Original Article

Targeted Strategies in the Treatment of Metastatic Colon Cancer

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Abstract
Advances in the understanding of tumor biology have led to the identification of important cellular processes involved in the pathogenesis of colon cancer. Drugs that interfere with these critical pathways are known as *targeted agents*. The goal of these therapies is to selectively interrupt the signal transduction pathways responsible for tumor growth and survival. Some of these targeted agents have made important, albeit modest, contributions to the treatment of patients with metastatic colorectal cancer. However, the activity levels with the currently available targeted therapies are far lower than experts had hoped, and toxicities are often nontrivial. This article reviews the available therapies, the data that justify their use, and the challenges of optimizing targeted therapies through combinations with cytotoxic chemotherapies and other targeted agents. Finally, some newer drugs and strategies currently being tested in clinical trials are discussed. (*JNCCN* 2007;5:983-990).

Combination and sequential chemotherapy regimens incorporating fluoropyrimidines with irinotecan and oxaliplatin have roughly doubled the expected median survival of patients with advanced colorectal cancer compared with historical 5-fluorouracil (FU)–based therapies.[1–3] In the past 5 years, agents directed at the epidermal growth factor receptor (EGFR; cetuximab, panitumumab) and vascular endothelial growth factor (VEGF; bevacizumab) pathways have emerged as additions to the roster of agents showing activity in metastatic colorectal cancer. Because of the rapid development of multiple active targeted agents, defining the most appropriate combinations to use in practice and clinical trials is challenging. Furthermore, despite the original optimistic presumptions that so-called targeted therapies would have minimal or trivial toxicities, significant and sometimes dangerous side effects have been encountered. This article discusses the treatment strategies for targeted agents both alone and in combination in first- and second-line therapies, and then reviews newer targeted agents currently being tested in clinical trials.

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Targeting the VEGF

Bevacizumab

Bevacizumab is a monoclonal antibody that binds to the VEGF-A, thereby abrogating the VEGF-receptor–mediated intracellular signaling and potentially blocking the growth of tumor through multiple mechanisms that may include antiangiogenesis, normalizing tumor vasculature, and reducing the number of circulating endothelial and endothelial progenitor cells.[4] Although doses of 5 mg/kg and 10 mg/kg have been used in different trials, most doses given in practice for colorectal cancer are 5 mg/kg. This low-dose strategy was recently justified in a non-small cell lung cancer trial known as AVAiL (Avastin in Lung) that showed the lower-dose bevacizumab to be as effective as the higher dose.[5] Because bevacizumab is an expensive agent that is priced by the milligram, using the lower dose until or unless randomized data suggest otherwise seems prudent. The traditional schedule for bevacizumab administration has been to give the first dose over 90 minutes, the second over 60 minutes, and all subsequent doses over 30 minutes. Recent data indicate that this time-consuming ritual is unnecessary, and that all 5-mg/kg doses, including initial doses, can be administered over 10 minutes without a change

in the safety profile, thereby making the treatment regimen simpler and more convenient for patients.[6]

In the Frontline Setting: Bevacizumab has not shown significant single-agent activity in patients with metastatic colorectal cancer.[7] However, in a landmark phase III trial involving more than 800 patients, Hurwitz et al.[8] added bevacizumab to front-line irinotecan, bolus 5-FU, and leucovorin (IFL) chemotherapy, which was a regulatory standard regimen for metastatic colorectal cancer in the United States at the time, and compared it with IFL plus placebo. Median overall survival was significantly increased from 15.6 months in the IFL plus placebo arm to 20.3 months in the IFL plus bevacizumab arm ($P < .001$). Secondary end points showed a 10.6 month progression-free survival in the IFL plus bevacizumab group and a 6.2 month progression-free survival in the IFL plus placebo group, with a 10% higher response rate in the IFL plus bevacizumab group (45% vs. 35% for IFL plus placebo; $P < .003$). Although bevacizumab was subjectively well-tolerated, some serious toxicities were encountered, the most serious being an increased risk for gastrointestinal perforations (1.5%) and arterial thrombotic events (approaching 3% higher in the IFL plus bevacizumab group). Hypertension was greater in the IFL plus bevacizumab arm (11% of patients with grade 3 hypertension with no related hypertensive crises or death). Three cases of grade 4 bleeding occurred in the bevacizumab group. This pivotal trial led to the approval of bevacizumab with 5-FU–based chemotherapy for the first-line treatment of patients with untreated metastatic colorectal cancer.

More recently, bevacizumab has been evaluated in the frontline setting in conjunction with oxaliplatin-based chemotherapy. Trial NO16966 evaluated oxaliplatin/leucovorin/5-FU (FOLFOX) versus capecitabine/oxaliplatin (CapeOx) plus either bevacizumab or a placebo in a 2×2 design.[9] In this trial, 1400 patients were involved in bevacizumab versus placebo randomization. The improvement of progression-free survival was statistically significant with the addition of bevacizumab to frontline oxaliplatin-based therapy (hazard ratio, 0.83; $P = .002$); however, the overall median improvement in progression-free survival was only 1.4 months, a far more modest difference than the 4.4-month median progression-free survival improvement that was seen in the initial IFL +/– bevacizumab study discussed earlier. Furthermore, response rates were absolutely identical in the bevacizumab- and nonbevacizumab-containing arms of NO16966. Overall survival trended toward but did not reach statistical significance in this trial ($P = .077$).[10] Although this study confirms that the addition of bevacizumab to frontline oxaliplatin-based chemotherapy improves progression-free survival and is therefore an appropriate frontline treatment consideration for patients with metastatic colorectal cancer, enthusiasm for this approach must be tempered by the lack of a response benefit or significant survival advantage. However, bevacizumab seems to have been discontinued early in this trial (several months before documentation of treatment failure), and this suboptimal use of bevacizumab may have blunted the effect of bevacizumab on progression-free and overall survival. Response rate, however, would not have been influenced by this discontinuation, which occurred after response would have been maximized.

One hypothesis explaining the less-than-expected results of the addition of bevacizumab to oxaliplatin-based chemotherapy in the NO16966 trial is that the effect of bevacizumab may be less pronounced than on irinotecan-based chemotherapy. However, the authors believe this explanation is unlikely for several reasons. Firstly, bevacizumab conferred a survival advantage on patients receiving FOLFOX in the Eastern Cooperative Oncology Group (ECOG) 3200 trial (discussed later).[11] Secondly, no mechanistic hypothesis has been identified whereby one drug should be better-influenced by a VEGF inhibitor than another. Nevertheless, the possibility cannot be excluded.

In the Second-Line Setting: The ECOG 3200 study evaluated bevacizumab as a component of second-line therapy in patients who did not receive it in the first-line setting. In this trial, 829 patients were randomized to receive bevacizumab plus FOLFOX4, FOLFOX4 alone, or single-agent bevacizumab. The single-agent arm of bevacizumab was closed early when lack of effectiveness was seen compared with the other treatment arms. Median overall survival was significantly increased from 10.7 months in the FOLFOX4 arm compared with 12.5 months in the FOLFOX4 plus bevacizumab arm ($P = .0018$). Time to tumor progression and response rate were also significantly increased by the addition of bevacizumab.[11] Combining bevacizumab with FOLFOX4 resulted in a 14% overall increase in grade 3 and 4 toxicity. As noted in the Hurwitz et al.[8] trial, grade 3 or 4 hypertension, bleeding, and vomiting were infrequent but were found to

be associated with the combination of bevacizumab and FOLFOX4.

Notably, studies have shown a role for bevacizumab in either first- or second-line therapy of metastatic colorectal cancer. However, whether bevacizumab confers any benefit in the second-line setting after progression through a bevacizumab-containing regimen in the first-line setting has not been established. This use of bevacizumab beyond progression seems to be supported by a retrospective review of nonrandomized data, but these are certainly prone to selection biases.[12] Bevacizumab use in multiple lines of therapy is the focus of the Southwest Oncology Group (SWOG) 0600 trial, which opened in June 2007. Pending the outcome of that trial, using bevacizumab in multiple lines of therapy after progression through a bevacizumab-containing regimen should be regarded as outside the labeled indication and investigational.

Targeting the EGFR

The EGFR is a transmembrane glycoprotein that is involved in the initiation of signal transduction pathways affecting cellular growth, differentiation, proliferation, and programmed cell growth. Cetuximab and panitumumab are monoclonal antibodies that block the ligand-binding site of the EGFR, thereby interrupting the intracellular signaling. Cetuximab is a human-mouse chimeric immunoglobulin (Ig) G_1 monoclonal antibody against the EGFR. Panitumumab is a fully human anti-EGFR IgG_2.

Cetuximab

United States Trials: The first phase II trial conducted in the United States combined cetuximab and irinotecan in 120 patients with metastatic colorectal cancer refractory to both 5-FU and irinotecan and reported a partial response rate of 22.5%.[13] Another trial of single-agent cetuximab in 57 patients reported a response rate of 10.5%.[14] These results suggested that cetuximab could potentially reverse resistance to irinotecan.

European Trial, Bowel Oncology with Cetuximab Antibody Study: Based on the initial U.S. trial, a European randomized phase II trial, known as the Bowel Oncology with Cetuximab Antibody (BOND) study, tested the combination of cetuximab plus irinotecan or cetuximab as single-agent therapy in a 2:1 ratio, respectively, in 329 patients.[15] The results were almost identical to the 2 prior U.S. studies, with a reported 22.9% response rate for combination cetuximab and irinotecan compared with 10.8% for single-agent cetuximab therapy. Median time to progression was 4.1 months for the combination regimen and 1.5 months for monotherapy. This study led to the approval of cetuximab either alone or in combination with irinotecan for patients who are refractory to irinotecan treatment. The mechanism of overcoming resistance is poorly understood but may result from the antibody's ability to inhibit antiapoptotic pathways, such as BCL2, or the ability to sensitize resistant cells to apoptosis through caspases and Bax pathways.[16]

Canadian Trial: CO.17: A recent Canadian study showed the first overall survival advantage with an anti-EGFR therapy in colorectal cancer. This trial, known as CO.17, included 572 heavily treated patients who were randomized to receive cetuximab plus best supportive care versus best supportive care alone. The primary outcome showed a median survival of 6.1 months in the cetuximab group compared with 4.6 months with best supportive care alone (hazard ratio, 0.77; 95% confidence interval, 0.64–0.92; $P = .005$).[17]

CRYSTAL Trial: Cetuximab in First-Line Setting with FOLFIRI: A large multinational phase III trial comparing frontline therapy with folinic acid, S-FU, and irinotecan (FOLFIRI) chemotherapy alone or FOLFIRI plus cetuximab was recently completed. Study results were announced in a press release in January 2007, which noted that the trial had met its primary end point of progression-free survival. The progression-free survival result, in fact, is statistically significantly better for the cetuximab-containing arm; however, the difference in progression-free survival is a modest 0.9 months. Whether this modest advantage will justify the toxicity and expense of cetuximab in the frontline setting is highly debatable.[18]

Panitumumab

Phase II trials suggested an approximate 8% to 10% response rate and approximate 20% to 30% stabilization of disease regardless of the number of prior therapies.[19,20] A phase III trial showed that panitumumab (6 mg/kg every 2 weeks) significantly improved progression-free survival and disease control (response rate and stable disease) compared with best supportive care in patients with metastatic colorectal cancer that failed to respond to standard chemotherapy. The study showed a 46% decrease in tumor progression on the panitumumab arm, but no difference in

overall survival was seen. Median progression-free survival was trivially improved: 8 weeks for panitumumab and 7.3 for best supportive care. The mean progression-free survival was 13.8 weeks for panitumumab and 8.5 for best supportive care,[21] indicating that a small number of patients derived a substantial benefit. Overall, although no direct comparisons have been performed, panitumumab and cetuximab as single agents seem to have similar antitumor activity and similar rates of skin rash.[15,21]

Of concern, however, is a report concerning the Panitumumab in Advanced Colorectal Cancer Evaluation (PACCE) trial, available as a press release only[22] (www.amgen.com. Accessed August 28, 2007). This frontline trial, in which 1000 patients were assigned to either FOLFOX/bevacizumab or FOLFIRI/bevacizumab and then randomized to either receive concurrent panitumumab or not, showed a progression-free and an early overall survival disadvantage for the panitumumab-containing arm. Further information regarding this is awaiting presentation of the data in an open forum, which had not occurred at the time of this writing because the scheduled presentation of this study at the American Society of Clinical Oncology (ASCO) June 2007 annual meeting was canceled as the release of these concerning safety data was deemed a violation of ASCO's data embargo. As noted earlier, nonrandomized[13,14] and randomized[15] studies showed that cetuximab has an approximate doubling of response rates when irinotecan is continued, compared with giving cetuximab alone, in patients with irinotecan-refractory disease. Notably, no chemotherapy combinations with panitumumab have been reported, and the absence of both safety and efficacy data in this regard must be factored into the selection of an anti-EGFR monoclonal antibody.

As noted in the NCCN Colon Cancer Clinical Practice Guidelines in Oncology (in this issue), no data support the use of panitumumab after cetuximab failure, or cetuximab after panitumumab failure, and the use of one of these agents after clinical progression on the other is not recommended.[23]

The major side effect of the EGFR inhibitors is an acne-like rash with drying and fissuring of the skin. Fatigue, abdominal pain, nausea, and diarrhea also may occur, although determining whether these events are drug- or disease-related is often difficult. Most trials report that approximately 85% of patients develop the acne-like skin rash (12%–14%, grade 3 or 4). In addition, the rash was found to correlate with response and survival, suggesting that it may be an important surrogate for response.[24,25] Contrary to some commonly held misconceptions, the skin rash is not an allergic reaction, and the incidence and severity with cetuximab and panitumumab seem to be similar.[26]

Unrelated to the acneiform skin reaction, a rare but serious hypersensitivity reaction characterized by wheezing, bronchospasm, oxygen desaturation, and hypotension can occur in approximately 2% to 3% of patients treated with cetuximab.[13,15] The incidence of these reactions seems to vary widely among regions, with serious reaction rates ranging from as high as 20% in North Carolina and Tennessee to as low as approximately 1% in New York and the Northeast.[27,28] Allergic reactions are virtually only seen during the first dose of cetuximab, and therefore at least the first dose of cetuximab is routinely given with an antihistamine premedication. Extensive experience at Memorial Sloan-Kettering Cancer Center indicates that antihistamine prophylaxis is not needed after the first 2 doses of cetuximab.[27] Panitumumab does not require premedication and only 1 patient (< 1% of patients) experienced a grade 3 infusion reaction in the phase III pivotal panitumumab trial.[21]

Combining Biologic Therapy in the Metastatic Setting: Cetuximab and Bevacizumab

BOND 2

Antitumor synergy for combined EGFR- and VEGF-targeted therapy has been shown in preclinical models of colon cancer where the interaction resulted in reduced tumor cell mitosis in the combination group.[29] In a multicenter randomized phase II trial sponsored by the National Cancer Institute (NCI), combination bevacizumab and cetuximab with or without irinotecan was tested in patients with irinotecan-refractory metastatic colorectal cancer. This trial, known as the BOND 2 study, combined cetuximab and bevacizumab in 83 patients whose disease advanced on standard chemotherapy agents.[30] The combination of the 2 biologic agents (cetuximab plus bevacizumab) led to a 20% response rate in the refractory setting. The addition of irinotecan to bevacizumab plus cetuximab led to a 37% response rate. Toxicities were similar to those observed from the sin-

gle agents alone, without clear evidence of synergistic toxicity, although skin rash may have been somewhat increased compared with historical experience of cetuximab without bevacizumab. Time to tumor progression was 4.9 and 7.3 months, respectively. These results suggested that biologic agents could be combined without clear evidence of undue toxicity, although the rate of grade 3 skin rash was at the upper limit of what had been previously reported for cetuximab alone and that dual targeting of various mediators of tumor progression may be efficacious. This study was the basis for combination anti-EGFR and anti-VEGF studies in the frontline setting. All patients on this trial were naïve to both anti-EGFR and anti-VEGF therapy.

BOND 2.5

A follow-up study of BOND 2, known as the BOND 2.5 trial, is in progress to assess the activity of cetuximab and bevacizumab–irinotecan combination in patients who have previously progressed through a bevacizumab-containing regimen.

Cancer and Leukemia Group B/SWOG 80405

The preliminary results of the BOND 2 study served as a safety/feasibility pilot for the current NCI intergroup trial (CALGB/SWOG 80405), which is testing the role of cetuximab and bevacizumab in first-line therapy in patients with metastatic colorectal cancer. Investigators can choose the chemotherapy regimen (FOLFOX or FOLFIRI) and patients are then randomized to receive cetuximab, bevacizumab, or a combination of both in addition to chemotherapy in the first-line setting. This trial is currently accruing patients.

PACCE

PACCE, a large industry-sponsored trial, has recently completed accrual. In this trial, approximately 800 patients received FOLFOX/bevacizumab +/– panitumumab, and 200 received FOLFIRI/bevacizumab +/– panitumumab. A press release reported a preplanned interim analysis, scheduled after the first 231 events (death or disease progression).[22] The actual data have not been made public at the time of this writing, but the results reportedly show a statistically significant difference in progression-free survival favoring the control arm. An unplanned analysis of overall survival also reportedly favors the control (non–panitumumab-containing) arm. More data are needed to better understand these results, but caution should be exercised when using panitumumab in combination with other therapies.[22]

Other Tyrosine Kinase-Targeted Agents (Against VEGF and EGFR)

Oral tyrosine kinase inhibitors have been tested also in colon cancer with minimal responses. Sunitinib (SU11248) is an oral multitargeted receptor tyrosine kinase inhibitor with activity against the major subtypes of the VEGF receptor (VEGFR-1, -2, and -3), platelet-derived growth factor receptor (PDGFR-α and -β), stem cell factor receptor (c-kit), glial cell-line derived neutrophilic factor receptor (RET), and Fms-like tyrosine kinase-3 receptor (FLT3). Sunitinib is currently approved by the U.S. Food and Drug Administration (FDA) for treating renal cell carcinoma and gastrointestinal stromal tumors after failure of imatinib therapy. A phase II trial failed to reach its prespecified end point in the first stage, but the side effect profile was tolerable.[31] Given the tolerable side effect profile and known responses of anti-VEGF treatments with chemotherapy in metastatic colorectal cancer, further investigation was initiated and 2 phase I, open-label trials with FOLFOX and FOLFIRI are currently ongoing.[32,33]

Vatalanib is an orally active, small, multitargeted agent that blocks VEGFR, PDGFR-β, and the stem cell factor receptor (c-kit). Vatalanib, like bevacizumab, does not have single-agent activity in patients with metastatic colorectal cancer. Unlike bevacizumab, however, vatalanib did not show a clear benefit when combined with FOLFOX4 therapy and compared with FOLFOX4 alone in first-line metastatic colon cancer.[34,35]

Gefitinib and erlotinib, tyrosine kinase inhibitors of the EGFR, also have not shown activity as single agents.[36,37] Why the EGFR tyrosine kinase inhibitors show relative inactivity is unknown. Tumor biopsies taken from patients who received gefitinib showed that the mitogen activation protein kinase (MAPK) and the serine-threonine kinase Akt (also known as protein kinase B) were not effectively inhibited.[16] One possibility is that, in addition to blocking the EGFR, monoclonal antibodies work by inducing complement-dependent cytotoxicity and antibody-dependent cell cytotoxicity. This mechanistic difference could explain the differences in clinical response.

Despite the lack of activity seen in single-agent tyrosine kinase inhibitors, combining anti-EGFR monoclonal antibodies and low-molecular-weight EGFR tyrosine kinase inhibitors—2 agents targeting the EGFR—showed promise in preclinical work.[38]

These findings led to a phase I trial by Baselga et al.,[39] combining the EGFR tyrosine kinase inhibitor gefitinib with cetuximab, which showed that 5 of 11 (45%) patients with colorectal cancer experienced partial responses. These combinations will be tested in upcoming trials.

Other New Agents

Activation of MAPK and phosphoinositide 3-kinase/Akt can occur independently of the EGFR pathways. These pathways play a critical role in effecting a range of cellular functions in response to extracellular signals, leading to cell growth, proliferation, and survival. Insulin-like growth factor 1 receptor works through the phosphoinositide 3-kinase/Akt pathway and may regulate proliferation and metastases.[40] Downstream of the phosphoinositide 3-kinase/Akt pathway is mTOR (mammalian target of rapamycin), which becomes activated in response to mitogenic stimuli of the phosphoinositide 3-kinase/Akt pathway. Several compounds under development in oncology, including CCI-779 and RAD001, are MTOR inhibitors. One partial response was seen in a patient with colon cancer in the phase I study.[41] Trials evaluating these agents alone, in combination with each other, or with the currently available anti-EGFR and anti-VEGF agents, are in the advanced planning stages and being initiated.

Conclusions

Tumor signaling mechanisms have proven far more complicated than initially anticipated. Multiple redundancies and backup systems exist that may activate clinically insignificant pathways when a targeted agent blocks a single pathway. As a result, the use of single-agent targeted therapies has been disappointing in the treatment of metastatic colorectal cancer. Combination therapies, however, may prove more useful in improving survival, progression-free survival, and response afforded by conventional therapy. Bevacizumab improves outcome when added to traditional cytotoxic chemotherapy in either the first- or second-line setting in metastatic colorectal cancer and, short of a specific contraindication, should be incorporated into the management of these patients. Cetuximab is recommended for non–first-line treatments and is useful in overcoming cellular resistance to irinotecan. Panitumumab was recently approved by the FDA for patients who have progressed on standard chemotherapy and has proven to have similar single-agent activity to cetuximab. The overall toxicity profile of panitumumab and cetuximab seem similar, with skin rash occurring with similar incidence and severity; however, panitumumab seems to have a lower incidence of reported hypersensitivity reactions. A clinician may choose to use either cetuximab or panitumumab, but no data support using one after progression on the other. Sequential use of one EGFR inhibitor after failure on another, outside of a clinical trial, would needlessly expose the patient to toxicity and would be a waste of resources. A patient who discontinues cetuximab because of a hypersensitivity reaction (although not skin rash because this seems to be similar between the agents) may reasonably be treated with panitumumab, because reactions to panitumumab in this setting have not been reported at this writing. Although the toxicities of these agents do not overlap with those of traditional chemotherapy, they can be significant and pose new challenges to oncologists.

A crucial challenge with important implications is to show which patients are more likely to respond to these newer agents, either alone, in combination with chemotherapy, or in combination with each other. This information would allow oncologists to better dictate treatment and enrich a population of patients who could greatly benefit from these treatments. Predictive markers may also allow toxicity to be minimized through avoiding treatment in those patients who are unlikely to respond. Given the immense price tag on these therapies, these markers would also potentially reduce health care costs.

A next generation of molecular targets will soon be explored for their therapeutic potential. Ongoing clinical trials will help further define these important mechanisms in hopes of improving outcome and progress in the treatment of colorectal cancer.

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