLFOX7, 70% had either tumour response or disease stabilization. However, since almost 30% of patients in Arm A were eventually re-treated with oxaliplatin off protocol, this trial made it difficult to make any conclusions regarding the role of oxaliplatin re-introduction.

The OPTIMOX2 trial was designed to further assess this issue as well as to explore the role of a

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stop-and-go strategy in treating metastatic patients long term.[43] A total of 212 patients were randomized to receive either six cycles of mFOLFOX7 followed by maintenance 5-FU/leucovorin until disease progression (Arm 1) versus the same six cycles of mFOLFOX7 followed by observation only (Arm 2). In both cases, mFOLFOX7 was restarted at the time of documented progression of disease. The use of maintenance 5-FU therapy was associated with a significant improvement in the duration of disease control (DDC) [13.1 months vs 9.2 months, $p = 0.46$] as well as PFS (8.6 months vs 6.6 months, $p = 0.0017$). Unlike the OPTIMOX1 data, over 80% of patients in both arms were reintroduced to chemotherapy at the time of progression. This likely contributed to the longer DDC of 13 months seen in the maintenance arm of OPTIMOX2 compared with 10.6 months in the group receiving maintenance 5-FU/leucovorin in OPTIMOX1. While this study suggested that discontinuing therapy altogether and observing until disease progression resulted in a negative impact on DDC and PFS, it can be argued that only 3 months of chemotherapy is not sufficient before affording patients a chemotherapy-free interval. Therefore, each patient's case should be analyzed separately as some patients including those with more indolent disease, modest bulk of disease, with no disease specific symptoms, or those who have endured cumulative toxicity from long treatment intervals surely can benefit from taking a break from chemotherapy. It must also be noted that because the OPTIMOX2 trial used DDC as its primary endpoint, the results, while interpreted as portending a survival advantage for those receiving continuous chemotherapy, are difficult to compare head to head with other studies with more traditional endpoints.

4. Combination Chemotherapeutics

While both FOLFOX and FOLFIRI have been shown to be equally effective regimens in the first-line setting, several studies have explored whether combining oxaliplatin with irinotecan with or without 5-FU is a comparable option. The previously described N9741 trial did include as one of its treatment arms the combination of oxaliplatin and irinotecan without 5-FU (IROX).[39] In a follow-up analysis of the nearly 1700 patients enrolled on this trial at a median follow-up of 5 years, patients receiving FOLFOX had a significantly prolonged OS and time to progression (TTP) when compared with IFL or IROX, setting the survival benefit from FOLFOX as one standard-of-care option in the first-line setting.[44] While the IROX regimen does not include infusional 5-FU, Souglakos et al. conducted a randomized phase III trial in which 283 patients received FOLFIRI versus FOLFOXIRI (5-FU, leucovorin, oxaliplatin and irinotecan) in the first-line setting with no significant difference seen between the two arms in terms of OS, TTP or RR.[45] The patients receiving FOLFOXIRI did, however, have a significant increase in toxicity, most notably alopecia, diarrhoea and neuropathy. Alternatively, Falcone et al. reported a significant improvement in both OS and PFS in patients randomized to receive FOLFOXIRI compared with FOLFIRI the following year, with an increased R0 resection rate of metastases.[46] The idea of using more aggressive combination therapy in the first-line setting prior to metastatectomy was further investigated in a phase II trial conducted by Ychou et al. in which 34 patients with potentially resectable liver metastases were treated with a similar FOLFIRINOX regimen every 2 weeks for a maximum of 12 cycles.[47] The RR prior to surgery was 70.6% with 26% of patients achieving an R0 resection at the time of surgery, resulting in a 2-year OS rate of 83%. While the majority of North American practitioners do not consider these combination chemotherapeutics standard of care outside of a clinical trial, the studies discussed do suggest a role for FOLFIRINOX or FOLFOXIRI in the neoadjuvant setting for patients with potentially resectable metastatic disease.

5. Targeted Therapy

5.1 Bevacizumab

VEGF, a family of endothelial growth factors, plays a central role in angiogenesis through its effects on endothelial cell migration, proliferation, permeability and survival.[48] While VEGF

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is critical in maintaining normal tissue function by inducing endothelial proliferation and vascular permeability, VEGF can also be produced by tumour cells and their associated stroma, promoting tumour growth and metastases. Bevacizumab is a humanized monoclonal antibody with a high affinity to soluble VEGF. By binding VEGF in the circulation, bevacizumab decreases the incidence of VEGF engaging its receptor and hence decreases tumour growth by halting angiogenesis (figure 1). VEGF-A is the most abundant of the VEGF family of ligands and binds to VEGF receptor (VEGFR)-1 and VEGFR-2, the latter being considered a critical receptor in regulating angiogenesis. Therefore, most anti-angiogenic therapies focus on preventing binding of VEGF-A to VEGFR-2. Preclinical studies have indicated a causal role for VEGF in the metastatic potential of colorectal cancer. A study of 52 human colon cancer specimens using immunohistochemistry staining for VEGF and the VEGFRs found that expression of VEGF and VEGFR-2 was increased in metastatic specimens with a direct association with higher degrees of proliferation, as determined by proliferating cell nuclear antigen staining.[49] Therefore, a number of clinical trials have been conducted to determine the efficacy of using bevacizumab in combination with chemotherapeutics to treat patients with mCRC.

Hurwitz et al. first reported a survival advantage for combining IFL and bevacizumab compared with placebo as first-line therapy for mCRC in 2004, which led to the FDA approval of bevacizumab in this setting.[50] A total of 813 patients were randomized with an increase in median OS of 20.3 months in the IFL plus bevacizumab group versus 15.6 months in the patients who received IFL plus placebo ($p < 0.001$). There was also a significant improvement in PFS,

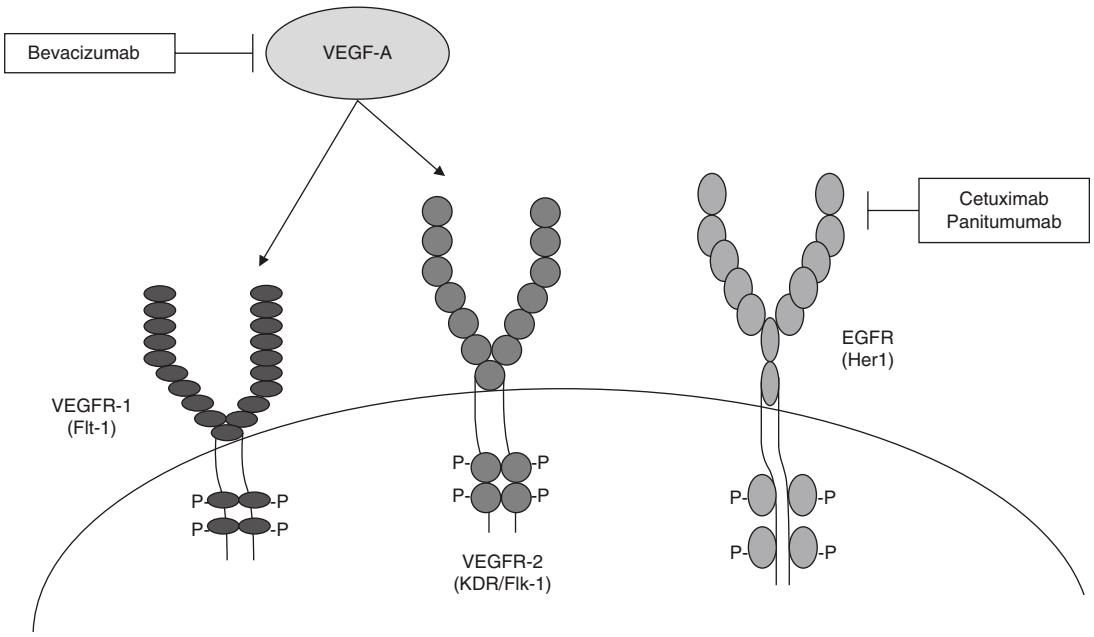

Fig. 1. Targeted therapies approved for metastatic colorectal cancer. Bevacizumab is a humanized monoclonal antibody with high affinity to soluble vascular endothelial growth factor (VEGF). VEGF-A is the most abundant of the VEGF family of ligands and binds to VEGF receptor (VEGFR)-1 and VEGFR-2, the latter being considered a critical receptor in regulating angiogenesis. By binding soluble VEGF-A in the circulation, bevacizumab decreases the incidence of VEGF engaging its receptor and hence decreases tumour growth by halting angiogenesis. Cetuximab and panitumumab are monoclonal antibodies that target the epidermal growth factor receptor (EGFR), leading to the inhibition of downstream signalling via the Kras, mitogen-activated protein kinase (MAPK) and Akt pathways, preventing cell migration and proliferation. **KDR** = Kinase insert domain receptor.

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RR and duration of response when patients were treated with bevacizumab. An increase in the incidence of grade 3 hypertension was noted in this group, but was manageable without difficulty. The previously described BICC-C trial, which randomized patients to receive first-line IFL using bolus 5-FU versus FOLFIRI with infusional 5-FU, was later amended to enrol patients on a 2×2 factorial design in which patients would be randomized to receive FOLFIRI plus bevacizumab (Arm A) versus IFL plus bevacizumab (Arm B).[33] After enrolment of an additional 117 patients, the median survival time had not been reached at the time of publication for the patients receiving FOLFIRI plus bevacizumab and was 19.2 months for those treated with IFL plus bevacizumab ($p = 0.007$). Therefore, an infusional regimen of 5-FU/leucovorin has been adopted as the preferred approach for patients being treated with irinotecan, with a survival advantage noted if bevacizumab is added.

The use of FOLFOX with bevacizumab as second-line therapy in patients with metastatic disease previously treated with 5-FU and irinotecan was reported in the phase III E3200 trial by Giantonio et al., in which 829 patients were randomized to receive FOLFOX4 plus bevacizumab, FOLFOX4 without bevacizumab or bevacizumab alone.[51] The addition of bevacizumab to chemotherapy resulted in a significant increase in RRs with 22.7% responding in the FOLFOX4 plus bevacizumab arm versus 8.6% in the FOLFOX4 group and 3.3% in those receiving bevacizumab alone ($p < 0.0001$). This corresponded to a significant improvement in both PFS and OS from 10.2 months in the bevacizumab alone arm versus 10.8 for the group treated with FOLFOX4 and 12.9 months in the FOLFOX4 plus bevacizumab group ($p = 0.0011$). Similar results were reported in the first-line setting via the smaller phase II TREE-2 study that randomized patients with untreated mCRC to receive bevacizumab with either mFOLFOX6 (bolus and infusional 5-FU/leucovorin and oxaliplatin), bFOL (bolus 5-FU and low-dose leucovorin with oxaliplatin) or CAPOX (capecitabine and oxaliplatin).[52] The results of this study were compared with those of TREE-1, which simply randomized patients to the same three regimens without bevacizumab. Overall, for patients treated in both studies, the median OS was 23.7 months for those receiving bevacizumab versus 18.2 months for those treated with chemotherapy alone. The addition of bevacizumab to mFOLFOX increased the RR from 41% to 52% with an improvement in median OS from 19.2 months to 26.1 months.

The TREE trial also confirmed the safety and tolerability of adding bevacizumab to regimens containing capecitabine, albeit at a reduced dose of 850 mg/m^2 twice a day, with an increase in RR from 27% for CAPOX alone to 46% with the addition of bevacizumab. The median OS was also improved from 17.2 months for patients reported in TREE-1 to 24.6 months in patients from the TREE-2 study. Saltz et al. went on to perform a direct comparison of regimens containing infusional versus oral 5-FU with or without bevacizumab in NO16966, a randomized phase III trial with a 2×2 factorial design in the first-line setting.[53] A total of 1401 mCRC patients were assigned to receive CAPOX versus FOLFOX4 followed by a second randomization to bevacizumab or placebo. Overall, the CAPOX regimen was found to be non-inferior to FOLFOX4 with or without the addition of bevacizumab.[38] The median PFS for all patients receiving bevacizumab was significantly longer (9.4 months vs 8.0 months, $p = 0.0023$) with OS not reaching statistical significance (21.3 months vs 19.9 months, $p = 0.077$). Interestingly, despite the protocol allowing patients to remain on treatment until disease progression, this only occurred in 29% and 47% of those receiving bevacizumab and placebo, respectively. Therefore, the authors suggested that perhaps continuing bevacizumab for longer periods of time until progression was noted would result in increased efficacy of this targeted therapy.

5.2 The Role of Bevacizumab as a Maintenance Therapy

The idea of maintaining metastatic patients on bevacizumab for longer durations was formally investigated in the phase III MACRO trial in which untreated mCRC patients having received six cycles of CAPOX combined with bevacizumab

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were randomized to receive maintenance CAPOX plus bevacizumab (Arm A) versus bevacizumab alone (Arm B) until disease progression.[54] There was no statistically significant difference in RR, PFS or OS between the two groups, suggesting that single agent bevacizumab was not inferior to CAPOX plus bevacizumab as maintenance therapy. However, almost 25% of patients in Arm A developed oxaliplatin-induced neuropathy compared with only 8% in the bevacizumab arm alone. Therefore, similar to the OPTIMOX trials, alternative strategies have been investigated that limit the duration of oxaliplatin exposure while treating disease progression without decreasing efficacy. Vaidyanathan et al. enrolled 67 mCRC patients using a stop and go regimen in the first-line setting in which all patients received FOLFOX with bevacizumab for eight cycles followed by 5-FU/leucovorin and bevacizumab maintenance until disease progression.[55] The overall RR in all patients was 58% with a median PFS of 10.6 months and a median OS of 26.7 months. For patients who were able to receive oxaliplatin again at the time of progression, the median DDC was 21 months. Therefore, strategies such as these may allow patients to remain on effective therapy for longer periods of time with fewer adverse effects and thus improve QOL.

5.3 Cetuximab

The expression of the EGF receptor has been shown to be increased in 60–80% of mCRC tumours.[56] The EGFR exists on cell surfaces and, upon activation by ligand binding, transitions from an inactive monodimer to an active homodimer. This dimerization results in the autophosphorylation of the receptor's tyrosine kinase domain, leading to downstream signalling via the Kras, mitogen-activated protein kinase (MAPK) and Akt pathways that promotes cell migration and proliferation.[57] Cetuximab is a chimeric antibody that targets the EGFR, acting as an inhibitor of the downstream activation of numerous signalling cascades (figure 1). It is approved for use in mCRC patients either in combination with chemotherapy or as a single agent in patients who have failed oxaliplatin- or irinotecan-based therapy. This was first shown in several promising single-arm phase II trials, leading to the BOND trial that enrolled 329 patients previously treated with irinotecan to receive cetuximab alone versus cetuximab plus irinotecan.[58-60] The patients receiving combination therapy experienced an increase in RR from 10.8 to 22.9%, with an improved time to progression of 4 months compared with 2.6 months with cetuximab alone. Additionally, the randomized phase III EPIC trial compared the efficacy of treating with cetuximab plus irinotecan versus irinotecan alone in patients who had failed first-line therapy with 5-FU/leucovorin plus oxaliplatin.[61] Administering cetuximab with irinotecan did significantly improve RRs (16.4 vs 4.2%, $p < 0.0001$), PFS (4.0 months vs 2.6 months, $p < 0.0001$) and QOL measures, but had no bearing on OS. The authors concluded that because a large majority of patients on the irinotecan alone arm eventually received cetuximab, an accurate determination of the drug's effect on OS was not possible.

In the first-line setting, cetuximab was also reported to provide benefit as per the CRYSTAL study, a phase III, randomized, controlled trial that compared FOLFIRI with or without cetuximab in untreated mCRC patients.[62] A total of 1198 patients were enrolled, demonstrating a significant improvement in PFS for the FOLFIRI plus cetuximab group compared with the FOLFIRI alone group. Again, there was no difference in OS (HR 0.93, $p = 0.31$). Similar efficacy was seen in the OPUS trial, in which patients were randomized to receive FOLFOX4 alone versus FOLFOX4 plus cetuximab with an increase in response from 36% to 46%.[63] Additionally, when FOLFOX plus cetuximab was compared head to head with FOLFIRI in combination with cetuximab in untreated mCRC patients, no significant difference was reported in terms of PFS, RR or OS, suggesting that both regimens were equally efficacious in the first-line setting.[64]

As these earlier trials were underway, more in-depth research was conducted to determine the underlying molecular mechanisms by which targeted therapies affected tumour growth. An hypothesis emerged that certain aberrations within the downstream effectors of the EGFR signalling

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pathway could affect the efficacy of these drugs. A correlative study in France reported on the tumour characteristics of 30 patients treated with cetuximab, including direct sequencing of the *Kras, Braf* and *PIK3CA* genes as well as EGFR copy number.[65] Mutations within the *Kras* gene were detected in 68.4% of the tumours that had no response to cetuximab versus 0% of the responder patients ($p = 0.0003$). This response pattern corresponded to a significantly higher OS for patients with wild-type *Kras* treated with cetuximab when compared to those in which a mutation was detected. Therefore, it became apparent that the mutational status of the *Kras* gene could serve as a predictive biomarker of both response and survival for patients being considered for anti-EGFR therapy. A retrospective analysis of about half of the patients enrolled in the CRYSTAL study for whom tissue was available for analysis found that 36% of tumours harboured a *Kras* mutation in either codon 12 or 13. It was this group that gleaned no benefit from the addition of cetuximab to FOLFIRI (RR of 36% vs 40%) with no improvement demonstrated in PFS between the two groups (7.6 months vs 8.1 months).[62] Alternatively, an OS benefit was noted for patients in the *Kras* wild-type population who received cetuximab compared with those who did not (24.9 months vs 21 months, HR = 0.84). A similar retrospective analysis was performed on tissue samples of patients enrolled in the OPUS trial with *Kras* wild-type tumours having a 2.5-fold increased chance of response when cetuximab was combined with FOLFOX compared to FOLFOX alone (61% vs 37%, $p = 0.011$).[63] However, in patients whose tumours had *Kras* mutations, a lower RR was observed when treated with cetuximab (33% vs 49%) as well as a shorter PFS when compared with FOLFOX alone (5.5 months vs 8.6 months). Therefore, screening for *Kras* mutations before treating with EGFR inhibitors has become the standard of care for mCRC patients.

While the studies described in this section suggest an advantage for combining cetuximab with regimens containing oxaliplatin or irinotecan in patients with *Kras* wild-type status, several other studies have produced conflicting results on the efficacy of oxaliplatin and cetuximab combinations. The COIN trial presented at the annual American Society of Clinical Oncology GI conference in 2010, randomly assigned 1630 patients in the first-line setting to receive oxaliplatin combined with either oral or intravenous 5-FU plus or minus cetuximab.[66] Among the 55% of patient with *Kras* wild-type alleles, no significant difference was noted in OS or PFS between the two groups (HR 1.038, $p = 0.68$). The NORDIC VII trial, which compared FLOX (oxaliplatin day 1, 5-FU bolus 500 mg/m^2 and leucovorin 60 mg/m^2 day 1-2) to FLOX plus cetuximab until disease progression versus intermittent FLOX plus continuous cetuximab, also did not show any statistically significant difference in RR, PFS or OS between the three groups, irrespective of *Kras* status.[67] The presence of a *Braf* mutation in 12% of the patients was, however, noted to be a strong negative prognostic factor with a median OS of 7.6 months compared with 20.4 months in patients with *Braf* wild-type tumours. Therefore, the exact role of EGFR inhibitors in the treatment of mCRC continues to be a moving target with the majority of practitioners reserving their use for second- or third-line therapy in patients with progressive or refractory disease.

5.4 Panitumumab

Unlike the chimeric nature of cetuximab, the EGFR inhibitor panitumumab is a fully humanized antibody that was approved for use as monotherapy in mCRC patients based on a phase III trial by Van Cutsem et al. that compared the agent with BSC after failure of 5-FU-, oxaliplatin- and irinotecan-based regimens.[68] A total of 231 patients were randomized to receive either panitumumab or BSC, with a trend towards improved OS in the group receiving panitumumab (14.5 months vs 12.5 months, $p = 0.12$). The median PFS in all enrolled patients was higher in the panitumumab arm (8 weeks vs 7.3 weeks); however, this effect was significantly greater in patients whose tumours had wild-type *Kras* than those with mutant *Kras* (12.3 weeks vs 7.4 weeks, $p < 0.0001$). The PRIME study then compared in a randomized fashion PFS in patients receiving

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FOLFOX versus FOLFOX plus panitumumab in the first-line setting.[69] Among patients with *Kras* wild-type tumours, the addition of panitumumab significantly improved PFS (9.6 months vs 8.0 months, p = 0.02) with a trend towards prolonged OS (23.9 months vs 19.7 months, p = 0.072). A negative impact was noted by administering panitumumab to patients with *Kras* mutant tumours with a decrease in OS (HR 1.29). In the second-line setting, Peeters et al. reported that combining panitumumab with FOLFIRI resulted in an increased RR (35% vs 10%) and an improvement in PFS from 3.9 months to 5.9 months when compared with FOLFIRI alone.[70] No difference in efficacy was observed in patients whose tumours possessed *Kras* mutations; therefore, this group of patients relies more heavily on cytotoxic therapies, VEGF inhibition and investigational agents.

6. Combinations of Cytotoxic and Biological Agents

Over the past several decades, the treatment for mCRC has advanced from relying on single agent 5-FU alone to a repertoire of cytotoxic and therapeutic agents. More recent trials have focused on the most effective ways of combining targeted agents with chemotherapy, either as concurrent combinations or in sequential fashion. The phase II BOND2 trial randomized irinotecan-refractory patients to receive irinotecan combined with cetuximab and bevacizumab (CBI), or cetuximab and bevacizumab without irinotecan.[71] The adverse effect profiles of both arms did not suggest a synergistic toxicity in combining multiple targeted agents with chemotherapy and the TTP in the CBI arm of 7.3 months compared favourably to historical controls. The CAIRO2 study randomized 755 patients to receive capecitabine, oxaliplatin and bevacizumab with or without cetuximab.[72] While the addition of cetuximab did not increase the frequency of grade 3/4 toxicity, besides skin toxicity, the patients receiving CAPOX with both antibodies had a shorter PFS and worsened QOL compared with CAPOX plus bevacizumab alone (9.8 months vs 10.7 months). Similar results have been seen with combinations containing panitumumab, such as the PACCE trial in which patients randomized to receive irinotecan and bevacizumab with or without panitumumab had no difference in PFS, with a higher percentage of patients withdrawing due to toxicity in the arm containing panitumumab.[73] Therefore, achieving a more substantial understanding of the molecular pathways that lead to tumourigenesis in mCRC patients is of upmost importance in order to determine the most effective way to combine targeted drugs without exposing the patients to worsened adverse effect profiles.

7. Conclusion

Based on the available published data, there are a variety of therapeutic options available that serve to prolong the overall and disease-free survival of mCRC patients. Practitioners should approach each patient individually, assessing whether the burden of metastatic disease is potentially resectable with the plan to treat unresectable patients with all applicable drugs in a sequential manner, as outlined in figure 2.[74] Regarding cytotoxic chemotherapy choices, both FOLFOX and FOLFIRI are standard first-line options with comparable RRs and OS.[40,41] While no mature data exists comparing the superiority of the FOLFOX or FOLFIRI backbone with bevacizumab, the relative equivalence of each combination in the first-line setting makes the pairing of either chemotherapy combination with bevacizumab a reasonable approach. Subsequent lines of therapy will depend on the initial choice and response of first-line therapy, the presence of a *Kras* mutation that would preclude anti-EGFR antibodies and the residual toxicity from prior therapies. While all patients who are fit to tolerate aggressive therapy should be offered combination cytotoxic therapy combined with a biological agent, the performance status of the patient and the response of each patient's tumour may dictate the need for chemotherapy holidays or downscaling to less intense maintenance therapy. Most importantly, as the molecular targets that drive tumourigenesis are better elucidated and more reliable biomarkers are discovered that can

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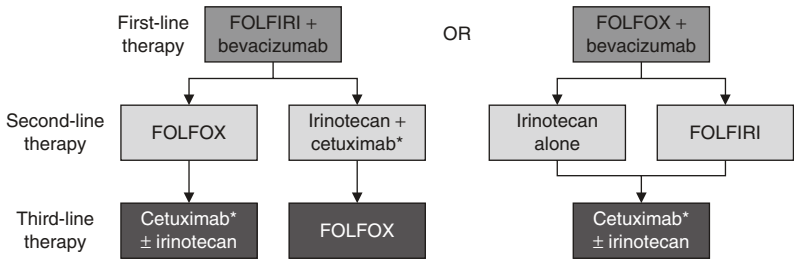

Fig. 2. Algorithm of treatment options for metastatic colorectal cancer patients deemed to be appropriate for intensive therapy (adapted with permission from Goldberg et al.[74]) * Cetuximab or panitumumab for patients with *Kras* wildtype tumours. **FOLFIRI** = irinotecan plus infusional 5-fluorouracil/leucovorin; **FOLFOX** = oxaliplatin plus infusional 5-fluorouracil/leucovorin.

predict response and prognosis, we aim to develop a more personalized and effective means of treating mCRC in which tumour shrinkage and OS rates will be maximized while sparing an increasingly heavily treated population undue toxicity.

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