ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

Section Editor: Clifford A. Hudis, MD

Colorectal Cancer In Focus

Panitumumab and Combination Chemotherapy in First- and Second-line Therapy for Colorectal Cancer

Emily Chan, MD, PhD
Assistant Professor of Medicine
Vanderbilt-Ingram Cancer Center
Nashville, Tennessee

H&O What do we know of the efficacy in first- and second-line treatment with panitumumab and chemotherapy?

EC Panitumumab (Vectibix, Amgen) is a fully human monoclonal antibody against epidermal growth factor receptor (EGFR). It was approved by the U.S. Food and Drug Administration (FDA) in 2006 for the treatment of patients with EGFR-expressing metastatic colorectal cancer (mCRC) with disease progression on or following fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens after a randomized, phase III, international trial of panitumumab versus best supportive care (BSC) in patients with refractory colorectal cancer demonstrated a statistically significant improvement in progression-free survival (PFS; 8 vs 7.3 weeks). There was no overall survival (OS) advantage, but this result may have been confounded by the fact that patients on the BSC arm were allowed to cross over at progression. Subsequent analysis demonstrated that this improvement in PFS was confined to patients with KRAS wild-type tumors (12.3 vs 7.3 weeks for panitumumab vs BSC). Patients with KRAS mutant tumors did not benefit from panitumumab (7.4 vs 7.3 weeks for panitumumab vs BSC).

This trial demonstrated a benefit for panitumumab monotherapy in the KRAS wild-type population. However, it raised some questions as well: Does panitumumab combine well with chemotherapy? Does KRAS status matter when panitumumab is combined with chemotherapy? Recent data have provided the answers to these questions.

Data from 2 studies were presented at the recent Joint Congress of the European CanCer Organisation and Congress of the European Society for Medical Oncology in Berlin. First, the PRIME trial (203) was a randomized phase III study of panitumumab (6 mg/kg every 2 weeks) plus fluorouracil, leucovorin, and oxaliplatin (FOLFOX) compared to FOLFOX alone as first-line therapy in mCRC. The patients had no prior chemotherapy for mCRC and no prior oxaliplatin use. The primary endpoint was PFS. The other study (181) was also a randomized phase III trial; it compared panitumumab (6 mg/kg every 2 weeks) with fluorouracil, leucovorin, and irinotecan (FOLFIRI) versus FOLFIRI alone in second-line treatment of mCRC. Patients were required to have documented disease progression of 6 or less months after only 1 prior fluoropyrimidine-containing regimen for mCRC. The primary endpoints in this study were PFS and OS. The KRAS wild-type group was the subset of patients in which the primary endpoints were evaluated.

In the PRIME trial, 593 patients received FOLFOX plus panitumumab, and 590 received FOLFOX alone. For patients with wild-type KRAS tumors, PFS was 9.6 months compared to 8 months in patients receiving FOLFOX alone. Response rate (55% vs 48%) and OS, although numerically improved, did not reach statistical significance

in patients receiving panitumumab. Not surprisingly, no benefit was seen with the addition of panitumumab in mutant KRAS patients receiving first-line therapy. In fact, it appeared that adding panitumumab was harmful for these patients. This finding provided further evidence that testing for KRAS prior to administering EGFR antibody therapy is necessary.

In the 181 study, 591 patients were randomized to panitumumab and FOLFIRI, and 595 received FOLFIRI alone. It was reported that the addition of panitumumab to FOLFIRI improved PFS from 3.9 months to 5.9 months in patients with KRAS wild-type tumors. A very good response rate was also observed in KRAS wild-type patients receiving panitumumab (35% vs 10%). This was an impressive response rate in the second-line setting compared to previous trials in second-line settings for mCRC. In regard to OS, similar to the PRIME trial, it was not statistically significant but was numerically improved in patients receiving panitumumab (14.5 vs 12.5 months). The KRAS mutant group did not benefit from the addition of panitumumab to FOLFIRI, although they did not appear to have done worse either, unlike in the PRIME trial. Both the 181 and PRIME studies confirm the benefit of adding panitumumab to chemotherapy with regard to improvement in PFS. However, this benefit is restricted to those patients with KRAS wild-type tumors.

H&O What kinds of adverse events were seen in these studies?

EC The adverse events seen in the 181 study and the PRIME study were those that we would expect to see with an EGFR antibody such as panitumumab. Skin toxicity, which was not seen in the control group, was observed in both studies. This is a very well-known class effect of EGFR antibody therapy. There were also several infusion reactions. Generally, the regimen appears to be well tolerated. It is evident that the main adverse events were due to a class effect, as cetuximab (Erbitux, ImClone/Bristol-Myers Squibb) is also known to cause skin toxicities and infusion reactions.

H&O What factors influence whether a patient should receive first-line or second-line panitumumab?

EC We do not know whether this regimen is better in the first- or second-line setting. However, in the first-line setting, improvement in PFS was observed in the KRAS wild-type group compared to FOLFOX alone. First-line therapy is usually the therapy on which patients stay the longest and thus the skin toxicity may be a quality of life issue for some patients; they need to stay out of the sun, and these toxicities can affect patients' social lives.

A patient who is receiving second-line treatment is usually a patient who has progressed on some type of chemotherapy, usually FOLFOX with bevacizumab (Avastin, Genentech). In certain cases, when a physician needs to do a liver resection or if the patient is very symptomatic from his or her disease and it is necessary to maximize the chance of tumor shrinkage, it would be very appropriate to administer a regimen like FOLFIRI with panitumumab because of the high response rate.

H&O How has the role of predictive markers evolved in CRC?

EC The FDA has issued a recommendation that KRAS testing be done before instituting EGFR antibody therapy; this applies for cetuximab and panitumumab. Currently, many studies have been modified or are now being written to incorporate KRAS testing when an EGFR antibody in CRC is involved. For studies that do not exclude patients based on KRAS status, a justification (rationale for drug's use, reason KRAS testing is excluded) is necessary. For example, if a study does not require patients to be KRAS wild-type, is it because another agent will be added that will negate this issue or is it being used for a different purpose, such as a radiation sensitizer, in which case EGFR status may not matter as much. Outside of clinical trials, it is highly recommended to do KRAS testing.

There are also data that patients with the V600E BRAF mutation do not benefit from EGFR antibody therapy. This mutation occurs in approximately 10% of all colon cancers, and the studies that demonstrated a lack of benefit to EGFR antibody therapy have all been retrospective and small in nature. However, the data are highly suggestive and warrant further study.

H&O Are there any ongoing studies with panitumumab and combination chemotherapy?

EC PEAK is a phase II study of panitumumab plus modified FOLFOX6 versus bevacizumab (Avastin, Genentech) plus modified FOLFOX6 in the first-line setting for wild-type KRAS patients with mCRC. It is currently recruiting patients. The primary endpoint is PFS. The study will hopefully provide data on which biologic is better in first-line treatment. Another study, SPIRIT, is also ongoing. This is a randomized phase II study of panitumumab plus FOLFIRI versus bevacizumab plus FOLFIRI in the second-line setting. The goal with this study is to answer the question of which biologic is better in the second-line

setting after treatment with an oxaliplatin and bevacizumab-containing regimen for KRAS wild-type tumors.

H&O What are some of the challenges of treating CRC with EGFR antibodies?

EC One of the challenges we see in patients with CRC is the lack of response in the KRAS mutant population. Although we are able to study EGFR therapies and evaluate their efficacy alone and in combination, we still do not have a treatment option for patients with mutant KRAS tumors. Therefore, clinical trials are very important for patients with this mutation. Although these patients do not benefit from EGFR antibodies now, it does not mean it is not a possibility in the future. If there was an agent that could bypass the KRAS mutation and work synergistically with EGFR antibodies, it could possibly be beneficial for these patients. For wild-type KRAS patients who have progressed on all of the classes of drugs FDA-approved for mCRC, best supportive care or a clinical trial are the only options. Therefore, it is clear that we need to develop more treatment options not only for mutant KRAS patients, but also for wild-type patients who become resistant to currently available therapies.

Suggested Readings

Peeters M, Price T, Hotko Y, et al. Randomized phase 3 study of panitumumab with FOLFIRI vs FOLFIRI alone as second-line treatment (tx) in patients (pts) with metastatic colorectal cancer (mCRC). *European Journal of Cancer Supplements.* 2009;7:9-10.

Douillard J, Siena S, Cassidy J, et al. Randomized phase 3 study of panitumumab with FOLFOX4 compared to FOLFOX4 alone as 1st-line treatment (tx) for metastatic colorectal cancer (mCRC): the PRIME trial. *European Journal of Cancer Supplements.* 2009;7:6.