

Targeted Therapy in Colorectal Cancer

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Keywords

Colorectal cancer, bevacizumab, cetuximab, vascular endothelial growth factor, epidermal growth factor receptor.

Abstract: Advances in chemotherapeutic agents have led to improved outcomes for patients with metastatic colorectal cancer (CRC). Chemotherapies, however, are limited by their toxicities and lack of specificity. Aberrations in the regulation and expression of growth factors have been implicated in the development of CRC, and this understanding has led to the development of targeted agents. In 2004, two novel agents, bevacizumab and cetuximab, were approved by the US Food and Drug Administration for the treatment of metastatic CRC. Bevacizumab, a humanized monoclonal antibody to vascular endothelial growth factor, and cetuximab, a human-mouse chimeric monoclonal antibody to the epidermal growth factor receptor, have changed the field dramatically. Bevacizumab appears to augment the efficacy of combination chemotherapy regimens for the treatment of metastatic CRC in both the first- and second-line settings, and the role of bevacizumab as part of adjuvant treatment is the subject of ongoing trials. However, because of the increased incidence of serious arterial thromboembolic events, gastrointestinal perforations, bleeding complications, and hypertension associated with bevacizumab, this agent is probably not indicated in all circumstances. Combination treatment with cetuximab and irinotecan appears appropriate in patients with advanced CRC who have failed irinotecan. Patients who are unable to receive additional irinotecan may be treated with cetuximab monotherapy. Positive epidermal growth factor receptor status by immunohistochemistry of a tumor specimen is presently mandated to determine candidacy for this therapy, although this assay appears to be suboptimal and newer assessment techniques to determine suitability for therapy must be developed. Phase III trials should shed light on the role of cetuximab in the first-line metastatic and adjuvant settings. Multitargeted strategies in CRC combining chemotherapy with bevacizumab and cetuximab are currently being explored. Further advances in the treatment of CRC are expected through continued scientific investigation and well-designed clinical trials.

In the United States, colorectal cancer (CRC) is the third most common cancer and second highest cause of cancer death after lung cancer.¹ In 2004, 146,940 new cases of large bowel cancer were diagnosed in the United States, and more than 56,000 Americans died of CRC, accounting for approximately 10% of all cancer deaths.¹ Mortality rates due to CRC have declined progressively over the last 20 years, which can be attributed, at least in part, to detection of the disease at earlier stages and to the development of more effective treatments.

For more than 50 years, 5-fluorouracil (5-FU) was the standard systemic treatment for patients with metastatic CRC. During the past decade, however, the addition of irinotecan and oxaliplatin to the chemotherapy armamentarium for metastatic disease has resulted in improved response rates (RR), prolonged time to disease progression, and prolonged overall survival.²⁻¹⁰ Based on the results of several phase III clinical trials, combination and monotherapy regimens incorporating these agents into the first- and second-line metastatic setting have supplanted single-agent 5-FU with reported median overall survival times in the range of 14.8–21.5 months.²⁻⁷ A recent meta-analysis of seven phase III trials in metastatic CRC demonstrated that median overall survival correlates significantly with the percentage of patients receiving 5-FU, irinotecan, and oxaliplatin over the course of their disease, suggesting the importance of exposure to all of these active agents.¹¹ Capecitabine (Xeloda, Roche), an oral fluoropyrimidine, may also prove to be a more convenient substitute for 5-FU. The best sequence of therapies remains to be defined.

Chemotherapies are limited by their lack of specificity and by toxicities. Aberrations in the regulation and expression of growth factors have been implicated in the genesis of CRC, and this understanding has led to the development of targeted agents.¹² In 2004, two novel agents, bevacizumab (Avastin, Genentech) and cetuximab (Erbix, ImClone/Bristol-Myers Squibb), were approved by the US Food and Drug Administration (FDA) for the treatment of metastatic CRC. The scientific development and clinical impact of these targeted therapies will be reviewed.

Vascular Endothelial Growth Factor

Vascular endothelial growth factor (VEGF) has become a major target of investigation in this area. Researchers have shown that the growth of tumors beyond 1–2 mm depends on the establishment of blood vessels to supply nutrients and oxygen for local tumor expansion and enable access to the systemic circulation for metastatic spread.¹³ VEGF, a proangiogenic factor critical to this process,¹⁴ has been detected in a large variety of human

tumors including breast, brain, lung, and gastrointestinal tract cancers.¹⁵ It is upregulated in most human tumors, including CRC.¹⁶ VEGF is thought to be the most potent direct-acting regulator of angiogenesis, with effects on a number of endothelial cell functions including proliferation, migration, and recruitment of endothelial progenitor cells.¹⁷ Furthermore, VEGF levels have been shown to increase in the local environment in the setting of chemotherapy-induced cell death and to serve as a key endothelial-cell survival factor for tumor vasculature.^{18,19} VEGF overexpression has been correlated with increases in tumor invasion, intratumoral microvascular density, and disease recurrence, as well as a poor prognosis.^{20,21} VEGF has other roles that may be important for cancer evolution and treatment, including altering vascular permeability, interacting with antigen presentation, and perhaps directly interacting with VEGF receptors on cancer cells.²² Based on these observations, strategies directed at VEGF blockade make perfect sense and have been pursued.

Preclinical studies have shown that a murine anti-human monoclonal antibody against VEGF can inhibit the growth of human tumor xenografts and dramatically reduce the size and number of liver tumors that form in a mouse xenograft model of human colon cancer metastases.^{23,24} The results are more profound when the antibody is used in combination with chemotherapy and are superior to those seen with either agent used alone.²³ It has been proposed that anti-VEGF therapy may improve the delivery of chemotherapy by “normalizing” tumor vasculature and by decreasing the elevated interstitial pressure in tumors such that intratumoral blood vessels serve as the path of least resistance.²⁵ Interestingly, no treatment-related toxicities were apparent in preclinical models treated with anti-VEGF therapy.^{26,27}

Compared to conventional chemotherapy, therapy targeting the vasculature theoretically limits the emergence of tumor-resistance mechanisms; host vascular endothelial cells are assumed to be genetically stable and lack the diverse genetic defects characteristic of cancer cells that lead to drug resistance.²⁸ These agents have been combined with chemotherapy in the clinical setting because of the potential for synergy and preclinical evidence that combining VEGF inhibitors with chemotherapy results in enhanced antitumor activity.

Bevacizumab

Bevacizumab, an anti-VEGF humanized monoclonal antibody, is the only agent in its class to receive FDA approval thus far. In the pivotal phase III trial, over 900 patients were randomized to bolus irinotecan/5-FU/leucovorin (LV)/bevacizumab (IFL/bev), bolus irinotecan/5-FU/LV (IFL), or 5-FU/LV/bevacizumab (5-FU/LV/bev) as first-

line treatment for metastatic CRC.²⁵ The 5-FU/LV/bev arm was halted when the safety of IFL/bev was confirmed in a prespecified interim analysis. Patients received second-line chemotherapies for disease progression at the discretion of the treating physician but were not allowed to cross over to bevacizumab. In an intention-to-treat analysis, the addition of bevacizumab to IFL led to significant improvements in progression-free survival and radiologic RR as well as a 4.7-month increase in median overall survival when compared to IFL alone (20.3 vs 15.6 mo, $P<.001$). This incremental improvement appeared to be attributable to the addition of bevacizumab, since the median overall survival for the IFL control arm was comparable to results from previous trials.² The survival benefit associated with the bevacizumab-containing regimen was observed for all prespecified patient subgroups and was independent of second-line therapy.²⁵ Bevacizumab did not appear to enhance chemotherapy-associated toxicity but was associated with an increased incidence of grade 3 hypertension (11% vs 2.3%, $P<.01$) easily managed with standard oral antihypertensives, and rare gastrointestinal perforations (6 vs 0 events, 1.5% vs 0%). Based on these results, the FDA approved bevacizumab for first-line treatment of metastatic CRC in combination with 5-FU-based therapy.

These findings are consistent with other smaller randomized trials in first-line metastatic CRC that have demonstrated a trend toward improved survival in patients treated with 5-FU/LV/bev over patients treated with 5-FU/LV.²⁹⁻³¹ In an early study comparing low- (5 mg/kg) and high-dose (10 mg/kg) bevacizumab combined with 5-FU/LV, the higher dose was less efficacious and more toxic (1 fatal pulmonary embolus) than the lower dose.²⁹ Therefore, the majority of subsequent studies have used the lower dose of bevacizumab. Another study enrolled patients who were not candidates for irinotecan because of advanced age or poor performance status, suggesting that

5-FU/LV/bev is a reasonable strategy in this subgroup of patients.³⁰ (Table 1)

With these phase III trial results, a number of other investigations exploring the potential role of bevacizumab in CRC were initiated. A phase III trial (Eastern Cooperative Oncology Group trial E3200) presented at the 2005 Gastrointestinal Cancers Symposium and at the 2005 American Society of Clinical Oncology (ASCO) annual meeting³² evaluated the safety and efficacy of infusional 5-FU/LV/oxaliplatin (FOLFOX) with or without bevacizumab in 829 patients with previously treated, irinotecan-refractory, metastatic CRC (Table 2). Initial median survival results favor the addition of bevacizumab to FOLFOX (12.5 vs 10.7 mo, $P=.0024$) with some added toxicity (1.1% incidence of gastrointestinal perforation, 3.1% grade 3 hemorrhage, and 3.1% grade 3 thromboembolic events in the bevacizumab arm) and no increase in treatment-related deaths.³³ The bevacizumab-alone arm in this trial was closed at an interim analysis due to a low RR (3%) and an apparent lack of activity in this setting. Final analyses are forthcoming. Another trial (TREE-2) is evaluating the efficacy of FOLFOX and other fluoropyrimidine-based oxaliplatin regimens in combination with bevacizumab as first-line treatment for metastatic CRC.³⁴ Finally, FOLFOX/bev is undergoing evaluation in the adjuvant setting in the National Surgical Adjuvant Breast and Bowel Project C-08 trial and in high-risk stage II colon cancer patients in the Clinical Trials Support Unit (CTSU) E5202 trial.

A compilation of five completed bevacizumab trials conducted after its FDA approval suggests a two-fold increase in serious arterial thromboembolic events, including cerebrovascular accidents, myocardial infarctions, transient ischemic attacks, and anginal episodes, in patients treated with bevacizumab-containing regimens compared to patients receiving combination chemotherapy alone.³⁵ While a heightened risk of thromboembolic

Table 1. Completed or Ongoing Trials Evaluating Bevacizumab in the First-line Setting

Study	Patients, n	Regimen	RR, %	OS, mo
Hurwitz ²⁵	411	IFL	34.8	15.6
	402	IFL/bev	44.8	20.3
Kabbinavar ²⁹	36	5-FU/LV	17	13.8
	35	5-FU/LV/low-dose bev	40	21.5 ($P=.137$ vs 5-FU/LV)
	33	5-FU/LV/high-dose bev	24	16.1 ($P=.582$ vs 5-FU/LV)
Kabbinavar ³⁰	105	5-FU/LV	15	12.9
	104	5-FU/LV/bev	26	16.6

bev = bevacizumab; 5-FU/LV = 5-fluorouracil/leucovorin; IFL = bolus irinotecan/5-fluorouracil/leucovorin; OS = overall survival; RR = response rate.

Table 2. Eastern Cooperative Oncology Group Study E3200: Preliminary Findings

Study	Patients, n	Regimen	RR, %		OS, mo	
Giantonio ³²	289	FOLFOX	9.2	<i>P</i> <.001	10.7	<i>P</i> =.0024
	290	FOLFOX/bev	21.8		12.5	

Bev = bevacizumab; FOLFOX = infusional 5-fluorouracil/leucovorin/oxaliplatin; RR = response rate; OS = overall survival.

events is expected in cancer patients, the risk was more pronounced in patients treated with bevacizumab.³⁵ In an analysis of CRC patients over 65 years of age included in the CRC trials (and who therefore met eligibility criteria), the improvement in median survival associated with bevacizumab therapy was maintained despite the increase in serious arterial thromboembolic events.³⁵ Because of this net benefit, older patients who are candidates for bevacizumab and who do not have major cardiovascular risk factors may still appropriately receive a bevacizumab-containing regimen.

There is interest in exploring the role of prophylactic antiplatelet agents and anticoagulation in addressing this concern. Early results suggest that concomitant full-dose anticoagulation with warfarin for treatment of thromboembolic events or concomitant low-dose aspirin for prophylaxis does not increase the risk of hemorrhagic complications in patients receiving bevacizumab.^{36,37} Of note, the terminal half-life of bevacizumab is approximately 17–21 days.³⁸ In the E3200 trial, 3 of the 5 patients who developed gastrointestinal perforations had undergone invasive procedures to the gastrointestinal tract within 3 weeks of initiating bevacizumab.³² Similarly, in a subgroup analysis of patients in the pivotal phase III trial who underwent surgery within 60 days of receiving a dose of bevacizumab, a small increase in postoperation wound-healing and bleeding complications was noted in the IFL/bev group compared to the IFL-treated patients (4 vs 0 events).³⁹ In contrast, no increased wound-healing and bleeding complications were found in patients who underwent cancer surgery 28–60 days prior to starting IFL/bev compared to the IFL arm.³⁹ Until more experience accumulates, a waiting period of 8 weeks around the time of nonemergent surgery and major procedures is currently recommended prior to initiating and during bevacizumab therapy.

In lung cancer, however, bevacizumab treatment does appear to significantly increase the risk of bleeding complications. In a randomized phase II trial of untreated, locally advanced or metastatic, non–small cell lung cancer patients treated with carboplatin/paclitaxel with or without bevacizumab, 6 of 66 bevacizumab-treated patients experienced life-threatening hemoptysis or hematemesis.⁴⁰ Four of these events were fatal. Centrally located lesions

that were necrotic or cavitory and squamous cell histology were identified as possible risk factors for bleeding. In a follow-up randomized phase II/III trial of 842 patients with untreated nonsquamous, advanced, non–small cell lung cancer who received carboplatin/paclitaxel with or without bevacizumab, 11 treatment-related deaths were reported.⁴¹ Five of nine of the bevacizumab-associated deaths were due to hemoptysis. Therefore, until more experience accumulates, it is recommended that bevacizumab be avoided in patients at high risk for bleeding from their primary or metastatic lesions. For some metastatic colon cancer patients with their primary tumors in place, it may make sense to delay bevacizumab treatment until their primary tumors have been removed to avoid bevacizumab-associated bleeding complications.

In summary, based on the available published data, bevacizumab should be incorporated into first-line combination chemotherapy regimens for the treatment of metastatic CRC unless otherwise contraindicated. IFL, 5-FU/LV, and FOLFOX all demonstrate a survival benefit when combined with bevacizumab in either the first- or second-line setting. Experience with infusional 5-FU/LV/irinotecan/bevacizumab (FOLFIRI/bev) and FOLFOX/bev as first-line treatment for metastatic CRC and with FOLFOX/bev as adjuvant treatment is eagerly awaited. As of now, bevacizumab has no demonstrated role in adjuvant therapy. Because of the increased incidence of serious arterial thromboembolic events, gastrointestinal perforations, bleeding complications, and hypertension associated with bevacizumab, this agent should be used with caution. The role of prophylactic antiplatelet agents and anticoagulation in this setting remains to be defined.

Other Anti-VEGF Strategies

Several small-molecule tyrosine kinase inhibitors of the VEGF pathways are in clinical development. PTK787/ZK222584 (Novartis) inhibits multiple receptors (VEGFR-1 and VEGFR-2) and has shown antitumor and antiangiogenic activity in preclinical *in vivo* models; however, preliminary results from a randomized phase III trial (CONFIRM-1) presented at the 2005 ASCO annual meeting comparing FOLFOX plus PTK787/ZK222584 to FOLFOX alone as first-line treatment for metastatic

CRC failed to demonstrate a significant improvement in the primary endpoint, progression-free survival.^{42,43} Final analyses are pending. Other agents being explored in clinical trials of CRC include VEGF Trap (Regeneron), a soluble receptor, IMC-1121b (ImClone), a monoclonal antibody, and other tyrosine kinase inhibitors (sunitinib-malate [Pfizer], ZD6474 [Zactima, AstraZeneca], CP-547,632 [OSI/Pfizer], and AZD2171 [AstraZeneca]).⁴⁴

Epidermal Growth Factor Receptor

The epidermal growth factor receptor (EGFR) signaling pathway is also thought to play a pivotal role in CRC pathogenesis.⁴⁵ EGFR, a transmembrane glycoprotein, consists of an extracellular ligand-binding domain, a transmembrane region, and an intracellular tyrosine kinase domain.⁴⁶ Binding of specific ligands, such as epidermal growth factor and transforming growth factor- α (TGF- α), to the extracellular domain of the receptor induces dimerization either with another receptor or other HER family members.⁴⁶ This dimerization leads to activation of the receptor's intrinsic tyrosine kinase activity and autophosphorylation, initiating downstream signaling through various pathways including the mitogen-activated protein kinase (MAPK), phosphatidylinositol-3-OH kinase (PI3K/Akt), and the signal transducer and activator of transcription (STAT)-mediated pathways.⁴² This signaling transduction cascade exerts action on gene transcription and protein translation, stimulating tumor cell proliferation, migration, adhesion, angiogenesis, and inhibition of apoptosis.⁴⁶ All of these processes may become dysregulated in cancer cells.⁴⁷

EGFR gene expression or upregulation occurs in 60–80% of CRC cases.⁴⁷ EGFR overexpression appears to be associated with poor survival, an increased risk of metastasis, and reduced sensitivity to chemotherapy.^{42,48} Twenty years ago, a murine monoclonal anti-EGFR antibody was created that could block the proliferation of tumor cells both in vitro and in xenograft models of epidermoid, prostate, colon, and renal cell carcinomas resulting in significant increases in mouse survival.^{42,49} Since then, other anti-EGFR monoclonal antibodies have confirmed these observations and have demonstrated that the antibodies inhibit tumor-induced angiogenesis, likely by reducing tumor expression of angiogenic factors such as TGF- α , VEGF, interleukin-8, and basic fibroblast growth factor.^{42,49}

It has been hypothesized that blocking EGFR signaling is insufficient for cytotoxicity but that EGFR inhibition may leave cells more vulnerable to the effects of chemotherapy, resulting in at least additive antitumor activity.⁵⁰ It is also possible that cellular damage induced by chemotherapy converts EGFR ligands from growth

factors into survival factors in cancer cells such that EGFR blockade in combination with cytotoxic chemotherapy could cause irreparable cancer cell damage leading to increased apoptosis.

Cetuximab

The human-mouse chimeric monoclonal antibody cetuximab is the furthest along in clinical development. This antibody binds with high affinity to the extracellular domain of EGFR and competes with the natural ligands, thereby blocking receptor activation and downstream receptor-dependent signaling pathways.⁴² Cetuximab has been shown to inhibit the growth of CRC cell lines both in vitro and in vivo.⁴² Moreover, preclinical in vivo studies demonstrated that the combination of cetuximab and irinotecan was superior to cetuximab alone in mice xenografts bearing human CRC refractory to irinotecan.⁴² In addition, cetuximab is thought to overcome irinotecan resistance by abrogating drug efflux, restoring apoptosis, or impairing DNA-repair activity.⁴⁷ Based on these preclinical observations, cetuximab was pursued in combination with chemotherapy in clinical trials.

Cetuximab was recently approved by the FDA for treatment of EGFR-expressing, irinotecan-refractory, metastatic CRC. The pivotal randomized phase II trial involved 329 patients with advanced, EGFR-positive (by immunohistochemistry [IHC]) CRC who had failed but tolerated at least 6 weeks of first-line irinotecan-based therapy.⁴⁷ Patients from 56 centers in 11 European countries were randomized to their previous irinotecan therapy combined with cetuximab (irin/cetux) or cetuximab alone (cetux). They were allowed to cross over to the combination regimen if they failed cetuximab monotherapy. In an intention-to-treat analysis, the irin/cetux arm demonstrated a significantly higher radiologic RR (22.9% vs 10.8%, $P=.007$) and longer time to disease progression (4.1 vs 1.5 mo, $P<.001$); however, no difference in median survival was achieved (8.6 vs 6.9 mo, $P=.48$). Significantly more patients in the combination group developed neutropenia (9.4% vs 0%, $P<.001$) and diarrhea (21.2% vs 1.7%, $P<.001$) while cetuximab monotherapy was associated only with a significantly higher rate of nonfatal grade 3/4 hypersensitivity reactions (3.5% vs 0%, $P=.01$). Grade 3/4 acne-like rashes were common in both treatment arms (9.4% irin/cetux, 5.2% cetux) but were easily managed with conservative measures and did not result in discontinuation of therapy. Two thirds of patients had had previous exposure to oxaliplatin, yet the combination regimen was still active (RR=22.2% for irin/cetux vs 8.5% for cetux, $P=.01$). It is likely that the investigators were unable to demonstrate a statistically significant survival difference in this study because they permitted crossover;

Table 3. Completed or Ongoing Trials Evaluating Cetuximab in the Second-line Setting

Study	Patients, n	Regimen	RR, %	OS, mo	
Cunningham ⁴⁷	111	cetux	10.8	6.9	<i>P</i> =.48
	218	irin/cetux	22.9	8.6	
Saltz ¹²	57	cetux	8.8	6.4	

Cetux = cetuximab; irin = irinotecan; OS = overall survival; RR = response rate.

Table 4. Ongoing Trials Evaluating Cetuximab in the First-line Setting

Study	Patients, n	Regimen	RR, %
Folprecht ⁵²	19	FOLFIRI/cetux	74
Taberero ⁵³	20	FOLFOX/cetux	70
Rougier ⁵⁴	22	FOLFIRI/cetux	46
Lordick ⁵⁵	79	FUFOX/cetux	50
Rosenberg ⁵⁶	25	IFL/cetux	44

Cetux = cetuximab; FOLFIRI = infusional 5-fluorouracil/leucovorin/irinotecan; FOLFOX = infusional 5-fluorouracil/leucovorin/oxaliplatin; FUFOX = bolus 5-fluorouracil/leucovorin/oxaliplatin; IFL = bolus irinotecan/5-fluorouracil/leucovorin; RR = response rate.

50% of the patients in the cetuximab monotherapy group who progressed went on to receive combination therapy. Moreover, the study was underpowered to detect a survival difference; the sample size was based on the primary endpoint, radiologic RR. Despite these shortcomings, the FDA approved cetuximab based on these trial results. (Table 3)

Following the randomized phase II trial, a number of other investigations exploring the role of cetuximab in CRC have been designed. Preliminary results have been encouraging. In phase I/II first-line trials, FOLFIRI, FOLFOX, or IFL combined with cetuximab appear to be well-tolerated and efficacious, with preliminary analyses suggesting RR on the order of 44–74% and increases in curative resectability rates.^{52–56} Phase III trial results (EXPLORE) comparing FOLFOX/cetux to FOLFOX in the second-line setting are eagerly awaited.⁵⁷ Results from phase II trials of single-agent cetuximab in heavily pretreated patients who have failed 5-FU, oxaliplatin, and irinotecan should be available soon.^{58,59} It appears that responses may be delayed in heavily pretreated patients with more than 25% demonstrating maximal responses at week 16. Underway are other phase III trials incorporating cetuximab into combination regimens for first-line metastatic and adjuvant treatment of CRC (Cancer and Leukemia Group B [CALGB] 80405 and CTSU N0147, respectively; Table 4).

Exploratory analyses have suggested a correlation between the development of a skin rash and survival.¹²

The rash may be an indicator of sensitivity to EGFR blockade and a surrogate for adequate receptor saturation by cetuximab.¹² Trials are underway to determine if cetuximab dose escalation to achieve a desired level of cutaneous toxicity can improve efficacy.

The current practice of excluding from cetuximab treatment patients whose tumors do not express EGFR by IHC has raised many questions. Earlier trials have noted a lack of correlation between response to cetuximab and degree of EGFR expression.^{12,47} In a recent retrospective analysis of 16 patients who failed to demonstrate EGFR-positivity by IHC, 4 patients with irinotecan-refractory metastatic CRC responded to treatment with cetuximab and irinotecan (RR=25%).⁴⁶ This evidence challenges the presumption that only EGFR-positive tumors respond to EGFR inhibitors. Several explanations have been proposed for this disconnect. First, subjective interpretation of EGFR IHC-staining intensity, lack of a uniform IHC scoring system, and variations in fixation procedures and antibody techniques make the establishment of EGFR status difficult.⁴⁶ Second, the use of archival tissue may not be representative of current tumor biology because of the decline in EGFR staining intensity over time and because of the differences in biology between primary and metastatic disease. Third, current IHC detection systems may be focusing on the incorrect receptor. Because IHC is the most commonly used method, new approaches are needed to address these issues. Increasingly refined assessment strategies evaluating receptor polymorphisms and

gene sequencing are underway. Prospective cetuximab trials including patients with IHC EGFR-negative tumors are also being conducted. The results should provide further guidance in the selection of patients likely to respond to cetuximab therapy.

In summary, based on current evidence, combination treatment with cetuximab and irinotecan should be pursued in patients with advanced CRC who have failed irinotecan. Patients who are unable to receive additional irinotecan may be treated with cetuximab monotherapy. EGFR status by IHC should not be used to determine candidacy due to its unreliability, although this approach may still be a requirement for third-party reimbursements; therefore, newer assessment strategies must be developed. Confirmatory phase III trials will hopefully shed light on the role of cetuximab in the first-line metastatic and adjuvant settings.

Other Anti-EGFR Strategies

Other anti-EGFR monoclonal antibodies similar to cetuximab are in clinical development. EMD72000 (matuzumab, Merck), a humanized IgG1 monoclonal antibody to EGFR currently being evaluated in phase I and II trials, has a prolonged half-life which may allow for less frequent administration.⁴² ABX-EGF (panitumumab, Abgenix), a fully human IgG2 monoclonal antibody to EGFR, has exhibited a RR of 9% in a phase I/II study with advanced CRC patients and is being pursued in follow-up trials.⁴² Small-molecule tyrosine kinase inhibitors directed at EGFR including gefitinib (Iressa, AstraZeneca), erlotinib (Tarceva, OSI Pharmaceuticals), and EKB-569 have not demonstrated objective responses in phase I studies of advanced CRC as single agents.⁴² When combined with standard cytotoxic chemotherapeutics, however, these agents may hold promise in the first-line and salvage settings.⁴² Randomized phase III studies are needed in order to reach definitive conclusions.

Combination VEGF/EGFR Therapy

Because of the potential blockade of multiple growth factors or targets on cancer cells, combination antibody strategies are being explored in advanced CRC. It has been shown that higher mRNA levels of VEGF were significantly associated with resistance to cetuximab in 39 patients with metastatic CRC.⁶⁰ Therefore, combinations with bevacizumab and cetuximab are being pursued. Interim data for a phase II randomized trial (BOND2) were presented at the 2005 Gastrointestinal Cancers Symposium and at the 2005 ASCO annual meeting.⁶¹ Seventy-five patients with irinotecan-refractory, bevacizumab- and cetuximab-naïve metastatic CRC were randomized

to treatment with irinotecan/bevacizumab/cetuximab (irin/bev/cetux) or bevacizumab/cetuximab (bev/cetux). EGFR-positive staining by IHC was not required for enrollment. Initial results suggest no unexpected toxicities with concurrent therapy (1 gastrointestinal perforation; 1 myocardial infarction; 2 gastrointestinal bleeds; 1 sepsis; 17–20% grade 3 rashes; 5% grade 3 headaches with first cetuximab infusion in bev/cetux arm possibly due to absence of decadron premedication for irinotecan; higher rates of diarrhea, neutropenia, and fatigue with irinotecan). Preliminarily, triple therapy appears more efficacious, with a higher RR (37% vs 20%) and longer time to progression (7.9 vs 5.6 mo). Final analyses are anticipated soon (Table 5). Along the same lines, the CALGB 80405 trial recently began randomizing untreated metastatic CRC patients to chemotherapy with bevacizumab, cetuximab, or a combination of the two.

Cost Considerations

The availability of all these active agents for metastatic CRC raises a difficult societal issue: can we afford these drugs? Table 6 lists wholesale prices of drugs for 2 months of therapy, the typical period before disease progression is assessed.⁶²

These estimates do not include expenses associated with administering the drugs in an infusion center, antiemetics, or physician time. For the standard patient who receives 8 months of first-line therapy and 4 months

Table 5. Ongoing Trial Evaluating Combination Bevacizumab/Cetuximab in the Second-line Setting

Study	Patients, n	Regimen	RR, %
Saltz ⁶¹	31	bev/cetux	20
	34	irin/bev/cetux	37

Bev = bevacizumab; cetux = cetuximab; irin = irinotecan; RR = response rate.

Table 6. Wholesale Prices for 2 Months of Advanced CRC Therapies⁶²

Regimen	Cost
5-FU Mayo Clinic	\$63
FOLFIRI/IFL	\$9,000
FOLFOX	\$12,000
FOLFOX/FOLFIRI + bevacizumab	\$21,000
Irinotecan/FOLFIRI + cetuximab	\$30,000

5-FU = 5-fluorouracil; FOLFIRI = infusional 5-FU/leucovorin/irinotecan; FOLFOX = infusional 5-FU/leucovorin/oxaliplatin; IFL = bolus irinotecan/5-FU/leucovorin.

of salvage therapy with cetuximab, the drug costs approximate \$161,000.⁶² For the 56,000 patients who will be diagnosed with de novo metastatic CRC or recurrent disease this year, the cost for only 2 months of therapy would reach \$1.2 billion.⁶² These staggering costs for noncurative treatment raise the question: are the extra costs worth the incremental benefit (months of survival)? With limited healthcare resources, this dilemma cannot be dismissed. This quandary will be especially poignant in the adjuvant setting if these agents prove effective. Future trials will hopefully include cost analyses to address these financial aspects of cancer care.

Conclusions

The recent FDA approvals of bevacizumab for use in combination with first-line chemotherapy for metastatic CRC and cetuximab for EGFR-expressing, irinotecan-refractory metastatic CRC represent important advances in the field and suggest that both VEGF and EGFR are valid targets for therapy. A number of other agents targeting the VEGF axis are in development including a chimeric soluble receptor, antibody-based strategies, and other receptor tyrosine kinase inhibitors. Similarly, other anti-EGFR monoclonal antibodies and small-molecule tyrosine kinase inhibitors are under investigation. Further advances in CRC are expected through continued scientific investigation and well-designed clinical trials.

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