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Several targeting agents are available or under clinical investigation for use in patients with colorectal cancer.

Current Progress in Targeted Therapy for Colorectal Cancer

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Background: Several molecular targeting agents are available and being used in patients with colorectal cancer, and many others are being tested clinically.

Methods: The authors review and present the biology and use, including predictive testing, of the agents currently approved for use in colorectal cancer as well as current data on several newer tyrosine kinase inhibitors that are undergoing clinical trials.

Results: The angiogenesis inhibitor bevacizumab and the two EGFR inhibitors cetuximab and panitumumab are currently the three targeted agents approved in colorectal cancer. Recent studies show that the combined use of bevacizumab and EGFR inhibitors may lead to increased toxicity and inferior outcome. Much remains to be understood regarding these drugs and other targeted therapies as well as the underlying mechanism of tumor resistance or responsiveness to treatment. Their optimal use and sequencing with other treatment modalities such as surgery need to be further refined.

Conclusions: There is a crucial need for identification of predictive markers of response and identification of possible negative interactions between targeted agents so that we can better select patients likely to respond to treatment.

Introduction

Colorectal cancer is a major health problem, with more than 800,000 new cases diagnosed worldwide every year. In the United States, colorectal cancer is the third most frequently diagnosed cancer in men and women. In

2009, an estimated 146,970 new cases were diagnosed, and approximately 49,920 patients died of this disease.¹ Statistics show that mortality from colon cancer has decreased slightly over the past three decades as a result of earlier diagnosis and improved treatment modalities.

Over the last decade, a better understanding of the processes involved in the transformation of normal cells into cancer cells has led to the development of new drugs called targeted therapies. The term *targeted therapy* refers to drugs that selectively target specific molecular pathways involved in tumorigenesis or tumor progression. Although traditional cytotoxic chemotherapies demonstrate some degree of selectivity by targeting cancer cells that are dividing, they are usually not considered targeted therapy since they are less selective and affect pathways that are common to normal tissues and tumors. In fact, the distinction between more conventional chemotherapy agents and targeted therapies is somewhat artificial since both may affect normal signaling pathways that can result in systemic toxicities.²

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The authors disclose that they briefly mention agents not yet approved by the US Food and Drug Administration but currently under investigation for patients with colorectal cancer: vatelanib, cediranib (AZ2171), aflibercept, brivanib, axitinib, sunitinib, AMG 706, enzastaurin, everolimus, and pertuzumab.

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To date, three targeted agents have been approved by the US Food and Drug Administration: bevacizumab, cetuximab, and panitumumab. Bevacizumab targets the vascular endothelial growth factor A (VEGF-A) ligand, while cetuximab and panitumumab both target the epidermal growth factor receptor (EGFR). This paper reviews the role of these three drugs in the treatment of colorectal cancer, as well as newer targeted drugs that are currently under clinical investigation.

Angiogenesis Inhibitors in the Treatment of Colorectal Cancer

Angiogenesis refers to the generation of new blood vessels that takes place in the context of wound repair, tissue remodeling (such as menstruation), inflammation, or tumor growth.³ Angiogenesis is a multistep process that involves vasodilation, enhanced vascular permeability, stromal degradation, and endothelial cell proliferation and migration that results in the formation of new or extended capillaries. In tumors, this process leads to inefficient tissue perfusion and hypoxia, which further stimulate angiogenesis. The process of angiogenesis is regulated by a number of growth factors and receptors including the VEGFs and their receptors (VEGFRs). The VEGF family consists of five members: VEGF-A through -E and placental growth factor PlGF. These ligands bind to the three VEGF receptors (VEGFR-1, -2, and -3) leading to the formation of VEGFR homodimers and heterodimers. VEGFR signaling is modulated by variable affinity of the ligands for specific receptors as well as co-receptors such as heparan sulfate proteoglycans (HSPGs) and neuropilins.⁴

Bevacizumab in Metastatic Colon Cancer

Bevacizumab, a humanized monoclonal antibody targeting VEGF-A, has been approved by the FDA for first- and second-line treatment of metastatic colorectal cancer. Bevacizumab was expected to have activity as a single agent by reducing the blood vessel density within tumors. In fact, when used as a single agent, bevacizumab provided only modest response rates, whereas it demonstrated significant efficacy when used in combination with conventional chemotherapy compared to chemotherapy alone.⁵ These clinical observations led to the hypothesis that perhaps by destroying some of the tumor vasculature, the compound might make the remaining vasculature more organized and less tortuous, thus improving tumor blood flow and raising oxygen levels in the tumor and thereby resulting in better chemotherapy delivery to the tumor.⁶

Bevacizumab and Irinotecan Combinations

A 2004 pivotal trial that gained approval of bevacizumab in the United States in first-line treatment of metastatic colorectal cancer showed that the addition of bevacizumab to a bolus 5-fluorouracil (5-FU) leucovorin, and irinotecan regimen (IFL) compared to IFL alone significantly improved response rates (45% vs 35%), time to progression (11 months vs 6 months), and overall sur-

vival (20 months vs 16 months).⁷ The IFL regimen proved later, in the BICC-C trial, to be inferior and is no longer used.

The BICC-C trial randomized patients to IFL vs FOLFIRI (a protracted infusion of 5-FU/irinotecan) vs capecitabine/irinotecan (CAPIRI) with or without celecoxib vs placebo.^{8,9} In January 2005, safety concerns regarding celecoxib led to the discontinuation of the drug in all study patients. Following the approval of bevacizumab in 2004, the study was amended to include bevacizumab in all treatment arms; the CAPIRI arm was discontinued due to significant toxicities. Of the 430 patients accrued to the study, 117 received bevacizumab. The median survival of patients receiving FOLFIRI with bevacizumab was significantly superior to that of patients receiving IFL/bevacizumab (28 months vs 19.2 months).

Bevacizumab and Oxaliplatin Combinations

In the first-line metastatic setting (N016966 trial¹⁰) in association with either FOLFOX or capecitabine/oxaliplatin (CAPOX), bevacizumab failed to increase response rates (38% in both arms) or survival (19.9 months vs 21.3 months compared with either combination alone), although a progression-free survival (PFS) benefit was observed in the trial (9.4 months vs 8.0 months). However, the magnitude of the benefit recorded with bevacizumab was smaller than expected; patients treated with bevacizumab had discontinued treatment early because of toxicity rather than disease progression. Premature discontinuation of bevacizumab before disease progression occurred may explain the less impressive (although statistically significant) difference in terms of PFS (hazard ratio [HR] = 0.83; 97.5% confidence interval [CI], 0.72-0.95, $P = .0023$) between the two treatment arms.

In an Eastern Cooperative Oncology Group trial (ECOG 3200),¹¹ the use of bevacizumab with FOLFOX in second-line treatment of metastatic colon cancer resulted in significantly improved PFS (7.3 months vs 4.7 months) and median survival (12.9 vs 10.8 months) compared with FOLFOX alone. Based on these results, bevacizumab was approved for second-line use in metastatic colorectal cancer.

Bevacizumab and 5-FU Combination

There is an added benefit to the use of bevacizumab with 5-FU/leucovorin in the in first-line treatment of metastatic disease. A combined analysis of the results from three different studies showed that the combination resulted in longer median survival compared with 5-FU alone (17.9 months vs 14.6 months) and in longer median PFS (8.8 months vs 5.6 months) compared with 5-FU/leucovorin.¹²

Bevacizumab-Related Toxicities

The most common side effect seen with bevacizumab across trials is hypertension, which occurs in approximately 25% of patients and requires medical treatment

Table 1. — Toxicities Associated With Bevacizumab

Adverse Events	BRiTE Study ¹⁴ (% Patients)	BEAT Study ¹³ (% Patients)	Hurwitz Study ⁷ (% Patients)
Hypertension requiring medication	19.4	5	11.0
Grade 3–4 event	2.2	NA	3.1
Gastrointestinal perforation	1.8	2	1.5
Arterial thromboembolic event	1.8	1	5.0
Postoperative bleeding or wound-healing complications	1.4	1	2.1

in about 10% of cases. Other more serious but less frequent complications include gastrointestinal perforations, wound-healing complications, and thromboembolic events (strokes or myocardial infarction). The BEAT study¹³ (conducted in Europe) and the BRiTE study¹⁴ (conducted in the United States) were two open-label phase IV registry studies. The purpose of both studies was to evaluate the incidence of toxicities in a more diverse patient population receiving bevacizumab in combination with any of the approved chemotherapy regimens for colon cancer. Rates of toxicities were comparable to those seen in the pivotal trial that gained the drug approval (Table 1).

Interestingly, patients in the BRiTE registry who continued chemotherapy with bevacizumab past first disease progression had an improvement in median survival compared with those who received chemotherapy only or no treatment at all. Yet, the use of bevacizumab beyond progression remains controversial and is not considered standard of care in the United States.¹⁵

Bevacizumab in the Adjuvant Setting

Full results from the NSABP C-08 trial were presented in 2009.¹⁶ In this study, patients with stage II and III colon cancer were randomly assigned to receive FOLFOX or FOLFOX plus bevacizumab for 24 weeks followed by maintenance bevacizumab for an additional 24 weeks in the experimental arm. The study did not reach its primary objective of improving disease-free survival at 3 years, with a modest improvement of 2% with the use of bevacizumab over that of FOLFOX alone. Interestingly, the trial showed a significant benefit for the bevacizumab arm in the first year of the trial when most patients were exposed to bevacizumab. However, that benefit became insignificant over time, suggesting that bevacizumab may have delayed recurrence but did not increase the cure rate. Results from another adjuvant study, the AVANT trial, are expected in 2010.¹⁵

EGFR Inhibitors in the Treatment of Colorectal Cancer

The epidermal growth factor receptor (EGFR) is a member of the ErbB family of closely related tyrosine kinase receptors: EGFR (ErbB-1/HER-1), ErbB-2 (HER-2/neu), ErbB-3 (HER-3), and ErbB-4 (HER-4). These receptors are transmembrane glycoproteins that consist of an extracellular binding domain, a transmembrane domain and

an intracellular domain with tyrosine kinase activity for signal transduction to areas downstream, signaling proteins involved into tumor cell proliferation, invasion, migration, and inhibition of apoptosis. Receptor activation occurs when one of its ligands, the epidermal growth factor (EGF), the transforming growth factor- α (TGF- α), or amphiregulin, binds to its extracellular domain. Cetuximab and panitumumab are monoclonal antibodies that block the ligand binding site of the EGFR, thus inhibiting intracellular signaling. Cetuximab is a chimeric human-mouse antibody, while panitumumab is a fully humanized monoclonal anti-EGFR antibody. Common side effects of these antibodies include acneiform rash, diarrhea, and hypomagnesemia and hypersensitivity reactions that can be particularly severe with the chimeric antibody.

Predictive Markers of Response

Initially it was thought that treatment should be limited to patients with tumors found to be EGFR-positive by immunohistochemistry (IHC), but early studies failed to demonstrate a correlation between the intensity of EGFR expression and the response to treatment. It became clear from more recent studies that another molecular determinant of response — the absence of KRAS activating mutation within tumor cells — was a better predictive marker in colon cancer of response to cetuximab and/or panitumumab given as monotherapy or in combination with chemotherapy. KRAS is a guanosine triphosphate protein that integrates the signal from cell surface receptors including EGFR, leading to activation of downstream effectors. Mutations of KRAS result in constitutive activation of the mitogen-activated protein kinase (MAPK) pathway downstream of EGFR. Recent retrospective analyses from several large trials show that patients with tumors bearing the KRAS mutation do not respond to either cetuximab- or panitumumab-based therapy (Tables 2 and 3).¹⁷⁻²² Nevertheless, the lack of KRAS mutation in tumors does not guarantee a response to EGFR inhibitors.

Monotherapy Trials of EGFR Inhibitors in the Metastatic Setting

Cetuximab and panitumumab have shown modest efficacy in two large randomized phase III trials in patients heavily pretreated with a fluoropyrimidine (5-FU or capecitabine), oxaliplatin, and irinotecan with response rates of 8% for cetuximab²³ and 10% for panitumumab²¹ when compared to best supportive care (BSC). A sig-

nificant improvement in PFS was obtained, with an HR of progression of 0.64 (95% CI, 0.57–0.80) for cetuximab and 0.54 (95% CI, 0.44–0.66) for panitumumab compared with BSC. Improvement in survival was seen with cetuximab (median survival of 6.1 months vs 4.6 months) but not with panitumumab, when the rate of crossover from BSC to active treatment was allowed per study protocol. Subsequent retrospective analyses of tumor samples for KRAS status from patients in each study^{17,24} showed that the treatment benefit with either drug was confined exclusively to patients with tumors bearing a wild-type KRAS (Tables 2 and 3). Response rates remained less than 15% for cetuximab and 17% for panitumumab, but a 5-month improvement in median survival was seen with cetuximab. The most frequent toxicities seen with either drug were rash, diarrhea, and hypomagnesemia, with most toxicities being grade 1 or 2 in intensity.

EGFR Inhibitors and Irinotecan Combinations

Several studies have been conducted based on preclinical observations suggesting that cetuximab might

reverse resistance to irinotecan.²⁵⁻²⁷ These promising results were later confirmed in a larger phase III study (EPIC trial)²⁸ in which patients with metastatic colorectal cancer and oxaliplatin-resistant disease were randomized to irinotecan with or without cetuximab. The PFS was significantly higher with the combined therapy (4 months vs 2.6 months) as well as the overall disease control (61% vs 46%). Since 50% of patients receiving single-agent irinotecan subsequently crossed over to cetuximab after progression, no difference in median survival was seen between the two arms (10.7 months vs 10.0 months).

In first-line treatment of metastatic disease, the CRYSTAL study¹⁸ compared FOLFIRI with or without cetuximab. The PFS was significantly improved with cetuximab (8.9 months vs 8 months). Again, a retrospective analysis of response according to KRAS status of tumors from patients included in the study showed no added value for cetuximab in patients whose tumors contained the KRAS mutation. A modest but significant improvement in PFS, from 8.7 months to 9.9 months, was seen in patients with tumors express-

Table 2. — Efficacy of Cetuximab According to KRAS Status

	Karapetis Study ¹⁷ Cetuximab vs BSC (N = 394)		CRYSTAL Study ¹⁸ FOLFIRI vs FOLFIRI + Cetuximab (N = 540)		OPUS Study ¹⁹ FOLFOX vs FOLFOX + Cetuximab (N = 233)		CAIRO2 Study ²⁰ CAPOX + Bevacizumab vs CAPOX + Bevacizumab + Cetuximab (N = 755)	
		HR (95% CI):		HR (95% CI):		HR (95% CI):		HR (95% CI):
Wild-type KRAS								
PFS (mos)	3.7 vs 1.9	0.42 (0.30–0.58)	8.7 vs 9.9	0.68 (0.51–0.93)	7.2 vs 7.7	0.57 (0.35–0.90)	10.7 vs 10.5	
MS (mos)	9.5 vs 4.8	0.55 (0.41–0.74)	21 vs 24.9	0.84 (0.64–1.10)	NR	—	20.3 vs NR	
Mutant KRAS								
PFS (mos)	1.8 vs 1.8	0.99 (0.73–1.35)	8.1 vs 7.6	1.07 (0.71–1.61)	8.6 vs 5.5	1.83 (1.09–3.05)	12.5 vs 8.1 (P = .003)	
OS (mos)	4.5 vs 4.6	0.98 (0.7–1.37)	17.7 vs 17.5	1.03 (0.74–1.43)	NR	—	24.9 vs 17.2 (P = .03)	

BSC = best supportive care, PFS = progression-free survival, MS = median survival, OS = overall survival, HR = hazard ratio, CI = confidence interval, NR = not reported.

Table 3. — Efficacy of Panitumumab According to KRAS Status

	Van Cutsem Study ²¹ PAN vs Best Supportive Care (N = 427)		PACCE Study ²² OX-CT or IRI-CT vs OX-CT or IRI-CT + PAN (N = 865)	
		HR (95% CI):		HR (95% CI):
Wild-type KRAS				
PFS	12.3 vs 7.3 (wks)	0.45 (0.34–0.59)	OX-CT vs OX-CT + PAN 11.5 vs 9.8 (mos)	1.36 (1.04–1.77)
MS	NS	1.02 (0.75–1.39)	24.5 vs 20.7 (mos)	1.89 (1.30–2.75)
PFS			IRI-CT vs IRI-CT + PAN 12.5 vs 10.0	1.5 (0.82–2.76)
MS			19.8 vs NE	1.28 (0.5–3.5)
Mutant KRAS				
PFS	7.4 vs 7.3 (wks)	0.99 (0.73–1.36)	OX-CT vs OX-CT + PAN 11 vs 10.4 (mos)	1.25 (0.67–1.54)
OS	NS	0.99 (0.75–1.29)	19.3 vs 19.3 (mos)	16.7 vs not estimable
PFS			IRI-CT vs IRI-CT + PAN 11.9 vs 8.3 (mos)	1.19 (0.65–2.21)
OS			20.5 vs 17.8 (mos)	2.14 (0.82–5.59)

PFS = progression-free survival, MS = median survival, OS = overall survival, PAN = panitumumab, OX = oxaliplatin, IRI = irinotecan, HR = hazard ratio, CI = confidence interval, NE = not estimable.

ing the wild-type KRAS when cetuximab was given with FOLFIRI compared with FOLFIRI alone. Some investigators contend that this small improvement may not justify its use, given the added toxicity associated with cetuximab.

Combination Chemotherapy With Oxaliplatin Regimens

The CALGB 80203 trial²⁹ randomized patients to FOLFOX vs FOLFIRI with or without cetuximab. The study was designed as a phase III trial but was closed prematurely when data on bevacizumab efficacy in metastatic colorectal cancer became available. It accrued 238 patients and showed increases in response rates for both FOLFOX and FOLFIRI (40% vs 36%) when associated with cetuximab (60% vs 44%).

The OPUS study¹⁹ randomized 344 patients to FOLFOX with or without cetuximab as first-line treatment for metastatic colorectal cancer. The primary endpoint of this study was overall response rate. It was determined that a subgroup analysis of 233 tumor samples were sufficient to assess the predictive value of KRAS mutation on response to treatment. Although the response rate was higher in the cetuximab-treated group, the difference was not significant (52% vs 36%) when compared with the group receiving FOLFOX alone (HR = 1.52; 95% CI, 0.98–2.36). Although the CRYSTAL study did not demonstrate a deleterious effect of panitumumab when given with FOLFOX in patients with KRAS-mutated tumors, the OPUS trial showed an inferior outcome for this patient population, with worse response rates (33% vs 49%, $P = .1$) and decreased PFS (5.2 months vs 8.6 months, $P = .02$) compared with those receiving FOLFOX alone. The underlying mechanism of tumor resistance explaining these results remains unclear.

EGFR Inhibitors in the Adjuvant Setting

In the United States, the NCCTG-N0147 trial is accruing patients to a phase III study comparing FOLFOX with or without cetuximab in stage III colorectal cancer. A similar study, PETACC-8, is ongoing in Europe.

Bevacizumab Plus Cetuximab or Panitumumab and Chemotherapy in Metastatic Colon Cancer

The obvious rationale of such studies was to combine drugs known to be effective in metastatic colorectal cancer while avoiding overlapping toxicities by using several targeted agents. In the first trial published, the BOND2 study,¹¹ patients with refractory colorectal cancer were randomly assigned to irinotecan/cetuximab/bevacizumab vs cetuximab/bevacizumab. The two monoclonal antibodies demonstrated significant efficacy that was enhanced by the addition of irinotecan. No overlapping or additional toxicities were encountered.

In two subsequent studies, the PACCE study²² and the CAIRO2 study,³⁰ patients receiving both monoclonal antibodies demonstrated increased toxicities and decreased efficacy as measured by response rate and PFS.

The PACCE trial²² had two cohorts of patients, one receiving an oxaliplatin-based regimen and the other receiving an irinotecan-based regimen per investigator choice. A decrease in PFS was observed in patients treated with panitumumab in the oxaliplatin cohort compared to those treated without (10 months vs 11.6 months). In the irinotecan cohort, the PFS was 10.1 months for panitumumab and 11.6 months for the control arm. KRAS status was obtained in 82% of patients on the study. In the oxaliplatin cohort, a significant difference in overall survival favoring the control arm was seen in patients with wild-type KRAS tumors compared with patients receiving panitumumab (HR = 1.89; 95% CI, 1.3–2.75, $P = .45$). A similar trend was seen in the irinotecan cohort (HR = 1.28; 95% CI, 0.5–3.25, $P = .44$). Patients had a higher incidence of grade 3 skin rash (38% vs 35%) and diarrhea (28% vs 24%) in the oxaliplatin and irinotecan cohorts, respectively, when treated with panitumumab compared to those treated without panitumumab. No skin rash was observed, and grade 3 diarrhea occurred less frequently (9% vs 14% in the oxaliplatin and irinotecan cohorts, respectively) in both of the control arms. There was also an increased incidence of deep venous thrombosis in the panitumumab/irinotecan cohort. The incidence of treatment-related deaths was identical regardless of treatment with panitumumab.

Patients in the CAIRO2 study³⁰ were randomized to capecitabine/oxaliplatin (CAPOX) plus bevacizumab with or without cetuximab. Results also showed a significant decrease in PFS and poorer quality of life in patients receiving cetuximab. Increased toxicities are an unlikely cause of reduction in PFS since the percentage of patients discontinuing treatment for toxicities was similar in the two arms.

Results from these two studies raise the possibility of negative interaction between EGFR inhibitors and bevacizumab when combined with chemotherapy, with a particularly worse outcome (as seen in the OPUS trial) with an oxaliplatin-containing regimen. Both studies also confirm the worse outcome of patients with tumors bearing the mutated form of KRAS.

Integration of Targeted Agents in the Surgical Management of Patients With Metastatic Disease

The liver is one of the major sites of metastases for patients with colorectal cancer. Approximately 25% of patients have resectable disease upfront, and an additional 10% to 15% of patients undergo curative intent surgery following chemotherapy (also known as conversion therapy).³¹ Curative intent resection of liver metastases results in significantly improved survival rates at 5 years, exceeding 50% in some retrospective series³² compared with less than 10% with systemic chemotherapy only.³³ The use of perioperative chemotherapy was evaluated in patients with resectable disease in a randomized phase III study comparing perioperative FOLFOX to surgery alone.³⁴ When including all eligible

patients, the study showed a trend toward improvement in PFS at 3.9 years favoring the chemotherapy arm. To date, most of the published data for conversion therapy in patients with initially unresectable disease come from single-institution retrospective analyses³⁵⁻³⁷ and few prospective phase II trials (Table 4).³⁸⁻⁴³ Complete resections of metastatic disease with negative margins (R0 resection) range from 12% to 30%, with a 5-year survival rate of 30% to 35%.³³

Bevacizumab Use for Liver Metastases and Incidence of Postsurgical Complications

It has been suggested that the addition of bevacizumab to chemotherapy may result in higher resectability rates than with chemotherapy alone without a significant increase in postsurgical complications. In a small subset of patients reported in the N016966 trial¹⁰ comparing FOLFOX to CAPOX with bevacizumab, a higher rate of curative intent surgery was seen in patients who received bevacizumab (8.4% vs 6.1%). Another phase II study of 56 patients with resectable liver metastases receiving six cycles of CAPOX with bevacizumab reported a 73% objective response rate, with 52 of the 56 patients able to undergo an R0 resection and with a complete pathological response seen in 8.9% of patients.⁴⁴ Postoperative complications were not significantly increased with the use of bevacizumab.

Given the possible interference of bevacizumab with physiologic wound healing and the increasing number of patients undergoing curative intent surgery of metastatic lesions, the safety of bevacizumab use in surgical patients was evaluated in several studies.^{44,45} Patients receiving bevacizumab had no increased rate of wound-healing complications. A discontinuation of bevacizumab 6 to 8 weeks prior to any major surgery is usually recommended, given its long half-life of approximately 20 days.⁴⁶ Two main types of liver injury have been reported with chemotherapy: vascular changes with sinusoidal dilatation and chemotherapy-associated steatosis.^{47,48} Interestingly, it has been reported that bevacizumab may reduce the incidence of oxaliplatin-induced toxicities.⁴⁹

Perioperative Use of EGFR Inhibitors in the Surgical Management of Liver Metastases

Similar to bevacizumab, the added benefit of EGFR inhibitors has been studied mostly in patients undergoing conversion chemotherapy treatment. A retrospective analysis from the CRYSTAL study, which randomized patients to FOLFIRI with or without cetuximab, showed that the rate of surgery with curative intent and the number of R0 resections were increased in patients receiving FOLFIRI and cetuximab compared with FOLFIRI alone (4.3% vs 1.5%).¹⁸ The benefit was limited to patients with KRAS wild-type tumors. In the OPUS study¹⁹ comparing FOLFOX with or without cetuximab, R0 resection rates were also increased in patients receiving cetuximab (4.7% vs 2.4%).

The CELIM study,⁴² another multicenter phase II study, demonstrated the same trend. It randomized patients to either FOLFOX or FOLFIRI with cetuximab. A combined analysis of both arms showed that 67 of 111 patients with wild-type KRAS tumors achieved a response rate of 70% compared with a 43% response rate in patients with KRAS-mutated tumors. R0 resection rates were 38% in the FOLFOX arm, 30% in the FOLFIRI arm, and 33% in the 67 patients with wild-type KRAS tumors. As in metastatic inoperable disease, the benefit of EGFR inhibitors seems to be limited to patients with wild-type KRAS tumors. Perioperative morbidity was not increased by the use of cetuximab. The role of panitumumab as conversion therapy in combination with FOLFOX or FOLFIRI is currently under investigation in a phase II study.¹⁵

Other Angiogenesis Inhibitors in Metastatic Colorectal Cancer

Vatalanib is an oral tyrosine kinase inhibitor targeting VEGFR-1, -2, and -3. The CONFIRM-1 study randomized patients to FOLFOX vs FOLFOX plus valatinib in first-line (CONFIRM-1 trial⁵⁰) and second-line (CONFIRM-2 trial⁵¹) treatment of metastatic colorectal cancer. The study failed to demonstrate any significant improvement in PFS, although response rates were slightly higher in patients treated with valatinib. One hypothesis for treat-

Table 4. — Conversion Therapy for Patients With Liver Metastases From Colorectal Cancer

Study	No. of Patients	Chemotherapy Regimen	R0 Resection (%)	Disease-Free Survival (mos)	Median Survival (mos)
With Chemotherapy					
Alberts ³⁸	42	FOLFOX	33	19	26
Masi ³⁹	71	FOLFOXIRI	19	18	40
Barone ⁴⁰	40	FOLFIRI	33	52	Not reached
Ychou ⁴¹	34	FOLFOXIRI	26	31	Not reached
With Chemotherapy and Targeted Therapy					
Folprecht ⁴²	111	FOLFOX or FOLFIRI + Cetuximab	35	NR	NR
Min ⁴³	23	FOLFIRI + Cetuximab	30	NR	NR

NR = not reported.

ment failure was that the short half-life of vatalanib (~ 6 hours), together with the once-daily dosing of the drug, may have prevented vasculature normalization to occur.

Cediranib (AZ2171) is a tyrosine kinase inhibitor that blocks VEGFR-1, -2, and -3 and c-kit. The phase II HORIZON I trial⁵² has shown activity within the same range as bevacizumab when comparing FOLFOX/cediranib (given at 20 or 30 mg) to FOLFOX/bevacizumab as second-line treatment for metastatic colorectal cancer. The median PFS for cediranib at a dose of 20 and 30 mg was 5.8 months and 7.2 months, respectively, compared with a median PFS for bevacizumab of 7.8 months. Two phase III studies comparing FOLFOX/bevacizumab to FOLFOX/cediranib (given at 20 mg) are being conducted outside the United States (HORIZON II) and in the United States (HORIZON III).¹⁵

Aflibercept is a recombinant fusion protein of VEGFR-1 and -2 extracellular domains and the Fc portion of human IgG. In a recent phase II study, aflibercept was well tolerated and resulted in disease control in 30% of patients and a PFS of 4 months when patients were previously treated with bevacizumab.⁵³ A phase III trial is currently ongoing in combination with FOLFIRI as second-line treatment after failure of an oxaliplatin-containing regimen.¹⁵

Brivanib, a dual kinase inhibitor of VEGFR-2 and fibroblast growth factor (FGF) receptor, showed clinical activity when combined with cetuximab in metastatic colorectal cancer.⁵⁴ A phase III trial (CAN-NCIC-C020) of cetuximab with or without brivanib in previously treated patients with colorectal cancer is ongoing.¹⁵

Axitinib, an oral tyrosine kinase inhibitor targeting VEGFR-1, -2, and -3, has been evaluated in several tumor types. In a recently published phase I study,⁵⁵ axitinib given with FOLFOX and bevacizumab resulted in no major increase in toxicities, with a partial response rate of 13% and a stable disease rate of 60%. The drug is currently being tested in first-line treatment of metastatic colorectal cancer in combination with chemotherapy and bevacizumab.¹⁵

Sunitinib, an oral multitargeted tyrosine kinase inhibitor, has been approved for the treatment of renal cancer that selectively inhibits several tyrosine kinase receptors including VEGFR and PDGFR. Although a phase II trial showed virtually no response to single-agent sunitinib,⁵⁶ a phase III study of FOLFIRI with or without sunitinib is currently ongoing.¹⁵

AMG 706 is a multi-target tyrosine kinase inhibitor targeting VEGF, PDGF, and c-KIT receptors. In a recent phase II study,⁵⁷ AMG 706 was tested with panitumumab plus either FOLFIRI or FOLFOX. The combination was well tolerated and resulted in response rates of 50% when given as second-line treatment for colorectal cancer.

Other Targeted Therapies Under Investigation in Colorectal Cancer

Pertuzumab is a recombinant humanized antibody that targets the epitope within the HER-2 dimerization domain. It belongs to a new class of drugs called HER-

2 dimerization inhibitors.⁵⁸ Its efficacy in colon cancer is being tested in an ongoing phase II trial in combination with cetuximab.¹⁵

Enzastaurin is a potent selective tyrosine kinase inhibitor that targets two downstream effectors of EGFR and VEGFRs, protein kinase C (PKC), and Akt. No major toxicities were reported in a recent study with bevacizumab.⁵⁹ A phase II trial of enzastaurin, bevacizumab, and 5-FU is ongoing.¹⁵

Everolimus is a mammalian target of rapamycin (mTOR) inhibitor, which has a central role in the regulation of cell growth. Everolimus is now approved for metastatic renal cancer. Studies have shown efficacy with 5-FU in refractory metastatic colon cancer. Phase II studies are ongoing.¹⁵

Conclusions

It is clear from past experience in colon cancer and other tumors that there is a need to identify clinically meaningful predictive markers of response to targeted therapy. Arguably, the small improvement in PFS and increased toxicities reported in some of the studies may not justify the use of these agents in an unselected population. Beyond the obvious clinical benefit for patients, it is likely that the identification of predictive markers can also reduce the costs of cancer treatments.^{60,61}

Many questions remain unanswered regarding the appropriate use of bevacizumab or EGFR inhibitors in patients with metastatic colorectal cancer. In the last few years, the treatment of metastatic colorectal cancer has evolved from successive lines of therapy after each disease progression to maintenance therapy with discontinuation of some but not all drugs until disease progression in order to minimize toxicities.⁶² Bevacizumab and the EGFR inhibitors are commonly used in this context, but their impact on survival in that setting needs to be further evaluated prospectively. As surgery becomes increasingly common, the optimal use of targeted therapy as part of conversion therapies or treatment of resectable liver disease with regard to sequence and number of cycles will also need to be better defined⁶³ to minimize any treatment-related liver toxicities. Although studies of combinations of targeted agents have been disappointing so far, it is likely that with our better understanding of tumor biology, more efficacious combinations of targeted therapy will emerge in the future.

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