Cancer Management and Research

Dovepress
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Open Access Full Text Article

REVIEW

Factors influencing choice of chemotherapy in metastatic colorectal cancer (mCRC)

This article was published in the following Dove Press journal:
Cancer Management and Research
18 November 2013
Number of times this article has been viewed

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Abstract: Management of metastatic colorectal cancer requires a multimodal approach and must be performed by an experienced, multidisciplinary expert team. The optimal choice of the individual treatment modality, according to disease localization and extent, tumor biology, and patient clinical characteristics, will be one that can maintain quality of life and long-term survival, and even cure selected patients. This review is an overview of the different therapeutic approaches available in metastatic colorectal cancer, for the purpose of defining personalized therapeutic algorithms according to tumor biology and patient clinical features.

Keywords: metastatic colorectal cancer, patient clinical features, tumor biology, multidisciplinary approach

Introduction

Approximately 20% of patients affected by colorectal cancer (CRC) present metastatic disease in early diagnosis, while 35% of patients, treated with curative intent, will develop advanced disease over time.[1] The prognosis of these patients is poor and the aims of chemotherapy are care (only in selected cases), survival prolongation, disease progression delay, quality of life improvement, tumor size reduction, or symptom palliation. Through available multidisciplinary therapeutic strategies (surgery, chemotherapy, biological agents, radiotherapy), the clinical approach to unresectable metastatic CRC (mCRC) should be potentially curative or palliative. Moreover, knowledge of both tumor biology and patient clinical features has allowed for the identification of four different patient classes, which correspond to four different therapeutic options, respectively: (1) patients with minimal disease that is immediately resectable (R0-resectable liver with/without lung metastases [group 0]); (2) patients with extensive disease that is not immediately resectable (potentially resectable metastatic disease after conversion chemotherapy [group 1]); (3) never-resectable metastatic disease in symptomatic patients whose quality of life and survival are compromised due to disease extension (palliation therapy [group 2]); and (4) never-resectable metastatic disease in asymptomatic patients (palliation therapy, continuum care [group 3]).[2] The purpose of this review is to summarize the different therapeutic approaches to adopt according to patient clinical characteristics and tumor biomolecular features (Table 1 shows the groups mentioned above and related treatments) and to explain current therapeutic options available in mCRC.

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Table 1 First-line treatment options according to tumor biology and patient clinical features

Group	Clinical presentation	Treatment aim	Treatment intensity	*KRAS* wild-type	*KRAS* mutated
0	R0-resectable liver and/or lung metastases	– Cure – Decrease risk of relapse	– Nothing – Moderate (FOLFOX)	–	–
1	Not R0-resectable liver or lung metastases but might became resectable after conversion CT	Maximum tumor shrinkage	Upfront most active combination regimen	FOLFIRI+cet FOLFOX+pan/cet FOLFOX/XELOX+bev FOLFOXIRI FOLFIRI/XELIRI+bev FOLFOX/XELOX FOLFIRI/XELIRI	FOLFOX/XELOX+bev FOLFOXIRI FOLFIRI/XELIRI+bev FOLFOX/XELOX FOLFIRI/XELIRI
2	Multiple metastases sites, with rapid progression and symptomatic patients	– Clinically relevant tumor shrinkage if possible – At least achieve control of DP	Upfront active combination: at least doublet	FOLFIRI+cet FOLFOX+pan/cet FOLFOX/XELOX+bev FOLFOXIRI FOLFIRI/XELIRI+bev FOLFOX/XELOX FOLFIRI/XELIRI	FOLFOX/XELOX+bev FOLFOXIRI FOLFIRI/XELIRI+bev FOLFOX/XELOX FOLFIRI/XELIRI
3	Multiple metastases sites, asymptomatic patients	– Abrogation of further progression – Tumor shrinkage less relevant	Sequential approach	5-FU/LV Cape 5-FU/LV+bev Cape+bev XELOX/FOLFOX FOLFIRI/XELIRI cet/pan watchful waiting triplets (±bev or cet/pan)	5-FU/LV Cape 5-FU/LV+bev Cape+bev XELOX/FOLFOX FOLFIRI/XELIRI FOLFOXIRI/Bev

Abbreviations: 5-FU, 5-fluorouracil; bev, bevacizumab; cape, capecitabine; cet, cetuximab; LV, leucoverin; FOLFIRI, infusional 5-FU/bolus folinic acid/irinotecan; FOLFOX, infusional 5-FU/bolus folinic acid/oxaliplatin; FOLFOXIRI, infusional 5-FU/bolus folinic acid/irinotecan/oxaliplatin; pan, panitumumab; DP, disease progression; XELOX, capecitabine/oxaliplatin; XELIRI, cape/irinotecan; CT, chemotherapy.

Surgical treatment of advanced disease

Surgery is feasible even in advanced disease. It is important to establish, in patients with unresectable mCRC and in whom the primary tumor has not been removed, whether or not the primary tumor is symptomatic; in fact, if the primary tumor is symptomatic (bleeding, bowel obstruction, bowel perforation), surgery is immediately necessary. Liver, lung, and ovarian metastases and primary site of disease should be evaluated for surgery, and surgery should be considered in all patients who have had an important tumoral mass reduction through chemotherapy. The chemotherapy should be discontinued as soon as the disease becomes resectable, because continuation of treatment exposes patients to liver toxicity and surgery risks. R0-resectable liver metastases represents the only curative option available,[3] while R1-resectable liver metastases is an acceptable strategy if it produces a significant benefit to patients.[4] Currently, patients diagnosed with potentially resectable mCRC should undergo an upfront evaluation by a multidisciplinary team, including surgical consultation, to assess resectability status.

Management of patients with minimal disease (R0-resectable liver and/or lung metastases [group 0])

Before explaining the therapeutic approach to be taken in this patient group (group 0), it is necessary to clarify resectability criteria. The criteria for determining patient suitability for resection of metastatic disease are the likelihood of achieving complete resection of all evident disease with negative surgical margins and maintaining adequate liver reserve (>30%).[4] It should be noted that metastasis number or size, bilobar extension disease, and vascular structure involvement are not contraindicative to resection of the tumor and its metastases. Patients with a single small (<2 cm) liver metastasis may be considered for upfront surgery and for postoperative chemotherapy with an infusional 5-fluorouracil (5-FU)/bolus 5-FU/leucoverin (LV)/oxaliplatin (FOLFOX)-based regimen for an overall treatment of 6 months.[5] For patients with up to four liver metastases, perioperative chemotherapy (3 months pre-chemotherapy and 3 months post-chemotherapy with FOLFOX regimen) should be applied. The European Organisation for Research and Treatment of Cancer 40983 trial has demonstrated an advantage in

progression-free survival (PFS) in patients undergoing resection plus chemotherapy versus resection alone (18.7 vs 11.7 months, respectively) and a rate of PFS at 3 years from 33.2% to 42.4% (hazard ratio [HR] 0.73; $P = 0.025$) in patients who underwent surgery after perioperative chemotherapy.[6] Furthermore, a recent meta-analysis identified three randomized clinical trials comparing surgery alone to surgery plus systemic perioperative therapy with 642 evaluable patients with CRC liver metastases. The pooled analysis showed a benefit of chemotherapy in PFS (HR 0.75; $P = 0.003$) and disease-free survival (HR 0.71; $P = 0.001$), but not in overall survival (OS) (HR 0.74; $P = 0.088$).[7] This approach represents the current standard for patients with minimal and resectable disease.[7] Pre- and postoperative chemotherapy versus postoperative chemotherapy alone, as well as the addition of biological agents, are being investigated in ongoing trials. In the new Early Presentation Of Cancer Project (EPOC) study, 272 patients with *KRAS* wild-type (wt) tumor operable liver metastases were randomized to receive FOLFOX plus or minus cetuximab for 12 weeks before, then 12 weeks following, surgery. The new EPOC study was stopped when the futility analysis was predefined by a protocol. With 45.3% of the expected events observed, PFS was significantly worse in the cetuximab arm (14.8 vs 24.2 months; HR 1.50; $P < 0.048$).[8] In clinical practice, postoperative adjuvant chemotherapy with FOLFOX/ capecitabine/ oxaliplatin (XELOX) or FOLFOX/XELOX plus bevacizumab is administered for an overall treatment of 6 months, despite lack of data favoring this approach and an unspecified chemotherapy duration (6 months).[9] As regards treatment of lung-only metastases, the issue is similar to liver metastases.[10] Results from a retrospective analysis of 795 previously untreated mCRC patients randomized in a Phase III trial evaluating the efficacy of mostly oxaliplatin-containing chemotherapy regimens indicated that patients with lung-only metastases (two out of 24 patients) were able to undergo curative resection after treatment. The median OS in these patients was 42.4 months.[11] Despite the lack of data from prospective trials regarding perioperative treatment, an approach similar to management of resectable liver metastases should be considered. Alternatively, an initial resection followed by postoperative adjuvant treatment with fluoropyrimidine with or without oxaliplatin for 6 months can be performed.[10]

Management of patients with extensive disease (potentially resectable metastatic disease after conversion chemotherapy [group 1])

The majority of patients diagnosed with metastatic colorectal disease have unresectable disease. However, for those with liver-limited unresectable disease that, because of involvement of critical structures, cannot be resected unless regression is accomplished, chemotherapy is being increasingly considered in highly selected cases in an attempt to downsize colorectal metastases and convert them to a resectable status. Usually, a doublet chemotherapy plus monoclonal antibody or a triplet chemotherapy is used for conversion chemotherapy.

Doublet chemotherapy regimens comprising infusional 5-FU/bolus 5-FU/LV/irinotecan (FOLFIRI) or FOLFOX have reported that a significant portion (32.5% and 40%, respectively) of the patients with initially unresectable liver metastases undergo liver resection.[12,13] Data emerging from randomized trials suggest that the addition of a targeted agent to a doublet chemotherapy might be more effective in treatment of liver-limited disease. In the CELIM Phase II trial, patients were randomized to receive cetuximab with either FOLFOX or FOLFIRI.[14] Retrospective analysis showed that, in both treatment arms, combined resectability increased from 32% to 60% after chemotherapy in patients with *KRAS* wt tumor ($P < 0.0001$) with the addition of cetuximab. A recent meta-analysis of four randomized controlled trials concluded that the addition of monoclonal antibody anti-epidermal growth factor receptor (EGFR) to chemotherapy significantly increased the resection rate (RR) ([R0] from 11% to 18%; odds ratio [OR] 1.59; $P = 0.04$), and PFS, but not OS in patients with *KRAS* wt tumor.[15] Also, bevacizumab was analyzed in this setting. Data seem to suggest that the combination of bevacizumab with an irinotecan-based regimen modestly improves the RR (<2%).[16] On the other hand, the association of FOLFOX with bevacizumab showed no benefit in RR and tumor reduction compared with chemotherapy alone (8.4% vs 6.1%, respectively).[17] However, because it is not known in advance whether resectability will be achieved, the use of bevacizumab with oxaliplatin-based therapy in this setting is acceptable. In addition, infusional 5-FU/LV/oxaliplatin/irinotecan (FOLFOXIRI) has been compared with FOLFIRI in unresectable patients.[18] FOLFOXIRI led to an increase in R0 secondary RRs, from 6% to 15% ($P = 0.033$). In a follow-up study of the Gruppo Oncologico Nord Ovest (GONO) trial, the 5-year survival rate was higher in the group receiving FOLFOXIRI (15% vs 8%), with a median OS of 23.4 versus 16.7 months ($P = 0.026$).[19] There are no available data regarding effectiveness comparisons between doublet chemotherapy plus bevacizumab versus doublet chemotherapy plus cetuximab or panitumumab in *KRAS* wt patients, but, at the same time, FOLFIRI or FOLFOX plus anti-EGFR antibodies appears to be more effective in terms of major tumor shrinkage and secondary resectability

than bevacizumab-based combination in potentially resectable patients with extensive disease. FOLFOXIRI plus bevacizumab is very effective, but data about liver metastases R0 are not yet available.[20]

First-line treatment of advanced disease

The current first-line management of disseminated mCRC involves various active drugs, either in combination or as single agents: 5-FU/LV, capecitabine, irinotecan, oxaliplatin, bevacizumab, cetuximab, and panitumumab. The association of 5-FU/LV revealed an advantage in terms of RR without any impact on OS.[21] The doublet chemotherapy FOLFIRI and FOLFOX led to a considerable increase in RR and prolonged OS, and similar RR and PFS times were obtained when these regimens were used as first-line therapy.[22,23] XELOX is comparable to FOLFOX in terms of activity and efficacy, while capecitabine/irinotecan (XELIRI) is burdened by severe gastrointestinal toxicity.[24,25] FOLFOXIRI is more effective than FOLFIRI in terms of PFS (9.8 vs 6.9 months; HR 0.63; $P = 0.0006$) and OS (22.6 vs 16.7 months; HR 0.70; $P = 0.032$), although this regimen has to be reserved for patients with appropriate conditions and without relevant comorbidities.[18] Currently, conventional first-line therapy of mCRC is based on the association of conventional chemotherapy regimens and biological drugs that include bevacizumab, cetuximab, or panitumumab; in fact, clinical trials have shown that targeted agents increase the efficacy of conventional chemotherapy regimens.[16,17,26,28–30] Bevacizumab has been shown to increase RR and PFS in association with all chemotherapy regimens. OS, however, appears to differ between the various combinations of treatment; specifically, OS is greater in FOLFIRI plus bevacizumab regimen than FOLFOX plus bevacizumab.[16,17] Recently, the TRIplet chemotherapu plus BEvacizumab (TRIBE) randomized, Phase III trial has proven a statistically significant advantage in FOLFOXIRI plus bevacizumab treatment group versus FOLFIRI plus bevacizumab in terms of PFS and objective response rate (ORR).[20]

Literature has shown that tumors with a mutation in codon 12 or 13 (exon 2) of the *KRAS* gene are essentially insensitive to EGFR inhibitors such as cetuximab or panitumumab;[26,27] it has also recently emerged that both rare *KRAS* mutations (exon 3) and *NRAS* mutations could invalidate the efficacy of panitumumab treatment.[28]

Cetuximab in first-line chemotherapy has shown a benefit in terms of PFS in patients with k-ras wt tumor; a retrospective analysis in this subgroup also demonstrated that cetuximab plus FOLFIRI gave a greater benefit in terms of OS than FOLFIRI alone.[26] Analogously, panitumumab plus FOLFOX showed a statistically significant advantage in all RAS wt patients in terms of PFS and OS.[28,29] Table 2 shows RR, PFS, and OS data of main mCRC first-line treatment clinical trials. Finally, FIRE-3 study results were presented during the 13th ASCO annual meeting.[31] In this Phase III trial, 592 patients with *KRAS* wt tumor were randomized to receive FOLFIRI plus cetuximab or FOLFIRI plus bevacizumab. The median duration of treatment was 4.7 months versus 5.3 months, respectively. The primary end point was RR, but the study did not meet this end point because RR was comparable in the two groups (62% vs 57%, OR 1.249); median PFS was nearly identical (10.3 vs 10.4 months; HR 1.04; $P = 0.69$); however, OS showed a significantly better outcome in the FOLFIRI plus cetuximab group (28.8 vs 25.0 months; HR 0.77; $P = 0.0164$). This study has several methodological limitations, therefore it does not decisively solve the riddle of which biological agent should be used in the first-line treatment of mCRC RAS wt patients.[31] We must await the results of a Phase III study conducted by the CALGB group in order to have solid data about cetuximab versus bevacizumab in mCRC first-line treatment.[32]

In conclusion, the choice of which therapeutic regimen to use in mCRC first-line treatment is based on consideration of the goals of therapy and the differing toxicity profiles of the constituent drugs.

Management of never-resectable and symptomatic patients (palliation therapy [group 2])

The treatment aim in group 2 is rapid tumor size reduction to resolve symptoms related to disease extension. Either triplet or doublet chemotherapy can be the first choice because each provides the chance of fast and major response (Tables 1 and 2). There is no clear preference for triplet or doublet chemotherapy; rather, the decision is based on tumor symptoms, dynamics, tumor biology, and clinical patient characteristics.

Management of never-resectable and asymptomatic patients (continuum care [group 3])

For those patients without present or imminent symptoms and limited risk for rapid deterioration, the aim is prevention of tumor progression with symptom disappearance and prolongation of life with minimal treatment, thus ensuring continuum care. Treatment is based on a single agent or doublet chemotherapy with low toxicity. Of great importance is the data of the AVEX trial, a Phase III study conducted on

Table 2 RR, PFS, and OS data of main clinical trials about mCRC first-line treatment

Author	Phase study	Treatment	Population	OS (months)	HR *P*-value	PFS (months)	HR *P*-value	RR (%)	OR *P*-value
Hurwitz et al[16]	III	IFL/placebo	923	15.6	0.66	6.2	0.54	34.8	$P = 0.004$
		IFL/BV		20.3	$P < 0.001$	10.6	$P < 0.001$	44.8	
		5-FU/FA/BV		18.3		8.8		40	
Saltz et al[17]	III	XELOX/FOLFOX4	1,400	19.9	0.89	8.0	0.83	49	0.90
		XELOX/FOLFOX+BV		21.3	$P = 0.0769$	9.4	$P = 0.0023$	47	$P = 0.31$
Falcone et al[20]	III	FOLFOXIRI+BV	508	31.0[a]	0.83	12.2	0.77	65	$P = 0.006$
		FOLFIRI+BV		25.8[a]	$P = 0.125$[a]	9.7	$P = 0.006$	53	
Van Cutsem et al[26]	III	FOLFIRI+C	348	23.5	$P = 0.093$	8.9	0.85	46.9	1.40
		FOLFIRI	(wt *KRAS* pts)	20.0		8.0	$P = 0.048$	38.7	$P = 0.004$
Bokemeyer et al[30]	II	FOLFOX+C	134	22.8	0.85	7.7	0.57	61	2.54
		FOLFOX	(wt *KRAS* pts)	18.5	$P = 0.39$	7.2	$P = 0.016$	37	$P = 0.19$
Douillard et al[29]	III	FOLFOX+P	656	23.9	0.83	9.6	0.80	55	1.35
		FOLFOX	(wt *KRAS* pts)	19.7	$P = 0.072$	8.0	$P = 0.02$	48	$P = 0.068$
Oliner et al[28]	III	FOLFOX+P	259	26.0	0.78	10.1	0.72	NR	NR
		FOLFOX	(all wt RAS pts)	20.0	$P = 0.04$	7.9	$P < 0.01$	NR	

Note: [a]Immature data.

Abbreviations: 5-FU, 5-fluorouracil; BV, bevacizumab; C, cetuximab; P, panitumumab; FA, folinic acid; FOLFIRI, infusional 5-FU/bolus folinic acid/irinotecan; FOLFOX4, infusional 5-FU/bolus FA/oxaliplatin; FOLFOXIRI, infusional 5-FU/bolus FA/irinotecan/oxaliplatin; HR, hazard ratio; IFL, bolus 5-FU/FA/irinotecan; mCRC, metastatic colorectal cancer; NR, not reported; OR, odds ratio; OS, overall survival; PFS, progression-free survival; pts, patients; RR, response rate; wt, wild-type; XELOX, capecitabine/oxaliplatin.

elderly mCRC patients that showed how the combination of fluoropyrimidines with bevacizumab is superior to fluoropyrimidines alone.[33] Initial therapy guidelines recommend a choice of five chemotherapy regimens: FOLFOX; FOLFIRI; XELOX, infusional 5-FU/LV; or capecitabine, plus or minus the association with a biological agent (Tables 1 and 2).[16,17,26,28,29]

Maintenance treatment strategies

There are several maintenance strategies that are used in mCRC after effective first-line chemotherapy in order to reduce disease progression and treatment toxicity.

The OPTIMOX1 study showed that a stop-and-go approach using oxaliplatin-free intervals resulted in decreased neurotoxicity, but did not affect OS, in patients receiving FOLFOX as initial therapy for metastatic disease.[34] Therefore, adjusting the schedule and timing of the administration of this drug can limit this adverse effect. From OPTIMOX1 trial results is derived another therapeutic strategy: reintroduction of a chemotherapeutic agent and residual sensitivity. In the investigational arm of the OPTIMOX1 study, oxaliplatin was reintroduced in 40% of patients and achieved a disease control rate of 69%. Thus, reintroduction of oxaliplatin should be considered in patients who have an initial benefit from FOLFOX or XELOX and who can tolerate it.

Another study, the CONcePT trial, evaluated alternating oxaliplatin administration according to the following schedule: eight doses of FOLFOX plus bevacizumab followed by eight maintenance doses of 5-FU/LV plus bevacizumab, alternating the two regimens until disease progression. Through this stop-and-go strategy, PFS of 12 months and a low toxicity profile were obtained.[35]

In addition to conventional chemotherapeutic drugs, biologic agents have also been tested in mCRC maintenance therapy; in particular, bevacizumab has been analyzed more in this setting than cetuximab.

The anti-EGFR monoclonal antibody was investigated as a maintenance single-agent in the NORDIC VII trial, but results were not encouraging.[36]

Diaz-Rubio et al, in a Phase III trial, suggested that maintenance therapy with single-agent bevacizumab represented an appropriate option after XELOX plus bevacizumab chemotherapy induction, on the basis of noninferiority results in terms of PFS obtained in a bevacizumab maintenance group versus a XELOX plus bevacizumab maintenance group (10.4 vs 9.7 months, respectively).[37] At the ASCO 13th annual meeting, two other clinical trials[38,39] about the use of bevacizumab in first-line treatment until progression were presented but having, in the control arm, exclusively observation. The CAIRO3 study was designed to investigate the efficacy of observation versus maintenance treatment with capecitabine plus bevacizumab after induction treatment with six cycles of XELOX plus bevacizumab. Maintenance treatment with XELOX plus bevacizumab is feasible and significantly prolongs PFS; there is also a

significant difference in OS in adjustment analysis.[38] In the noninferiority Phase III SAKK 41/06 trial, noninferiority of maintenance treatment with bevacizumab alone versus observation arm, after 4–6 months of first-line chemotherapy plus bevacizumab was investigated. The noninferiority in time to progression could not be demonstrated, although advantageous data for PFS were shown (9.5 months in bevacizumab group vs 8.5 in the observation group; $P = 0.02$); no difference in OS was observed in the two arms.[39] At present, there are no clear data on the use of bevacizumab in the maintenance setting. In order to attain precise indications, it is necessary to wait for data from the Phase III AIO KRK 0207 trial, which compares maintenance therapy with bevacizumab alone versus bevacizumab plus fluoropyrimidines versus observation.[40]

Associations between targeted agents have also been investigated in maintenance treatment: the GERCOR-DREAM trial evaluated bevacizumab combined with erlotinib after first-line oxaliplatin- or irinotecan-based chemotherapy. After 31 months of follow-up, median PFS was 4.6 months in the bevacizumab group versus 5.8 months in the bevacizumab plus erlotinib group (HR 0.73; $P = 0.005$).[41]

As the maintenance strategy we reported treatment-free interval, which was investigated in two trials, OPTIMOX2 and COIN.[42, 43]

In the Phase II OPTIMOX2 trial,[42] patients were randomized to receive either an OPTIMOX1 approach or an induction FOLFOX regimen followed by discontinuation of all chemotherapy until tumor progression reached baseline, followed by reintroduction of FOLFOX. Results of the study showed no difference in OS for patients receiving the OPTIMOX1 approach compared with those undergoing an early, preplanned, chemotherapy-free interval (OS 23.8 vs 19.5 months; $P = 0.42$). However, the median duration of disease control, which was the primary end point of the study, reached statistical significance at 13.1 months in patients undergoing maintenance therapy and 9.2 months in patients with a chemotherapy-free interval ($P = 0.046$).

The MRC COIN study[43] compared continuous oxaliplatin-based chemotherapy until disease progression and treatment holiday after 3 months of induction treatment, followed by chemotherapy reintroduction, on disease progression. Although this trial did not show noninferiority of intermittent compared with continuous chemotherapy in terms of OS, chemotherapy-free intervals remain a treatment option for some patients with advanced colorectal cancer, offering reduced time on chemotherapy, reduced cumulative toxic effects, and improved quality of life.

Second-line chemotherapy after first disease progression and further treatment lines

Second and further chemotherapy lines in mCRC depend on previous therapies. Particularly, based on clinical evidence, there are four different chemotherapeutic modalities to use after first-line disease progression. For patients who received an oxaliplatin-based regimen for initial therapy, FOLFIRI or irinotecan alone are recommended options. Usually in patients with *KRAS* wt tumor, irinotecan-based chemotherapy can be combined with cetuximab or panitumumab,[44,45] while in patients with *KRAS* mutant tumor can be combined with bevacizumab[46,47] or aflibercept.[48] Anti-vascular endothelial growth factor treatment use beyond first-line bevacizumab-based chemotherapy progression has been analyzed by the TML and VELOUR trials, which observed patients continuing on bevacizumab or aflibercept having a modest improvement in OS.[47,48]

For mCRC patients who received an irinotecan-based regimen as initial treatment, FOLFOX or XELOX alone or with bevacizumab,[46] cetuximab or panitumumab plus irinotecan, or single-agent cetuximab or panitumumab are recommended options.[44,45,49,50] In patients treated with 5-FU/LV or capecitabine as initial therapy, options after first progression include FOLFOX, XELOX, FOLFIRI, single-agent irinotecan, or irinotecan plus oxaliplatin. These can varyingly be combined with bevacizumab or aflibercept.[46,47] Finally, for patients who received FOLFOXIRI as initial therapy, cetuximab or panitumumab plus irinotecan or cetuximab or panitumumab alone are recommended options for those with *KRAS* wt tumor.[44,45,49,50] However, regarding later chemotherapy lines, the possible options for patients with *KRAS* wt not previously treated with anti-EGFR antibodies are cetuximab with or without irinotecan and panitumumab with or without FOLFIRI.[44,45,49,50] In patients who are refractory to 5-FU, oxaliplatin, irinotecan, anti-EGFR antibodies (*KRAS* wt tumor only), bevacizumab, and regorafenib, treatment with fluoropyrimidines and mitomycin or reintroduction of oxaliplatin (and irinotecan) results in very limited improvement in some patients treated as last line. However, despite poor results in the data, this might be justified in some patients. Finally, regorafenib demonstrated an advantage in terms of OS versus placebo in last-line salvage treatment.[51]

Table 3 RR, PFS, and OS data of main clinical trials about mCRC non-first-line treatment

Author	Phase study	Line treatment	Treatment	Population	OS (months)	HR *P*-value	PFS (months)	HR *P*-value	RR (%)	OR *P*-value
Giantonio et al[46]	III	II	FOLFOX4	823	12.9	0.75	7.3	0.61	22.7	$P < 0.001$
			FOLFOX4+BV		10.8	$P = 0.0011$	4.7	$P < 0.0001$	8.6	
			BV		10.2		2.7		3.3	
Bennouna et al[47]	III	II	CT+BV	820	11.2	0.81	5.7	0.68	6	NR
			CT		9.8	$P = 0.0062$	4.1	$P < 0.0001$	4	
Van Cutsem et al[48]	III	II	FOLFIRI+A	1226	13.5	0.758	6.9	0.758	19.8	$P = 0.0001$
			FOLFIRI		12.06	$P = 0.0032$	4.67	$P < 0.0001$	11.1	
Sobrero et al[45]	III	II	CPT-11+C	1298	10.7	0.975	4.0	0.692	16.4	$P < 0.0001$
			CPT-11		10.0	$P = 0.71$	2.6	$P < 0.0001$	4.2	
Peeters et al[44]	III	II	FOLFIRI+P	1186	14.5	0.85	5.9	0.73	35	NR
			FOLFIRI		12.5	$P = 0.12$	3.9	$P = 0.004$	10	
Cunningham et al[49]	III	Further lines	CPT-11+C	329	8.6	0.91	4.1	0.54	22.9	$P = 0.007$
			C		6.9	$P = 0.48$	1.5	$P < 0.001$	10.8	
Van Cutsem et al[50]	III	Further lines	P	463	NR	1.00,	8.0[a]	0.61	10	$P < 0.001$
			BSC		NR	$P = 0.81$	7.3[a]	$P < 0.0001$	0	
Grothey et al[51]	III	Further lines	R	760	6.4	0.77	1.9	0.49	1.0	$P = 0.19$
			BSC		5.0	$P = 0.0052$	1.7	$P < 0.0001$	0.4	

Note: [a]Weeks.

Abbreviations: A, aflibercept; BSC, basic supportive care; BV, bevacizumab; C, cetuximab; CPT-11, irinotecan; CT, chemotherapy; FOLFIRI, infusional 5-fluorouracil/bolus folinic acid/irinotecan; FOLFOX4, infusional 5-fluorouracil/bolus folinic acid/oxaliplatin; HR, hazard ratio; mCRC, metastatic colorectal cancer; NR, not reported; OR, odds ratio; OS, overall survival; P, panitumumab; PFS, progression-free survival; R, regorafenib; RR, response rate.

Table 3 illustrates RR, PFS, and OS data of main clinical trials evaluating mCRC second- and further-line treatments.

Conclusion

Treatment of mCRC involves the use of active cytotoxic drugs and biological agents, either in combination or as single agents. Until recently, the only biological agent with proven first-line efficacy was bevacizumab, but options have expanded from the data generated with anti-EGFR monoclonal antibodies. Anti-EGFR agents can be added to first-line FOLFIRI or FOLFOX in patients whose tumors express RAS wt. These agents may improve outcomes when added to chemotherapy, particularly in PFS and, in the case of cetuximab, OS and ORR. The selection of first-line therapy should be based on the individual treatment goals after considering the efficacy and tolerability of each regimen. For patients with metastases confined to the liver, surgical resection offers a potentially curative approach. For initially unresectable lesions, treatment regimens offering high response rates may produce sufficient tumor shrinkage to permit complete resection. Regimens with high response rates are also preferable for patients requiring symptom relief or for those with large tumor burdens. The choice between intensive and nonintensive management also depends on other factors, including the patient's functional status, comorbidities, and desires. A sequential single-agent strategy or an intermittent approach (combination therapy followed by maintenance) may minimize toxicity and be appropriate for patients who are not surgical candidates, irrespective of treatment response. Finally, the choice of second or further chemotherapy lines is closely related to the drugs used in prior-line treatment and has been shown to improve both PFS and OS.

Disclosure

The authors report no conflicts of interest in this work.

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