Colorectal Cancer Treatment: What's Next? (or: Is There Life After EGFR and VEGF?)

Leonard Saltz

ABSTRACT

In the past 10 to 15 years, the number of approved agents for treatment of colorectal cancer has expanded from only one (in 1995) to seven (as of 2006), with the most recent additions being the targeted agents cetuximab, bevacizumab, and panitumumab. While real progress has been made, these advances have translated into more modest improvements in patient outcomes than had been anticipated. Better understanding of the molecular underpinnings of colorectal cancer and of each patient's genetic makeup will likely improve the selection of treatment for each individual, leading to reduced toxicity and cost in patients spared therapy because they are unlikely to respond, and higher benefit in the subset of patients harboring the target of interest. KRAS mutational status was recently identified as an important marker for response to EGFR-directed therapies, and other pathways being explored include the immune system (anti-cytotoxic T lymphocyte antigen 4 [anti-CTLA4] monoclonal antibodies), insulin-like growth factor 1 receptor (IGF1R) (IGF1R monoclonal antibodies), the mammalian target of rapamycin (mTOR) (mTOR kinase inhibitors), and others. Results of trials evaluating agents targeting these pathways are awaited. New paradigms and treatments are needed to advance the landscape for patients with advanced and metastatic colorectal cancer.

Gastrointest Cancer Res 2(suppl 2): S20–S22.

L. Saltz, MD: Gastrointestinal Oncology Service, Memorial Sloan-Kettering Cancer Center, New York, NY

Colorectal cancer treatment options have undergone enormous changes over the past 10 to 15 years. In 1995, the only drug approved for treatment of colorectal cancer was 5-fluorouracil (5-FU). Leucovorin, a reduced folate in the B-vitamin family, was also approved, but as an adjunct to 5-FU, and with absolutely no antitumor activity of its own. New targets were identified and new agents were tested, and by 2004, the number of approved agents for colorectal cancer had increased substantially, with the additions of irinotecan (1996), the oral 5-FU analogue capecitabine (1998), oxaliplatin (2002), cetuximab (2004), and bevacizumab (2004). Most recently, in 2006, panitumumab was added to the list of approved agents in the United States. It was also recently approved in Europe, but only for colorectal cancer patients whose tumors are demonstrated to have a wild-type KRAS gene.

Although, initially, these newer drugs appeared to offer enormous promise to radically change the landscape for patients with metastatic colorectal cancer, the passage of time has begun to show us that the advances that have been made, while real, are more modest than we had expected or hoped. The emergence of new paradigms for the treatment of patients with colorectal cancer has somewhat plateaued since 2003, and the expectation that was strong 5 years ago, that median progression-free survival (PFS) duration would routinely reach 1 year or more with first-line combination treatments, has not been realized. In the current setting, one must confront the possibility that further improvements will not be attained with use of available agents and strategies, and new paradigms are sorely needed. While newer agents that attack similar targets, such as other vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR) pathway antagonists, are under investigation, these agents are variations on an available theme, and are unlikely to produce quantum leaps in therapeutic efficacy. Sadly, much effort and many resources are going into the development of these "me too" strategies, as commercial concerns drive many pharmaceutical companies to compete for market share in an established area of therapeutic efficacy, rather than to focus on the more difficult and riskier strategy of developing a new treatment paradigm.

Greater understanding of the molecular underpinnings of an individual patient's tumor and of each patient's genetic makeup may lead to a more careful and scientifically elegant selection of therapies for

Address correspondence to: Leonard Saltz, MD, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, Room H917, New York, NY 10021. Phone: 212-639-2501; Fax: 212-794-7816; E-mail: saltzl@mskcc.org.

each person. Selective indicators, such as those recently seen for KRAS mutational status, in which it appears that patients with mutations in at least codon 12 or 13 are incapable of responding to EGFR-targeted agents, and so can be spared needless exposure to these drugs, are likely to increase. For many patients, this will likely reduce the toxicity profile as well as exposure to drugs that are unlikely to be effective. For a smaller, selected subset of patients treated with such a drug, the likelihood of benefit will be higher. However, because most patients currently receive all of the available agents at some point during the course of their disease, this degree of selectivity will not substantially "raise the bar" for the general population. Only the identification of new classes of drugs that attack new targets can be expected to substantially improve the state of the art for colorectal cancer care.

DRUGS IN THE PIPELINE

More sophisticated understanding of signal transduction pathways, and of immune surveillance and immunologically mediated cytotoxicity, will help to reveal potential therapeutic options for colorectal cancer. Current drug development is moving rapidly along these pathways. It is still too early to determine whether any or all of these approaches will be useful for patients with colorectal cancer. One prediction that can be made with a reasonable degree of certainty is that no single targeted therapy will be a panacea for colorectal cancer. It is more likely that colorectal cancers will be subtyped based on underlying genetic mutations, with targeted therapies selected for tumors driven by mutation, amplification, or constitutive activation of those particular targets. As such, it is possible that inhibitors of the RAS/RAF/MEK pathway or the PI3-kinase/AKT/mTOR pathways may be useful in patients with growth or survival-driving mutations in those kinases, and some agents targeting these kinases are being evaluated in colorectal cancer. Other selective mutational analyses may produce further treatment guidance. For example, mutations in the Src gene are rare in colorectal cancer, and use of specific Src inhibitors would not be expected to show meaningful activity in the general patient population. In the small patient subset in whom Src is mutated, however, Src inhibitors, such as dasatinib, might be of some clinical utility.

As an initial example of appropriate patient selection, KRAS mutational status has become recognized as a critical determinant in the activity of anti-EGFR therapy, first in patients with lung cancer, and now in patients with colorectal cancer. Data presented initially by Khambata-Ford et al for a set of 80 patients treated with single-agent cetuximab demonstrated that patients with mutations in the KRAS gene had a very low degree of disease control with cetuximab, whereas patients with wild-type KRAS had a better chance of response or prolonged disease stabilization.[1] More recently, a more definitive trial was presented at the 2007 European Cancer Conference (ECCO)[2]: Patients were treated with single-agent panitumumab, and response was seen in 20% of patients whose tumors exhibited a wild-type KRAS gene, but in none of those whose tumors harbored KRAS mutations. Only codons 12 and 13 of the KRAS gene were interrogated for mutations, but more than 98% of known KRAS mutations occur in these regions. This suggests that we will be able to select patients most likely to benefit from EGFR-directed therapy, and spare patients with mutated KRAS the toxicity and expense of ineffective treatment with panitumumab or other EGFR-targeted therapies. It is noteworthy that wild-type KRAS is necessary but not sufficient for EGFR activity and other determinants of activity or resistance will need to be identified. Work by Khambata-Ford et al also identified overexpression of the EGFR ligands amphiregulin and epiregulin as determinants of activity, with all responding patients having over-expression of these ligands.[1]

NOVEL APPROACHES: HARNESSING THE IMMUNE SYSTEM (OR RATHER, UN-HARNESSING IT)

There is enormous potential to exploit the immune system for the treatment of cancer in general, and for colorectal cancer in particular. A number of antitumor vaccine strategies have been explored, albeit with minimal success thus far. More recently, the anti-cytotoxic T lymphocyte antigen 4 (anti-CTLA4) monoclonal antibodies have become of interest as agents for stimulation of antitumor activity. Ongoing studies of the fully human monoclonal antibody tremelimumab are exploring this approach. Thus far, clinical activity has been limited: only one of 47 patients with chemotherapy-refractory colorectal cancer had a major objective response. It is noteworthy, however, that five patients in this trial, all of whom had received previous fluoropyrimidine, oxaliplatin, irinotecan, as well as anti-EGFR therapies, were alive 1 year after initiation of tremelimumab treatment.[3] The major toxicity was diarrhea, which developed as a result of an immune-mediated colitis and which was manageable clinically. Episodes of autoimmune colitis, hypophysitis, and thrombocytopenia were noted, all of which were reversible. While it was determined that the activity of this anti-CTLA4 monoclonal antibody did not warrant further investigation as monotherapy, its novel mechanism of action and potential for synergism with chemotherapy, as well as the signal of potential activity, have led to the design of trials evaluating tremelimumab combined with chemotherapy, which are scheduled to open in 2008. Trials combining another anti-CTLA4 monoclonal antibody, ipilimumab, in conjunction with the IgG1 monoclonal antibody cetuximab, in order to exploit the potential antibody-dependent cellular cytotoxicity (ADCC) of cetuximab, have been proposed.

Another strategy being explored in colorectal cancer is blockade of the insulin-like growth factor 1 receptor (IGF1R). Preclinical evidence suggests that blockade of IGF1R interferes with antiapoptotic and prosurvival signals that are transduced as a result of receptor stimulation, and that this can have deleterious effects on colon cancer cell lines. Clinical trials of IGF1R monoclonal antibodies have been initiated, both in cetuximab-refractory colorectal cancer patients, and combined with cetuximab in cetuximab-naïve patients. Data have not yet been reported.

Another ongoing area of investigation is the mammalian target of rapamycin (mTOR). mTOR kinase has been identified as an anticancer target, with the mTOR inhibitor temsirolimus (CCI-779) now approved for treatment of renal cancer. These agents are being explored in colorectal cancer; however, results have not

been reported thus far. Other specific tyrosine kinase inhibitors of members of signal transduction cascades, such as RAS, RAF, MEK, as well as cMET, are under clinical development and will be explored in colorectal cancer. Whether any of these approaches will turn out to be useful in patients with colorectal cancer remains to be seen.

CONCLUSION

The treatment of metastatic colorectal cancer has advanced considerably in the past 10 to 15 years; however, the advances have been modest, and progress appears to have plateaued in recent years. New paradigms and the identification of new, vulnerable molecular targets are needed. To date, these new paradigms have not been clearly identified, and no new drug class has yet emerged as having clear activity in even a substantial subpopulation of patients with colorectal cancer. Molecular profiling may reveal subsets of patients that can benefit from a particular targeted therapy. This individualized therapeutic approach likely represents the wave of the future in the management of patients with this disease.

REFERENCES

1. Khambata-Ford S, Garrett CR, Meropol NJ, et al: Expression of epiregulin and amphiregulin and K-ras mutation status predict disease control in metastatic colorectal cancer patients treated with cetuximab. *J Clin Oncol* 25:3230–3237, 2007
2. Amado RG, Wolf M, Freeman D, et al: Analysis of KRAS mutations in patients with metastatic colorectal cancer receiving panitumumab monotherapy. 14th European Cancer Conference (ECCO), Barcelona, Spain, September 23–27, 2007 (abstr 7LB)
3. Chung K-Y, Gore I, Fong L, et al: A phase II study of the anti-CTLA4 monoclonal antibody (mAb), CP-675,206, in patients with refractory metastatic adenocarcinoma of the colon or rectum. 2007 ASCO Annual Meeting Proceedings. *J Clin Oncol* 25:18S, 2007 (abstr 3035)

Disclosures of Potential Conflicts of Interest

Dr. Saltz has served as a paid consultant and has received research support from Genentech, ImClone, Pfizer and Merck. He also served as a paid consultant to YM BioScience and Celgene and received research support from Roche, Amgen, Taiho and Bayer.