

ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

Section Editor: Clifford A. Hudis, MD

Colorectal Cancer In Focus

Expanding the Arsenal for Metastatic Colorectal Cancer: A Discussion of Current Clinical Trials

Tanios Bekaii-Saab, MD
 Medical Director, Gastrointestinal Malignancies
 Assistant Professor of Medicine and Pharmacology
 The Ohio State University Medical Center
 Columbus, Ohio

H&O Can you provide some background on the EGFR inhibitors cetuximab and panitumumab?

TBS Both cetuximab (Erbix, ImClone/Bristol-Myers Squibb) and panitumumab (Vectibix, Amgen) target the epidermal growth factor receptor (EGFR), which is over-expressed in more than 70% of colorectal cancer (CRC) samples. EGFR plays an important and aggressive role in the carcinogenesis pathway by leading the cancer cell into division and the tumor into growth and metastases. Cetuximab and panitumumab are monoclonal antibodies; cetuximab is a chimeric antibody with approximately one third of its composition being murine, whereas panitumumab is a fully human antibody with no murine residual. Both drugs are approved mostly for refractory CRC patients who have had at least one prior therapy before receiving either agent. Cetuximab is approved in CRC for use in combination with irinotecan or alone if patients cannot tolerate chemotherapy and have already failed irinotecan. Panitumumab is approved for patients who failed at least 2 prior lines of therapy, and is typically used as a single agent. Both agents are used mostly along these approvals; however, there are emerging data in the first-line setting, especially with cetuximab, which have shown efficacy in a cetuximab and irinotecan regimen for the treatment of metastatic CRC. Although this has not become the standard of care, and despite reimbursement concerns, the National Comprehensive Cancer

Network (NCCN) guidelines find it as an acceptable treatment option.

When evaluating toxicity profiles, the 2 agents are about equal in regard to toxicities such as rash, diarrhea, and hypomagnesemia. The only difference is the incidence of infusion reactions—cetuximab seems to confer a higher risk of infusion reactions compared to panitumumab. Approximately 5% of all patients treated with cetuximab will have severe infusion reactions, and in some southern states such as Tennessee and North Carolina, these reactions occur at a much higher rate (22%). An overall mortality rate of 1% has been observed in patients developing infusion reactions on cetuximab. With panitumumab, approximately 1% of all patients will experience a severe infusion reaction, and to date, no fatalities have been reported.

H&O What were the results of the STEPP trial?

TBS The STEPP (Skin Toxicity Evaluation Protocol with Panitumumab) study was an open-label randomized study of preemptive versus reactive skin toxicity treatment in metastatic CRC patients who received panitumumab with irinotecan-based chemotherapy in the second line. Preemptive treatment referred to patients who were administered moisturizer, sunscreen, topical corticosteroid, and oral doxycycline for weeks 1–6, starting on day -1. This was a small study with approximately 48 patients in each arm. The investigators found that with preemptive skin treatment, the incidence of grade 3 or higher skin toxicities was lower than in patients who received reactive treatment (doxycycline started when rash was observed). The rate of grade 3 or higher skin toxicities in the preemptive group versus the reactive group was 29% versus 62%. Similar results were seen with other grade 3

toxicities—much less patients had toxicities in the preemptive group (6%) versus the reactive group (21%). The overall incidence of adverse events grade 3 or higher was 29% in the preemptive group and 38% in the reactive skin group. Preemptive treatment did not seem to affect the activity of the drug, and some improvement in other toxicities and in quality of life measures were also seen. At our institution, we have adopted a similar preemptive strategy—all patients who are to receive an EGFR inhibitor, whether cetuximab or panitumumab, are started on a regimen of minocycline (thought to be safer and probably as effective as doxycycline) the day before and throughout the whole treatment. Of course it is difficult to predict at this time if our results will reflect the STEPP results, but we will be collecting more data as it becomes available.

H&O Can you highlight any recent trial data on panitumumab?

TB We have interim safety analyses from the 203 (Panitumumab Randomized trial In combination with chemotherapy for Metastatic colorectal cancer to determine Efficacy) and 181 studies. Study 203 is a phase III study that combined FOLFOX (leucovorin, fluorouracil [5-FU], oxaliplatin) chemotherapy with panitumumab versus FOLFOX alone in the first-line treatment of patients with metastatic CRC. Patients enrolled in the study were randomized to receive either 6.0 mg/kg of panitumumab and FOLFOX every 2 weeks or FOLFOX alone. The 181 study is another phase III study investigating panitumumab in combination with FOLFIRI (leucovorin, 5-FU, irinotecan) as a second-line treatment. Patients in the study were randomized to receive either 6.0 mg/kg of panitumumab and FOLFIRI every 2 weeks or FOLFIRI alone. These were global trials conducted mostly outside the United States. The pooled analysis of the safety data on more than 1,300 patients has been analyzed and there were no concerning safety signals found so far. The results of both studies will be presented at the joint European CanCER Organisation and European Society for Medical Oncology in September.

H&O What have been the findings in studies evaluating KRAS gene mutation?

TB The PRECEPT (Pmab Regimen Evaluation in Colorectal Cancer to Estimate Primary Response to Treatment) study was an interesting trial that was designed to prospectively evaluate the efficacy of panitumumab combined with FOLFIRI according to KRAS status. A larger study analyzing KRAS gene mutation with panitumumab therapy was led by Van Cutsem and colleagues. This large

randomized trial of panitumumab versus best supportive care (BSC) in patients crossing over to panitumumab led to the eventual approval of the drug in colorectal cancer. Subsequently, Amado and colleagues took the tissue samples from this study (approximately 92% of 463 patients had tissue samples available) and retrospectively analyzed KRAS status as it related to efficacy. This study suggested that patients with KRAS mutations who received panitumumab had no benefit in terms of progression-free survival (PFS) or response rate compared to those who were KRAS wild type. For the latter patients, there was a significant improvement in the median PFS (12.3 weeks with panitumumab to 7.3 weeks with BSC) and response rate (17% with panitumumab vs 0% with BSC). Another study evaluating KRAS was conducted with cetuximab versus BSC. In this trial, patients with KRAS mutations did not benefit from cetuximab, whereas patients with wild type KRAS had the best survival rates. In conclusion, in the presence of KRAS mutations, patients will have no benefit from monoclonal antibodies targeting EGFR (specifically panitumumab and cetuximab). In the absence of a mutation, the so-called KRAS wild type patients will have a higher likelihood, but no guarantee, of a response.

H&O Do we have any idea why KRAS mutated patients do not respond?

TB It has to do with the biology of KRAS. KRAS stands for human homolog of the Kirsten rat sarcoma-2 virus oncogene. We know that in colorectal cancer, oncogenic mutations in that gene yield a constitutively active protein in approximately half (45–50%) of patients with CRC. RAS is downstream from EGFR; so if there is aberrant signaling in the KRAS mutant type, which happens when there is a mutation, it leads to dysregulation of the RAS-dependent signaling pathway. If this occurs, the signaling pathway acts independently from EGFR activation, and thus is not affected by what is happening at the EGFR level and whether or not the upstream receptor is silenced by anti-EGFR monoclonal antibodies. This is one of the main reasons why, when there is a mutation in KRAS, blocking EGFR does not matter.

H&O What kind of patients benefit from panitumumab?

TB When evaluating what group of patients will benefit from EGFR therapy, testing for KRAS is essential before committing patients to EGFR inhibitors. If a mutation is present, the patient should not get the drug. For patients with wild type KRAS, EGFR inhibitors should be used when possible in combination with chemotherapy and

preferably with irinotecan. For now, cetuximab and panitumumab should be used in the more refractory setting. It is unlikely that the choice of therapy in the first-line setting will be affected by these data; however, evidence is emerging to help support a potential role for EGFR inhibitors in selected patients with metastatic CRC, specifically those with liver metastases.

H&O What data do we have on combining biologic agents?

TB To date, there are 2 studies that provide insight into combining biologics: PACCE (Panitumumab Advanced Colorectal Cancer Evaluation) and CAIRO2 (Capecitabine, Irinotecan, Oxaliplatin) studies. The PACCE study compared standard chemotherapy and bevacizumab (Avastin, Genentech) with the addition of panitumumab versus chemotherapy plus bevacizumab. What this study suggested is that patients who received the dual biologics (bevacizumab with panitumumab) had a worse outcome and a higher level of toxicity when compared to those who received a single-agent biologic (bevacizumab). The relevant question was whether this is a drug effect (panitumumab) or a class effect (monoclonal antibodies against EGFR). CAIRO2, which was a combination of CAPOX (capecitabine and oxaliplatin), bevacizumab and cetuximab versus CAPOX plus bevacizumab, established once more the futility of combining an EGFR inhibitor with bevacizumab and chemotherapy in the first-line treatment of metastatic CRC. Essentially, this means that combining a monoclonal antibody targeting EGFR with bevacizumab and chemotherapy results in an overall worse outcome. Interestingly, when patients were stratified for KRAS, the mutant group fared worse in the combined biologic arms, whereas the wild type group did neither worse nor better in the combined arm, although the toxicities were somewhat worse.

H&O Should panitumumab be used as a single agent, or in combination with chemotherapy?

TB Studies 181 and 203 will confirm whether panitumumab will perform when combined with chemotherapy (FOLFOX or FOLFIRI) in the first- and second-line setting, respectively, when compared to chemotherapy alone. We know that the toxicity profile seems to be acceptable so far, with no concerning safety signals as the ones seen in the PACCE study. These studies will hopefully confirm the utility of combining panitumumab with chemotherapy. What is also noteworthy about studies 181 and 203 is that KRAS status will be analyzed prospectively. As such, we will have the first prospective validation of the role of KRAS as a predictive marker for the use of EGFR inhibitors in metastatic CRC. These 2 studies will provide the best prospective insight into what KRAS means and will probably validate everything we currently know about KRAS.

Suggested Readings

Van Cutsem E, Peeters M, Siena S, et al. Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. *J Clin Oncol*. 2007;25:1658-64.

Amado RG, Wolf M, Peeters M, et al. Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. *J Clin Oncol*. 2008;1;26:1626-34.

Allegra CJ, Jessup JM, Somerfield MR, et al. American Society of Clinical Oncology provisional clinical opinion: testing for KRAS gene mutations in patients with metastatic colorectal carcinoma to predict response to anti-epidermal growth factor receptor monoclonal antibody therapy. *J Clin Oncol*. 2009;27:2091-2096.

Karapetis CS, Khambata-Ford S, Jonker DJ, et al. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. *N Engl J Med*. 2008;359:1757-1765.