Current Opinion on Optimal Treatment Choices in First-line Therapy for Advanced or Metastatic Colorectal Cancer: Report From the Adelaide Colorectal Tumour Group Meeting; Stockholm, Sweden; September 2008

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Abstract

The medical treatment of patients with metastatic colorectal cancer (mCRC) has evolved greatly in the past 10 years, involving complex combined chemotherapy protocols and, in more recent times, new biologic agents. Clinical benefit from the use of the targeted monoclonal antibodies bevacizumab, cetuximab, and panitumumab in the treatment of patients with mCRC is now well-established, but the optimal timing of their use requires careful consideration in order to derive the maximal benefit. Evidence to date suggests potentially distinct roles for bevacizumab and epidermal growth factor receptor–targeted biologic agents (cetuximab and panitumumab) in the treatment of patients with mCRC. This article reviews the evidence in support of modern treatments for mCRC and the decision making behind the treatment choices as well as their benefits and toxicities. An evidence-based algorithm is proposed that incorporates the use of these biologic agents early in the treatment of patients with initially nonresectable mCRC based on clearly defined tumor-related factors dependent on the immediate treatment goal. Real-world application of this algorithm is dependent on an individual countries’ approval of access to new biologic agents.

Keywords: 5-Fluorouracil, Bevacizumab, Capecitabine, Cetuximab, KRAS, Vascular endothelial growth factor

Introduction

Fluoropyrimidine monotherapy has been the mainstay of colorectal cancer (CRC) palliative chemotherapy for almost 40 years, with meaningful improvements in progression-free survival (PFS), overall survival (OS), and response rates (RRs) having been attained over the past decade with the addition of oxaliplatin and irinotecan. A positive correlation exists between the number of cytotoxic agents used and OS, reflecting that patients who live longest will have received all active chemotherapy agents over the course of their therapy.1 The recent addition of the targeted monoclonal antibodies (MoAbs) bevacizumab, cetuximab, and panitumumab has provided more options for treatment to extend survival and improve clinical outcomes in metastatic CRC (mCRC). In addition, the use of these biologic agents could improve the resectability rate of liver metastases and contribute to improved long-term survival in patients with mCRC.

This article reviews the clinical trial evidence, addressing issues for consideration when choosing the “optimal” first-line combina-
treatment for the individual patient with mCRC, incorporating the “best” active biologic and chemotherapy agents together. The review and its suggestions follow a formal consensus meeting among 6 Australian specialist clinicians and 3 international CRC experts (1 each from the United States, United Kingdom, and Europe), incorporating the evidence as it currently stands. Clinical scenarios lacking clear scientific evidence to guide treatment decisions are also highlighted.

Factors Affecting First-line Treatment Decisions in Metastatic Colorectal Cancer

In selecting a first-line treatment for patients with mCRC, the initial consideration is whether the overall aim of the treatment is curative (initially resectable disease) or noncurative. The majority of patients with mCRC and liver metastases are considered to have unresectable disease at presentation, although a minority of these patients might eventually be able to be treated with curative intent if a good response to initial chemotherapy is achieved.

The standard of care for the treatment of patients with initially nonresectable mCRC is palliative therapy, with the overall aims of prolongation of survival, symptom control, and maintenance of quality of life. Classic determinants affecting the choice of systemic treatment can be divided into those related to the patient, such as age, performance status (PS), the presence of comorbidities, and patient preferences; and those related to the disease, including potential tumor resectability, disease burden, the presence of symptoms, the rate of disease progression, and previous treatment history. In addition, drug-related factors such as toxicity, availability, and cost also need to be considered (Table 1). The primary consideration when selecting a first-line therapy for initially nonresectable mCRC should be the immediate treatment goal, with additional consideration given to maximizing the utility of future treatment options given the success or failure of the initial treatment. In general, this immediate treatment goal, taking into account individual patient needs, is either (1) disease control for prolongation of survival with maintenance of quality of life or (2) rapid tumor response for disease stabilization or symptom control or with a view toward downsizing tumors for curative resection.

An algorithm is proposed herein for the first-line treatment of patients with initially nonresectable mCRC based on clearly definable tumor-related determinants and dependent on the immediate treatment goal (Figure 1). The approach discussed is congruent with the current notion of treatment of patients with mCRC as a “continuum of care” in which the concept of distinct lines of therapy is now largely redundant as a treatment approach.3

### Table 1 Classic Determinants of Treatment Choice for Metastatic Colorectal Cancer

<table>
<thead>
<tr>
<th>Patient Factors</th>
<th>Disease Factors</th>
<th>Drug Factors</th>
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<tbody>
<tr>
<td>Age</td>
<td>Resectability (potential for cure)</td>
<td>Trial data</td>
</tr>
<tr>
<td>Performance status (comorbidities)</td>
<td>Disease burden/tumor volume</td>
<td>Toxicity</td>
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<tr>
<td>Patient preferences (toxicity, convenience)</td>
<td>Presence of symptoms</td>
<td>Availability</td>
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<td></td>
<td>Natural history (previous therapy, time to relapse)</td>
<td>Cost</td>
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### Figure 1 Choosing Between Combination Chemotherapy and Monotherapy, With or Without the Addition of Biologic Agents, for the First-line Treatment of Patients With Initially Nonresectable Metastatic Colorectal Cancer

For patients eligible for nonaggressive treatment, no initial therapy may be an option; palliative care may be an option for some patients, especially those with high tumor burden. Abbreviations: 5-FU = fluorouracil; BEV = bevacizumab; CAP = capecitabine; CT = chemotherapy; EGFR = epidermal growth factor receptor; MoAb = monoclonal antibody; ND = not determined; WT = wild type

Combination Therapy for Metastatic Colorectal Cancer

Combination treatment for mCRC should be considered in patients for whom the first-line treatment priority is immediate tumor control, in order to stabilize rapidly progressing disease or to ameliorate significant disease-related symptoms. In a smaller group of patients with limited metastatic disease, an alternate goal would be reduction of the metastases to the point where surgery is possible, as this can provide a chance for cure (Figure 1).

It is generally accepted that an “aggressive” approach would involve a doublet chemotherapy backbone. Available evidence suggests that, although their toxicity profiles are different, there is little difference in efficacy between chemotherapy doublets of 5-fluorouracil (5-FU)– and irinotecan-based regimens or 5-FU– and oxaliplatin-based regimens, ie, they are generally considered interchangeable.4-7 Several variations of these combinations exist,
with commonly used ones being FOLFOX (leucovorin [LV], oxaliplatin, and infusional 5-FU) and FOLFIRI (LV, irinotecan, and infusional 5-FU) and where the oral 5-FU produg capcitabine is substituted for infusional 5-FU (XelOx or CapeOx; XelIri or CapIri). Table 2 summarizes commonly used regimens.

These combination chemotherapies currently constitute the backbone of systemic treatment of patients with mCRC, and the choice of one over the other depends on factors such as patient preference, toxicity, and drug availability. Trial data have shown that patient outcomes are further improved with the addition of biologic agents to these combination chemotherapy regimens in first and subsequent therapeutic lines, and such regimens are currently recommended over chemotherapy doublets alone for first-line mCRC in suitable patients.8

The use of all 3 active cytotoxic agents together as triplet first-line therapy (FOLFOXIRI) in mCRC has also been investigated in phase III studies, with uncertain survival benefit compared with doublet chemotherapy. FOLFOXIRI was found to significantly increase RR, complete resection (R0) rate, PFS, and OS compared with FOLFIRI doublet chemotherapy in one study,9 whereas another study could demonstrate no superiority of FOLFOXIRI over FOLFIRI.10 Because of uncertainty regarding the efficacy of triplet therapy, along with concerns about increased toxicity, triplet regimens are not considered part of standard practice. However, it is arguable that they could be appropriate in carefully selected patients in whom maximizing tumor response might lead to curative surgery or in situations in which biologic agents are unavailable or contraindicated.

### Addition of Biologic Agents to Combination Chemotherapy: Role of Bevacizumab and Cetuximab/Panitumumab

**Bevacizumab.** In randomized phase III studies of chemotherapy-naive patients, the addition of bevacizumab to both oxaliplatin- and irinotecan-based combination chemotherapy regimens has been shown to significantly improve PFS and, with irinotecan, OS in patients with mCRC compared with chemotherapy alone, with acceptable toxicity.11,12 When combined with irinotecan/bolus 5-FU chemotherapy in patients with previously untreated mCRC, bevacizumab treatment conferred a significant improvement in survival (20.3 months vs. 15.6 months; \( P < .001 \)).11 The addition of bevacizumab to oxaliplatin-based chemotherapy regimens has also been shown to improve PFS in the first-line setting (9.4 months vs. 8 months; \( P = .0023 \)) and both PFS (7.3 months vs. 4.7 months; \( P < .0001 \)) and OS (12.9 months vs. 10.8 months; \( P = .0011 \)) in the second-line setting.12,13 Severe toxicity associated with bevacizumab treatment appears to be uncommon, with the majority of adverse events (eg, hypertension and proteinuria) being clinically manageable.11,14 The RRs observed with bevacizumab in these studies have varied, and this needs to be taken into account if there is a potential for tumor downsizing (see the Potentially Resectable Disease section). There is no phase III trial evidence for any clinical benefit from the use of bevacizumab after 2 previous chemotherapy regimens or as a single agent in any line of therapy.

**Cetuximab/Panitumumab.** Recent data confirms that, for patients with mCRC, KRAS gene mutation is predictive of nonresponse to epidermal growth factor receptor (EGFR)–targeted MoAb therapy across all treatment lines, either as a single agent or in combination with irinotecan- or oxaliplatin-based chemotherapy.15-19 Furthermore, patients with mutant KRAS might experience inferior outcomes with cetuximab/potinumabumumab treatment in combination with some chemotherapy schedules (predominantly oxaliplatin-based), and further prospective data are awaited.16,18,20,21 Thus, determination of KRAS status is essential in patients with mCRC being selected for EGFR-targeted therapy, and current evidence suggests that patients with mutated KRAS should not receive such therapy. Consequently, many world drug-regulatory approval bodies have approved EGFR-inhibiting MoAbs only on the basis of patient selection by tumor KRAS status. However, the science around the biologic predictive profile is evolving—there is emerging evidence that the presence of other genetic alterations, such as B-Raf kinase mutations or loss of phosphatase and tensin homolog (PTEN) expression, could also potentially affect sensitivity to EGFR inhibitors.22,23 thereby further reducing the patient population that actually benefits.

In previously untreated mCRC, the addition of cetuximab to irinotecan- or oxaliplatin-based combination chemotherapy increased RRs in patients with wild-type (WT) KRAS by 16% (from 43% to 59%) in the phase III CRYSTAL (Cetuximab Combined With Irinotecan in First-Line Therapy for Metastatic Colorectal Cancer) trial (\( P = .0025 \)) and by 24% (from 37% to 61%) in the randomized phase II OPUS (Oxaliplatin and Cetuximab in First-Line Treatment of mCRC) trial (\( P = .01 \)).16,20 There was an improvement in PFS with cetuximab in both trials (9.9 months vs. 8.7 months, \( P = .0167 \) in CRYSTAL; and 7.7 months vs. 7.2 months, \( P = .02 \) in OPUS); however, there was no significant difference in OS between treatment arms in the CRYSTAL trial, even for the WT KRAS subgroup, although a trend was evident (24.9 months vs. 21 months; \( P = .22 \)).20 As expected, no treatment benefit was observed with cetuximab in the mutant KRAS populations, and in the OPUS study, these patients were shown to experience poorer PFS outcomes with the addition of cetuximab to chemotherapy.20 In second-line mCRC, the addition of cetuximab to irinotecan-based chemotherapy improved PFS (but not OS) in the whole study population,24 but it did not significantly improve either
PFS or OS in the analysis of patients with WT KRAS. It is in the refractory setting, however, that the benefits of cetuximab treatment appear the most pronounced. In this setting, cetuximab monotherapy doubled PFS (3.8 months vs. 1.9 months; \(P < .0001\)) and significantly improved OS by 4.7 months (9.5 months vs. 4.8 months; \(P < .0001\)) in patients with WT KRAS, whereas no significant benefit was observed in patients with mutated KRAS. Similarly, panitumumab monotherapy in refractory mCRC has been shown to significantly prolong PFS in patients with WT KRAS (2.8 months vs. 1.7 months; \(P < .0001\)). Of note, the OS and PFS benefit of bevacizumab in mCRC appears to be independent of KRAS mutation status, with similar improvement observed for both patients with WT KRAS and mutated KRAS. The data for bevacizumab and the data for the EGFR MoAbs regarding the role of B-Raf and PTEN loss come from retrospective analyses of outcomes within subpopulations of clinical trials or selected patient cohorts treated with these agents. Inherent selection biases, therefore, affect the validity of these findings, although the clinical observations are biologically plausible and consistent. Therefore, the strongest evidence lies with tumor WT KRAS phenotype as a selection marker for benefit when we want to use an anti-EGFR MoAb, although it is not required for a decision to use bevacizumab. When considering the evidence we can ask, is it necessary to wait for these observations to be validated prospectively before such agents are approved for use? Waiting for validation could further define the optimal populations for greatest benefit and cost-effectiveness but will take years of further study and deny many current and future patients drug access and clinical benefit.

**Combination of Bevacizumab and an Epidermal Growth Factor Receptor–Targeted Agent With Chemotherapy.** Based on the benefits observed with the use of a single MoAb in combination with fluoropyrimidine-based chemotherapy doublets, the combination of anti–vascular endothelial growth factor and EGFR-targeted biologic agents with chemotherapy in first-line mCRC is an appealing concept. However, in 2 phase III trials, the addition of an anti-EGFR MoAb (cetuximab or panitumumab, respectively) to standard first-line chemotherapy plus bevacizumab resulted in decreased PFS and increased serious toxicity compared with the standard therapy.

**Toxicity of Biologic Agents.** There are broad differences in the toxicity profiles of the biologic agents that might affect choice. For example, gastrointestinal perforation, hemorrhage, hypertension, proteinuria, and risk of venous thromboembolism can occur with bevacizumab, and rash, which can also be problematic, can occur with the EGFR-targeted MoAbs.

**Chemotherapy Duration Beyond 6 Months.** The duration of chemotherapy remains an area of clinical controversy in terms of its impact on survival and is currently still mostly determined by patients’ tolerance of the specific treatments and their individual preferences.

**Potentially Resectable Disease**

Complete resection of limited liver metastases (and/or limited lung metastases) is currently the only potentially curative treatment for mCRC, with a 5-year survival rate after hepatectomy of 40%-60% across many series if patients are carefully selected. Survival outcomes after “conversion” treatment in patients with initially unresectable disease, although inferior to those for patients with resectable disease at presentation, are also better than those treated with chemotherapy alone. As resection rate after chemotherapy has been shown to correlate with tumor RR, an aggressive combination chemotherapy regimen (with highest tumor RR) should be the treatment of choice for patients for whom the aim is tumor downsizing to achieve resectability. Reported R0 resection rates of 26%-45% have been attained following an aggressive oxaliplatin- or irinotecan-based doublet, or triplet, chemotherapy in selected patients with initially unresectable liver-only disease. The timing of surgery after chemotherapy is an important consideration in these patients. With early surgery potentially resulting in increased perioperative complications, a minimum of 4 weeks from the final chemotherapy dose has been recommended.

The use of targeted agents with combination chemotherapy can further improve RR, enabling increased numbers of patients undergoing potentially curative resection. In phase III randomized trials, bevacizumab has been shown to improve radiologic RRs by around 10% when added to combination chemotherapy with prolonged chemotherapy avoided in order to minimize potential chemotherapy-related hepatic toxicity.

**Nonresectable but Symptomatic (High-Volume) or Progressive Metastatic Disease**

Palliative therapy is the standard treatment approach for patients with nonresectable disease. In the case of symptomatic or rapidly progressing nonresectable disease, the goal of treatment is tumor control to prevent further disease progression or to ameliorate significant disease-related symptoms. For such patients, combination chemotherapy with bevacizumab (or cetuximab in patients with WT KRAS) has been shown to improve radiologic RRs by around 10% when added to combination chemotherapy. A combined analysis of data from an observational registry of bevacizumab in the community setting and a phase III study of bevacizumab with oxaliplatin-based chemotherapy found that surgery with curative intent in patients with initially unresectable disease after treatment with bevacizumab and chemotherapy is effective, feasible, and safe, with no increase in wound-healing complications or bleeding events.

The potential impact of bevacizumab on wound healing and surgical morbidity might be minimized by controlling the timing of surgery, with a recommended interval before liver resection of 6-8 weeks from bevacizumab discontinuation.

The EGFR-targeted MoAb cetuximab consistently has improved RR in patients with WT KRAS by > 15% when added to combination chemotherapy in randomized trials. The increased RR observed with cetuximab in patients with WT KRAS with liver-limited metastases (77.1% vs. 50%; \(P = .025\)) suggests that the resection rate could be further improved in this subgroup.

Hence, either bevacizumab or cetuximab used in combination with chemotherapy (oxaliplatin- or irinotecan-based) is appropriate for patients with WT KRAS requiring aggressive treatment with the goal of tumor downsizing for curative resection, with no direct comparison data between these regimens available to date. Bevacizumab with combination chemotherapy should be the treatment of choice for patients with a mutated KRAS gene. The optimal duration of preoperative chemotherapy is not defined, but it is generally considered that surgery should be undertaken as soon as deemed technically possible, with prolonged chemotherapy avoided in order to minimize potential chemotherapy-related hepatic toxicity.

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KRAS) or triplet chemotherapy would be an appropriate first-line treatment choice (Figure 1).

**Sequential Treatment of Patients With Metastatic Colorectal Cancer**

**Rationale**

For patients who cannot tolerate combination chemotherapy or who have slowly progressing and/or asymptomatic disease, a sequential approach can be considered in order to maximize survival and quality of life and to provide a greater range of future treatment options. Combination chemotherapy could be associated with considerable toxicity and might not be justified in this patient group. A potentially low-toxicity chemotherapy regimen, such as fluoropyrimidine monotherapy, could enable the addition of a single biologic agent more safely.

Two clinical studies (CAIRO [Capecitabine, Irinotecan, and Oxaliplatin in Advanced Colorectal Cancer] and FOCUS [Fluorouracil, Oxaliplatin and CPT-11 (irinotecan), Use and Sequencing]) have demonstrated that, in patients in whom a sequencing of regimens is suitable, initial single-agent 5-FU followed by combination chemotherapy is noninferior to up-front combination chemotherapy, providing strong support for this treatment approach. In patients with previously untreated mCRC, bevacizumab has been shown to improve PFS, OS, and RR when added to 5-FU monotherapy, with this regimen at least as effective in terms of PFS and RR as combination chemotherapy, without compromising survival. Because bevacizumab has been shown to improve PFS and OS for patients receiving 5-FU-based therapy irrespective of age, baseline risk, or prognosis, the combination of bevacizumab with 5-FU monotherapy is an appropriate option in a wide group of patients. The efficacy of a combination of capecitabine and bevacizumab (with or without mitomycin-C) is currently being assessed in the Australian-based MAX (Mitomycin C, Avastin and Xeloda) phase III study. Recent safety data suggest that both regimens are well tolerated, including by the elderly. Efficacy data are expected shortly.

Observation could be considered in selected patients who are asymptomatic and/or have nonprogressive disease; however, care should be taken to monitor such patients closely with tumor marker and computed tomography scans in addition to regular clinical assessment, in order to preserve the “window of opportunity” to benefit from active treatment if it is the patients’ decision to be treated.

**Poor Performance Status at Presentation**

It is important to distinguish poor PS caused by comorbidity from that caused by disease. Comorbidities need to be addressed, including the optimization of noncancer medications, because improved symptom control could increase patient tolerance of chemotherapy. In the case of disease-related poor PS, the tolerability of chemotherapy regimens is an important consideration when deciding upon a treatment strategy.

Extensive metastases in the livers of patients with mCRC often lead to hepatic dysfunction, usually defined by serum bilirubin levels and other tests of hepatic synthetic function. In patients with mCRC and poor liver function, dose modification should be considered where appropriate, although for the majority of chemotherapy agents, there is a paucity of data to guide clinicians because these patients are generally excluded from trials. Caution in treating patients with hepatic dysfunction is essential; however, some agents appear to be relatively well tolerated, including continuous-infusion 5-FU and oxaliplatin. If dysfunction is severe, a common practice is to administer 5-FU at 50% of the dose initially, increasing it only if toxicity is not observed. 5-Fluorouracil treatment is not recommended if bilirubin levels are > 85 µmol/L, unless secondary to biliary obstruction. Similarly, although oxaliplatin appears to be safe in patients with mild to moderate liver dysfunction, it remains unclear if full-dose oxaliplatin is safe in patients with markedly elevated serum bilirubin levels.

By contrast, irinotecan could cause unacceptable toxicity if administered to patients with poor hepatic function. Dose reduction of 20% has been suggested for the use of irinotecan in patients with Gilbert syndrome, which occurs with a frequency of 5%-10% in the general population, although there is no scientific evidence to support this. Importantly, the use of biologic agents in patients with hepatic impairment has not yet been tested because these patients are largely excluded from trials.

Because of the lack of available data on treatment outcomes for this patient subgroup, the potential use of fluoropyrimidine monotherapy could be considered in the first instance. These patients should be subsequently assessed, with the goal of considering a more aggressive therapy at a later stage. Specialist palliative care input should be sought early.

**Further Considerations**

**Impact of Previous Adjuvant Treatment on First-line Treatment Decisions**

The recent wide acceptance of oxaliplatin-based regimens (FOLFOX, FLOX) as the standard of care in the adjuvant therapy of stage III CRC has resulted in this patient group becoming more prevalent, despite still being largely excluded from trials of oxaliplatin in first-line mCRC. In published randomized trials in first-line mCRC, very few, if any, patients had previous adjuvant oxaliplatin-based therapy despite the fact that some 15%-25% of the patients had received adjuvant chemotherapy. It is unclear at present how previous adjuvant oxaliplatin therapy affects patient outcomes after relapse and whether retreatment will be effective. Residual oxaliplatin neurotoxicity could also limit any attempt to rechallenge. The MOSAIK (Multicenter International Study of Oxaliplatin/5-Fluorouracil/Lucovorin in the Adjuvant Treatment of Colon Cancer) trial, for example, reported 30% residual peripheral sensory neuropathy at 1 year and 15% at 4 years (including 3% severe grade 2/3 neurotoxicity), and in practice, this is likely to be higher.

In general, for patients relapsing after previous adjuvant oxaliplatin treatment, irinotecan-based chemotherapy combined with an appropriate biologic agent, or fluoropyrimidine monotherapy in selected patients, could be considered. Oxaliplatin-based therapy would usually not be the preferred first-line treatment, with the possible exception of those patients relapsing late (eg, after 12-24 months) with no residual toxicity. Previous adjuvant chemotherapy regimens should not affect the choice of targeted agents in first-line mCRC.

A consideration of increasing importance will be the previous use of adjuvant biologic therapy, currently occurring only in the clinical trial setting. At present, there are insufficient data to ascertain the impact of adjuvant bevacizumab use in the first-line treatment of patients with mCRC.
Unresolved questions related to the treatment of patients with mCRC include (1) the role of biologic agents in maintenance therapy, either as monotherapy or with fluoropyrimidine monotherapy; (2) the role of continuation of biologic therapy with a change in chemotherapy partner in patients with good tolerance but progressive disease; (3) the role of biologic therapy after previous adjuvant treatment with biologic agents, assuming randomized phase III studies of these agents show efficacy in the adjuvant setting; and (4) the optimal biomarkers to define patient subgroups for response to each class of agents. It is hoped that ongoing translational research and clinical trials will provide timely answers to these clinically important questions.

Conclusion

This review has attempted to examine the currently available evidence for the use of the new biologic agents such as bevacizumab and the EGFR-targeted MoAbs, cetuximab and panitumumab, in the treatment of patients with mCRC. These concluding remarks are based on a consensus opinion by the authors for best use of the available drug treatments for maximum clinical benefit based on the best available evidence. It does not consider overall cost-effectiveness of these agents and their likely restricted indications in Australia to specific settings by the Pharmaceutical Benefits Advisory Committee. Ideally, as more evidence emerges for the optimal use of these agents in the treatment path of patients with mCRC, it is hoped that the approved indication wording will have flexibility for clinician choice to derive maximum benefit for the individual patient.

The ability of biologic agents such as bevacizumab and cetuximab to provide a survival benefit in mCRC is now well established, with a large body of clinical evidence confirming their efficacy. These agents should clearly form part of any treatment strategy for suitably eligible patients with mCRC, although their introduction and ongoing management require careful consideration in order to derive the maximal benefit from their use. Biologic agents should be used in the treatment algorithm where they provide the most benefit, and chemotherapy should be managed to minimize treatment failure and resistance while minimizing toxicity.

The algorithm for the first-line treatment of patients with initially nonresectable mCRC proposed herein (Figure 1) aims to maximize the benefit of these biologic agents within an overall treatment strategy that takes into account immediate treatment goals while maintaining as many future therapeutic options as possible. This opinion is not based on direct clinical trial evidence, but rather on the comparison of data across the key phase III trials, so true differences in the efficacy of chemotherapy in combination with cetuximab/panitumumab or bevacizumab will require a head-to-head randomized study. Until these data are available, the evidence to date suggests potential distinct roles for bevacizumab and EGFR-targeted biologic agents (cetuximab and panitumumab) in the treatment of patients with mCRC. The OS and PFS benefits conferred by bevacizumab in first- or second-line mCRC (with minimal evidence for activity beyond second line) provide a rationale for its early use. The OS benefit provided by cetuximab (and PFS benefit for both cetuximab and panitumumab) in chemotherapy-refractory patients with WT KRAS provides a rationale for its use later. However, a subpopulation of patients with WT KRAS may also be considered for first-line combination chemotherapy with EGFR-targeted MoAb therapy where aggressive treatment for rapid tumor control or downsizing for curative resection is required. Ultimately, the timing of therapy will depend on the approved indication for use. Decisions on anti-EGFR MoAb use now might change as more data are published concerning the impact of the expression of other important predictive molecular markers such as B-Raf and PTEN.

Finally, when making decisions for an individual patient, it should be noted that there is a need to consider all available options up front, including treatment intent (curative or not), in order to determine the best treatment strategy for the given patient where disease, patient, and drug factors are all considered. With multiple treatment options available, such strategic, individualized treatment should enable improved survival, quality of life, and functional outcomes for patients with mCRC.

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