Therapeutic Armamentarium in Metastatic Colorectal Cancer

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Abstract

Colorectal cancer is one of the most frequently diagnosed malignancies in both men and women and, despite recent advances, the prognosis in the metastatic setting remains poor. In the last decade the introduction of new chemotherapeutic agents has improved the median overall survival of these patients. The demonstration that deregulation and/or activation of selected kinase proteins are common phenomena in patients with colon cancer has prompted the development of new biologic therapies targeting such proteins. Further, inhibition of the angiogenesis process can result in efficacy advantage. To date, three targeted therapies have been approved for the treatment of patients with metastatic colorectal cancer: bevacizumab, cetuximab and panitumumab. New treatments directed against other molecular targets are being developed in order to improve these results.

Keywords

Colon cancer, chemotherapy, bevacizumab, cetuximab, panitumumab, targeted therapies

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Colorectal cancer (CRC) remains one of the most common tumour types and a leading cause of cancer death worldwide. The American Cancer Society (ACS) estimates that 148,610 people were diagnosed with, and 55,170 people died of, CRC last year in the US.[1] Despite these statistics, mortality from CRC has decreased over the past 30 years, possibly because of better treatment modalities. Until a few years ago, treatment options for CRC patients were limited to 5-fluorouracil (5FU). However, the introduction of two new cytotoxic drugs, irinotecan and oxaliplatin, has resulted in significant progress in the treatment of metastatic CRC (mCRC).[2,3] Recently, three novel targeted agents have been approved for the treatment of mCRC: bevacizumab, cetuximab and panitumumab. As a consequence, the armamentarium of treatment options for patients with CRC is rapidly expanding. In spite of these advances, the prognosis for patients with mCRC remains poor, with a five-year survival rate less than 5%. Therefore, new strategies are needed to improve this prognosis. In this article we review the therapeutic options in mCRC.

The Chemotherapy Era

Until a few years ago, 5FU and 5FU in combination with leucovorin (LV) were the treatment options for patients with CRC. Some clinical trials evaluated different schedules and doses of these two drugs, infusional schedules of 5FU and combinations with LV being the most attractive regimens. Nevertheless, the median overall survival (mOS) remained around 12 months.[4] Saltz et al.[2] demonstrated in a phase III trial with 628 patients that the addition of irinotecan to bolus 5FU/LV (IFL) increased the mOS from 12.6 to 14.8 months (p=0.04). Another study, conducted by Douillard et al. (with an infusional 5FU/LV regimen),[5] confirmed this data. The results of these two prospective phase III randomised, controlled, multicentre, multinational clinical trials in patients with previously untreated mCRC served as the basis for US and European approval of irinotecan/5FU/LV for this indication. At the same time, de Gramont et al.[3] published the results of a phase III trial which concluded that the combination of infusional FU/LV and oxaliplatin (FOLFOX) prolonged progression-free survival (PFS) (median 9 months versus 6.2 months; p=0.0003) with acceptable tolerability. However, this combination failed to demonstrate a statistically significant increase in OS (median 16.2 months versus 14.7 months; p=0.12). For this reason the FOLFOX regimen was only approved in Europe as first-line treatment in mCRC. With the results of the Goldberg trial in 2004,[6] oxaliplatin was approved in the US for the treatment of mCRC. In this study, 795 patients with mCRC were randomised to receive IFL, FOLFOX or irinotecan and oxaliplatin (IROX). The results of the FOLFOX group were significantly superior to the IFL and IROX groups. At that time, two 5FU-based infusional regimens with oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) became the most popular schedules used worldwide for the treatment of patients with mCRC.

The Gruppo Oncologico del Nord-Ovest (GONO) Italian group published the results of a very provocative trial evaluating a new chemotherapy combination.[7] In this phase III trial, 244 patients were randomised to receive FOLFIRI or the combination of oxaliplatin, infusional 5FU/LV and irinotecan (FOLFOXIRI). The response rate (RR)

confirmed by an external panel was 34% in the FOLFIRI arm versus 60% in the experimental arm (p=0.0001). Interestingly, the R0 secondary resection rate of metastasis was greater in the triplet arm (6 versus 15% [p=0.33] and 12 versus 36% [p=0.017] among patients with only liver metastasis). Median OS was significantly improved in the FOLFOXIRI arm (16.7 versus 22.6 months, hazard ratio [HR] 0.70; p=0.032). The safety profile of the experimental arm was acceptable. Since these results were published an important number of patients have been treated with the FOLFOXIRI combination, especially those that can be considered for salvage surgery if tumour shrinkage occurs. Some patients, especially those very fragile or with a very indolent disease, may still be treated with single-agent fluoropyrimidine, either 5FU or capecitabine.[8] Salvage treatment after failing first-line chemotherapy has become a more complicated field, as many treatment options are available depending on the treatment that has been chosen as a first-line option. The potential treatment options have been reviewed elsewhere.[8]

The Molecular Target Era

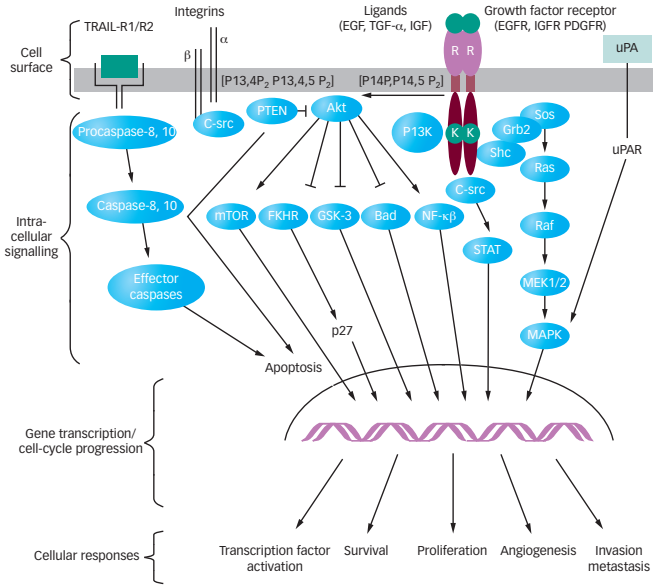
A better understanding of the molecular pathways that characterise cell growth, apoptosis, angiogenesis and invasion, has established novel targets in cancer therapy (see *Figure 1*). Several drugs directed against these and other molecular targets are being evaluated at different stages of development; recently, three novel targeted agents have been approved for the treatment of mCRC.

Targeting Vascular Endothelial Growth Factor

The regulation of angiogenesis is a complex, multistep process resulting from a dynamic balance between pro-angiogenic and anti-angiogenic factors. Among the most important regulators of this process are the vascular endothelial growth factors (VEGF) and their receptors (VEGFR). Because of its central role in tumour-associated angiogenesis in a wide range of malignancies, VEGF-A has emerged as an attractive and central therapeutic target in cancer.

Bevacizumab (Avastin®), a humanised monoclonal antibody against VEGF-A, reduces the availability of the VEGF-A ligand for its corresponding receptor, VEGFR, and thereby prevents receptor activation. The first clinical trial of bevacizumab in combination with chemotherapy in previously untreated mCRC patients was reported by Kabbinavar in 2003.[9] This randomised phase II trial involving 104 patients randomised to two different doses of bevacizumab (5mg/kg or 10mg/kg) every other week in combination with 5FU/LV, or to 5FU/LV alone. The RR, median time to progression (TTP) and mOS were superior with the addition of bevacizumab, with better results with the low dose of bevacizumab, suggesting that 5mg/kg bi-weekly would be the dose to take forward for further studies. The larger phase III study randomised 923 patients with mCRC into three treatments groups: IFL plus bevacizumab, IFL plus placebo or 5FU/LV (Roswell Park schedule) plus bevacizumab.[10] The addition of bevacizumab to the IFL schedule showed a statistically significant improvement in RR (44.8 versus 34.8%; p=0.004), median OS (20.3 versus 15.6 months; p<0.001) and median PFS (10.6 versus 6.2 months; p<0.001). The incidence of any grade 3/4 toxicities was higher among the patients receiving IFL plus bevacizumab with moderate increase of grade 3 hypertension and small increases in the incidence of grade 4 diarrhoea and leukopenia (see *Table 1*). Two rare but serious toxicities related to bevacizumab treatment were observed: gastrointestinal perforations and arterial thrombotic events. As a result of this study, bevacizumab was licensed for first-line treatment of mCRC by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMEA).

Figure 1: Intracellular Signal Transduction Pathways



Ligands bind to the extracellular domain of membrane receptors, which are phosphorylated, leading to activation of several cytoplasmatic messengers, which activate transcription factors in the nucleus. The activation of transcription factors in the nucleus involves some target genes that are implicated in the proliferation, angiogenesis, apoptosis and tumour invasion processes. PTEN = phosphatase and tensin homologue; PI3K = phosphatidylinositol 3-kinase; mTOR = mammalian target of rapamycin; $PI_{34}P_2$ = phosphatidylinositol (3,4) biphosphate; $PI_{345}P_3$ = phosphatidylinositol (3,4,5) triphosphate; TRAIL® = tumour necrosis factor-related apoptosis-inducing ligand; TRAIL-R = tumor necrosis factor-related apoptosis-inducing ligand receptor; EGFR = epidermal growth factor receptor; EGF = epidermal growth factor; TGF-α = transforming growth factor alpha; IGF = insulin-like growth factor; IGFR = insulin-like growth factor receptor; PDGFR = platelet-derived growth factor receptor; MAPK = mitogen-activated protein kinase; MEK = MAP kinase kinase; FKHR = forkhead transcription factor; GSK-3 = glycogen synthase kinase-3; STAT = signal transducers and activators of transcription protein; NF-kβ = nuclear factor kappa-light-chain-enhancer of activated B cells; SHC = Src homology 2 domain-containing transforming protein; GRB2 = growth factor receptor-bound protein 2; SOS = son of sevenless protein; uPA = urokinase-type plasminogen activator; uPAR = urokinase-type plasminogen activator.

Table 1: Adverse Events Presented in Patients with Metastatic Colon Cancer Treated with Irinotecan-bolus with or without Bevacizumab as a First-line Treatment[10]

Adverse Events	IFL plus Bevacizumab (%) (n=393)	IFL plus Placebo (%) (n=397)
Any grade 3/4 adverse event	89.4	74 (p<0.01)
Grade 3/4 leukopenia	37	31.1
Grade 3/4 diarrhoea	32.4	24.7
Any grade hypertension	22.4	8.3 (p<0.01)
Grade 3 hypertension	11.0	2.3 (p<0.01)
Grade 3/4 bleeding	3.1	2.5
Any grade proteinuria	26.5	21.7
Grade 3 proteinuria	0.8	0.8
Any grade thrombotic events	19.4	16.2
Deep thromboflebitis	8.9	6.3
Gastrointestinal perforation	1.5	0.0

IFL = irinotecan-bolus, 5-fluorouracil and leucovorin.

The efficacy of bevacizumab in the second-line setting was probed in the phase III E3200 trial,[11] in which 829 patients with mCRC who had failed irinotecan and 5FU chemotherapy were randomised to FOLFOX plus a high dose of bevacizumab (10mg/kg), FOLFOX alone or bevacizumab alone. Again, the addition of bevacizumab resulted in significant gains in terms of RR (21.8, 9.2 and 3%, respectively; p<0.001), PFS (median 7.2, 4.8 and 2.7 months, respectively; p<0.001)

and OS (median 12.5, 10.7 and 10.7, respectively; p<0.0024). Bevacizumab has been approved in the second-line setting in combination with chemotherapy in patients with mCRC.

When oxaliplatin-based chemotherapy was combined with bevacizumab (FOLFOX or CAPOX) in the first-line setting the expected benefit was proved too, albeit to a lesser magnitude. A randomised 2x2 factorial phase III trial was presented by Cassidy.[12] In this study, 1,401 untreated mCRC patients were randomised to one of four arms: CAPOX (capecitabine plus oxaliplatin) plus placebo, CAPOX plus bevacizumab, FOLFOX plus placebo or FOLFOX plus bevacizumab. The results of the study met the primary end-points: CAPOX was non-inferior to FOLFOX with a similar safety profile and offered the advantage of oral fluoropyrimidine administration. Bevacizumab added clinically meaningful and statistically superior benefit in terms of PFS (eight months in the placebo arms versus 9.4 months in the bevacizumab arms; p=0.0023).

The observational cohort study Bevacizumab Regimens: Investigation of Treatment Effects and Safety (BRITE) has recently been published suggesting that continuation of VEGF inhibition with bevacizumab beyond initial progression could prolong OS.[13] Two ongoing prospective randomised trials (ML18147 and SWOG S0600) are comparing the value of adding bevacizumab to second-line chemotherapy after failing first-line chemotherapy in combination with bevacizumab in patients with mCRC.

The efficacy demonstrated in mCRC with bevacizumab generates the question of its usefulness in the adjuvant setting. At the last American Society of Clinical Oncology (ASCO) meeting, Wolmark presented the results of the National Surgical Adjuvant Breast and Bowel Project (NSABP) C-08 trial.[14] The objective of this two-arm randomised, prospective study was to determine whether mFOLFOX6 plus bevacizumab was superior to the chemotherapy alone in terms of disease-free survival (DFS). A total of 2,672 patients with stage II (24.9%) and III CRC were included in the study. The HR was 0.89 (95% CI 0.76–1.04; p=0.15), the study failing to demonstrate statistically significant prolongation of DFS. The international community is awaiting the results of some other trials that are evaluating the role of bevacizumab in the adjuvant setting, such as the AVANT and the QUASAR2 studies. In the AVANT trial, patients with high-risk stage II and stage III colon cancer after radical surgery are randomised to one of three arms: FOLFOX4 alone (control arm), FOLFOX4 plus bevacizumab or XELOX plus bevacizumab.

The inhibition of tyrosine kinase (TKI) signalling of VEGFR is another strategy to hinder tumour-induced angiogenesis. A variety of small-molecule tyrosine TKIs targeting the VEGF receptors are being developed such as PTK-787 (valatanib), SU-5416 (semaxanib), SU-11248 (sunitinib), AZD-2171 (cediranib), BAY-43-9006 (sorafenib) and ZD-6474 (vandetanib). Of these compounds, three drugs have failed so far to demonstrate additional clinical benefit when combined with standard chemotherapy schedules. Semaxanib was the first to fail clinical development, with an early interruption of the registrational studies. More recently, valatanib was the first TKI to complete the clinical evaluation. Two randomised phase III studies have evaluated the efficacy of valatinib in combination with standard chemotherapy in patients with mCRC. In the first, 1,168 patients with untreated mCRC were randomised to receive FOLFOX4 plus valatinib or FOLFOX4 plus placebo (CONFIRM 1).[15] The primary end-point for an advantage in median PFS was not met (7.7 versus 7.6 months in the PTK/ZK and placebo arms, respectively; p=0.11). Nevertheless, patients with high levels of lactate dehydrogenase (LDH) who received valatinib achieved a significant improvement in median PFS compared with patients with high levels of LDH who received placebo (7.7 versus 5.8 months, respectively; p=0.010), suggesting that LDH could be a predictive marker. The second trial was performed in previously treated mCRC patients with identical randomisation, but the primary end-point was to demonstrate an improvement in median OS (CONFIRM 2).[16] While the primary objective was not met (12.1 versus 11.8 months in the valatinib and placebo arms, respectively; p=0.511), median PFS was significantly longer in the valatinib-containing arm (5.5 versus 4.1 months, respectively; p=0.026). Patients with higher levels of LDH showed the greatest benefit in median PFS with the addition of valatinib (5.6 versus 3.8 months, respectively; p<0.001). A meta-analysis of these two randomised phase III trials aimed at determining clinical benefit in PFS in patients with high LDH levels was conducted. The study suggests that valatinib improves PFS in this subgroup of patients.[17] More recently, an early press release has announced that the phase III study SUN1122 that was evaluating sunitinib plus FOLFIRI versus FOLFIRI alone in the first-line treatment of mCRC was discontinued, having failed to achieve its primary end-point.[18]

Targeting Epidermal Growth Factor Receptor

The epidermal growth factor receptor (EGFR) is a member of the family of transmembrane protein kinase receptors known as the erbB or HER receptor family. EGFR is overexpressed in 75–90% of CRC and it seems to confer a poor prognosis.[19] While multiple strategies of targeting the EGFR are under development, two modalities have been the most developed: small molecule inhibitors of the intra-cellular kinase domain of the EGFR and molecular antibodies designed to block the extra-cellular ligand-binding domain of EGFR. Currently, several trials have reported that K-Ras mutations are associated with lack of response to anti-EGFR monoclonal antibodies. K-Ras mutations are found in about 40% of CRC and a high concordance between primary tumour and related metastases has been reported.

Cetuximab, the most advanced anti-EGFR agent in clinical development, and panitumumab, a fully human monoclonal antibody against EGFR, have been approved in the US and in Europe for the treatment of mCRC K-Ras wild-type patients. The approval for cetuximab is in combination with chemotherapy in first-line and in the refractory setting whereas panitumumab has only been approved as a single-agent treatment in the refractory setting. Nevertheless, the FDA has not yet positioned on the K-Ras mutation status-based indication for both compounds.

Both anti-EGFR monoclonal antibodies were originally developed in the refractory setting. The pivotal study for the approval of cetuximab in the refractory setting was the BOND randomised phase II study.[20] In this study, patients refractory to irinotecan-based chemotherapy (and half of them also previously treated with oxaliplatin-based chemotherapy) with EGFR-expressing tumours were randomised to receive cetuximab plus irinotecan (218 patients) versus cetuximab alone (111 patients).[20] The combination arm was the most effective, with a RR of 23% (11% with cetuximab alone; p=0.007), and a median TTP of 4.1 months (1.5 months with cetuximab as single agent; p<0.001). The mOS was 8.6 months for cetuximab plus irinotecan and 6.9 months in the cetuximab

Table 2: Randomised Clinical Trials Demonstrating the Relationship of K-Ras Mutation Status with the Efficacy of Cetuximab in Patients with Metastatic Colorectal Cancer in the First-line Setting

	Treatment	Variable	K-RAS WT		K-RAS mut	
			Cetux	Control	Cetux	Control
CRYSTAL[26]	FOLFIRI ± cetuximab	RR (%)	59.3	43.2	36.2	40.2
		PFS (months)	9.9	8.7	7.6	8.1
OPUS[27]	FOLFOX ± cetuximab	RR (%)	60.7	37	37.2	48.9
		PFS (months)	7.7	7.2	5.5	8.6
CAIRO 2[37]	Cap + OXL + bev ± cetuximab	PFS (months)	10.5	10.7	8.6	12.5
		OS (months)	22.2	23	19.1	24.9

Cap = capecitabine; OXL = oxaliplatin; Bev = bevacizumab; RR = response rate; PFS = progression-free survival; OS = overall survival; WT = wild type; mut = mutated; cetux = cetuximab.

Table 3: Clinical Trials with Panitumumab

Treatment	Phase	Population	Status
FOLFOX + panitumumab or bevacizumab	II	First-line (K-RAS wild-type)	Recruiting
FOLFOX ± panitumumab (PRIME trial)	III	First-line	Active, not recruiting
FOLFIRI ± panitumumab	III	Second-line	Active, not recruiting
Panitumumab ± AMG-102 or AMG-479	Ib/II	Refractory (K-RAS wild-type)	Recruiting
Irinotecan ± panitumumab	II	Refractory (K-RAS wild-type)	Recruiting
FOLFIRI + panitumumab or bevacizumab (SPIRITT trial)	II	Refractory (K-RAS wild-type)	Recruiting

FOLFOX = leucovorin/5-fluorouracil/oxaliplatin; FOLFIRI = leucovorin/5-fluorouracil/irinotecan.

arm (p=0.48). The switch to the combination arm was allowed for the patients who progressed in the monotherapy arm.

Following the results of the BOND study, two phase IV studies were conducted to demonstrate the effect of cetuximab and panitumumab in the refractory setting of patients having failed fluoropyrimidin-, oxaliplatin- and irinotecan-based chemotherapy.[21,22] Briefly, in this chemorefractory setting panitumumab significantly improved PFS (median eight weeks versus 7.3 weeks, respectively, HR 0.54; p<0.001) and cetuximab significantly improved OS (6.1 versus 4.6 months, HR 0.77; p=0.005) and PFS (HR 0.68; p<0.001) in comparison with best supportive care alone in the ITT population. In these two studies, a retrospective analysis was conducted evaluating the efficacy according to K-Ras mutation status. Patients with K-Ras wild-type tumours benefit more from the treatment, the HR for OS and PFS being 0.55 and 0.4, respectively, in the cetuximab study and the HR for PFS being 0.45 in the panitumumab study.[23,24]

In the second-line setting, the phase III EPIC study compared cetuximab plus irinotecan with irinotecan alone. The combination arm showed a statistically significant benefit in PFS and RR, but no significant difference was observed in terms of OS (the primary end-point of this study), probably due to the cross-over therapy.[25]

The phase III CRYSTAL study investigated the effectiveness of cetuximab in combination with the standard FOLFIRI regimen compared with FOLFIRI alone in the first-line treatment of unselected patients with EGFR-expressing mCRC.[26] A total of 1,217 patients were included in the study. The addition of cetuximab significantly prolonged PFS (median 8 versus 8.9 months, HR 0.85; p<0.005), the primary end-point of the study, and increased the RR (47 versus 39%; p<0.005). In a 2008 ASCO meeting, Van Cutsem et al. presented the results of the retrospective analysis of the CRYSTAL trial according to the K-Ras mutation status performed in 587 of the patients included in the study. By selecting the population of patients with K-Ras wild-type status, the benefits of the addition of cetuximab were more favourable in terms of PFS (HR 0.68; p=0.0167) and RR (59.3 versus 43.2%; p=0.0025).[26] Similar results have also been observed with the combination of cetuximab- plus oxaliplatin-based chemotherapy (FOLFOX) in the OPUS study[27] (see *Table 2*).

The Cancer And Leukemia Group B (CALGB)/Southwest Oncology Group (SWOG) 80405 National Cancer Institute (NCI) Intergroup trial is designed as a large six-arm randomised study in the first-line treatment of mCRC. Chemotherapy treatment, modified FOLFOX6 or FOLFIRI, is a decision for doctor and patient together to make. The targeted therapy combination partner is randomised between cetuximab alone, bevacizumab alone, and the combination of cetuximab and bevacizumab. CALGB/SWOG 80405 is aiming to enrol 2,289 patients. The primary objective is demonstrating an increase in OS in the double-antibody arm. Multiple studies are currently evaluating the efficacy and safety of panitumumab in mCRC in first- and second-line settings. Some of these trials are summarised in *Table 3*.

The efficacy demonstrated with cetuximab in mCRC treatment generates the question about their usefulness in the adjuvant setting. A European randomised phase III study (PETACC-8) has been launched to evaluate the efficacy of cetuximab in addition to FOLFOX4 for six months in patients with fully resected stage III colon cancer. Patients are randomised to receive FOLFOX4 alone every two weeks, or cetuximab every week plus FOLFOX4 every two weeks. A study with similar design is being conducted in the US by the North Central Cancer Treatment Group (NCCTG NO147). These two studies have been amended and currently are only recruiting patients with K-Ras wild-type tumours.

There are a large number of TKIs directed to EGFR in clinical development. So far, three TKI treatments have been specifically evaluated in mCRC: gefitinib and erlotinib, reversible EGFR-specific TKIs and EKB-569, an EGFR-specific and irreversible TKI. Response and disease control rates observed in some phase I/II combination studies, in the first-line setting and in the refractory population, are encouraging compared with the results obtained with standard chemotherapy in the same population, although randomised phase III studies are needed in order to reach definitive conclusions.[28–33]

Double Epidermal Growth Factor Receptor and Vascular Endothelial Growth Factor Inhibition

Combining therapies that inhibit different signalling pathways has the potential to be more effective than inhibition of a single pathway and to overcome tumour resistance. Pre-clinical models suggest that at least additive efficacy can be achieved blocking the EGFR and VEGF pathways.[34] Recently, Saltz et al. have reported the results of a randomised phase II trial that compared the concurrent administration of two monoclonal antibodies – cetuximab and bevacizumab – with or without irinotecan in irinotecan-refractory mCRC patients.[35] This study showed that the three-drug combination produced better results than the two-drug combination with a higher RR (37 versus 20%) and an increased median TTP (7.9 versus 5.6 months). Although the combination of cetuximab and bevacizumab appeared to be effective in a refractory setting, these interesting results of double VEGF and EGFR inhibition were not confirmed in the first-line setting in two recently reported phase III trials: the Panitumumab Advanced Colorectal Cancer Evaluation (PACCE) and the CAIRO-2 studies.

With the increasing number of new targeted agents that are being clinically evaluated, hopefully to be approved in the near future, there is an ongoing need to identify predictive biomarkers of efficacy.

The first trial reported, the PACCE study, is a phase III trial evaluating oxaliplatin- and irinotecan-based chemotherapy and bevacizumab with or without panitumumab in the first-line treatment of patients with mCRC.[36] The second study, the CAIRO-2 trial, is a phase III study of capecitabine, oxaliplatin and bevacizumab with or without cetuximab in the first-line therapy of patients with mCRC.[37] Both studies showed a detrimental effect in the arms that contained bevacizumab and the anti-EGFR monoclonal antibody. The results of these two studies suggest that there is a lack of biological synergistic effect between monoclonal antibodies against EGFR (panitumumab or cetuximab) and bevacizumab in combination with oxaliplatin-based chemotherapy in first-line therapy of mCRC patients.

Conclusions

In recent years the increased knowledge of human cancer biology and the development of new targeted therapies have improved outcomes for patients with CRC. So far, three targeted therapies have been approved for the treatment of mCRC patients. The FDA and the EMEA have approved bevacizumab in combination with fluoropyrimidine-based chemotherapy for the treatment of first- and second-line mCRC patients. Cetuximab has been approved in combination with chemotherapy in the first-line setting and in combination with irinotecan in the refractory situation. Whereas the FDA's approval is for the whole population, EMEA has restricted the licence to K-Ras wild-type mCRC patients. Finally, the FDA has approved panitumumab as a single agent in mCRC patients refractory to other chemotherapy regimens and the EMEA exclusively for those patients with tumours that bear K-Ras wild type.

With the increasing number of new targeted agents that are being clinically evaluated, hopefully to be approved in the near future, there is an ongoing need to identify predictive biomarkers of efficacy. Successful development of these predictive biomarkers will translate into the concept of personalised medicine whereby we give 'the right drug to the right patient'. Thus, patients with mCRC would benefit from the sequence of drugs that would more optimally control their malignant disease yet avoid the potential toxicities of those drugs that will not benefit them. Additionally, with new drug approvals pushing up the cost of therapy, this tailored treatment approach would reduce the economic impact of treatment. Several molecular predictive biomarkers are under evaluation in pharmacodynamic, genomic and proteomic translational studies in order to achieve this aim. K-Ras mutation status analysis constitutes the first step in this process of personalising targeted therapies in mCRC by defining the population that will benefit most from anti-EGFR monoclonal antibodies. As has already occurred with K-Ras, these biomarkers will be integrated in the treatment decision algorithms, thus leading to an optimised therapeutic strategy. ■

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