

ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

Section Editor: James L. Abbruzzese, MD

Integration of the Anti-EGFR Agent Panitumumab into Clinical Practice in Metastatic Colorectal Cancer

Eric Van Cutsem, MD, PhD
Professor, Digestive Oncology Unit
University Hospital Gasthuisberg
Leuven, Belgium

H&O What is the mechanism of action of panitumumab?

EVC Panitumumab (Vectibix, Amgen) is a human monoclonal antibody that binds to the epidermal growth factor receptor (EGFR), thereby blocking and inhibiting different downstream signaling cascades, leading to inhibitory effects on tumor growth, metastasis, and cell proliferation. In preclinical models, it has been shown that the EGFR is important in activating different signal transduction pathways. By blocking this receptor, panitumumab interferes with such signaling, also inducing apoptosis, decreasing proinflammatory cytokine and vascular endothelial growth factor production, and internalizing EGFR.

H&O How does panitumumab differ from other EGFR inhibitors in clinical use for metastatic colorectal cancer?

EVC Panitumumab is a human IgG2 monoclonal antibody approved in the US as a single agent for EGFR-expressing chemorefractory colorectal cancer. There are also small-molecule tyrosine kinase inhibitors of EGFR under investigation in the setting of metastatic colorectal cancer. Cetuximab (Erbix, Bristol-Myers Squibb/ImClone) is another anti-EGFR monoclonal antibody approved in the United States for use in EGFR-expressing irinotecan (Camptosar, Pfizer)-refractory metastatic colorectal cancer as a single agent or in combination with irinotecan. Cetuximab is a chimeric IgG1 antibody. Unlike panitumumab, cetuximab has been shown to affect antibody-dependent cellular cytotoxicity. Another anti-EGFR agent

under investigation is matuzumab (EMD Pharmaceuticals/Merck), which is a humanized monoclonal antibody. There are also small-molecule tyrosine kinase inhibitors of EGFR under investigation in metastatic colorectal cancer, but available data indicate that tyrosine kinase inhibitors of EGFR are less active in colorectal cancer.

H&O Which patients are candidates for therapy with panitumumab?

EVC Clinical data on the efficacy of panitumumab exist only in metastatic colorectal cancer patients who are chemorefractory and are shown to express EGFR by immunohistochemistry (IHC). Data do not exist in other disease sites outside of colorectal cancer for this agent. Cetuximab, however, has been shown to be active in combination with platinum-based chemotherapy and in combination with radiotherapy for head-and-neck cancer. It is not known whether expression of EGFR as determined by IHC is actually a good predictor for response for the anti-EGFR agents. Whether a tumor is EGFR1-, EGFR2-, or EGFR3-positive, or whether a large number of tumor cells versus a relatively low number of tumor cells express EGFR, does not appear to affect the activity of these agents. For panitumumab, few data are available in EGFR-nondetectable tumors, but it is known that cetuximab is active in the EGFR-nondetectable tumors as determined by IHC. Therefore, it is expected that panitumumab will also be effective in patients with EGFR-nondetectable tumors, as determined by IHC. At present, EGFR assessment by IHC is not a good tool for predicting response.

H&O Is panitumumab active in combination with cytotoxic chemotherapy?

EVC Whether panitumumab is active in combination with cytotoxic chemotherapy and whether it is active in less advanced stages of colorectal cancer are important questions. The registration study of panitumumab versus best supportive care published in the *Journal of Clinical Oncology* in May 2007 was conducted in chemorefractory colorectal cancer patients. Until recently, there were no data on panitumumab in the frontline treatment of metastatic colorectal cancer. At the World Congress of

Gastrointestinal Cancers in Barcelona, Spain, in June 2007, results from the Panitumumab Advanced Colorectal Cancer Evaluation (PACCE) study were presented. In this randomized phase IIIb trial, patients were treated with a cytotoxic combination of FOLFOX (leucovorin, 5-fluorouracil, and oxaliplatin [Eloxatin, Sanofi-Aventis]) or FOLFIRI (leucovorin, 5-fluorouracil, and irinotecan), and all patients were also treated with bevacizumab (Avastin, Genentech/Roche), with an additional randomization to panitumumab or no panitumumab. The research plan intended 80% of the patients in the study to be treated with FOLFOX and 20% with FOLFIRI, according to the preference of the treating clinicians. The statistical analysis of survival, tumor progression, and progression-free survival in the PACCE study was conducted in the cohort of patients who received FOLFOX; in fact, more than 80% of patients received FOLFOX. The four-drug combination of the two cytotoxics, bevacizumab, and panitumumab was more toxic, and moreover, the time to tumor progression, as well as the survival, was inferior, compared to the combination without panitumumab. There is no clear explanation for this lack of superiority for panitumumab. Why was more toxicity observed in this setting? Is this finding because of some specific properties of the antibodies and in particular, the strong binding nature of panitumumab? Or, is this finding simply a coincidence that will not be the case in future studies? Other trials are ongoing with the four-drug combination of chemotherapy plus bevacizumab with or without cetuximab, which binds less strongly than panitumumab.

Until now, in the setting of colorectal cancer, the cetuximab-including four-drug combination does not appear to be associated with any great safety concerns based on assessment by a data-monitoring committee. Moreover, there is ongoing phase III research with FOLFOX or FOLFIRI with or without panitumumab (ie, without bevacizumab). In this case as well, safety data were assessed and early termination was not recommended.

To make a complex story short, we do not yet have any data that indicate the use of panitumumab outside the setting of chemorefractory patients. We have only data that demonstrate the efficacy of single-agent panitumumab in chemorefractory patients. In the other settings, further results are awaited before any clinical use of panitumumab can be recommended.

H&O Could you discuss the use of anti-EGFR agents in combination with other biologic agents in the setting of chemorefractory colorectal cancer?

EVC An upcoming article in the *Journal of Clinical Oncology* will discuss cetuximab plus bevacizumab in the setting of colorectal cancer, with or without irinotecan-based chemotherapy. To my knowledge, no data have been published on the combination of panitumumab

with another biologic agent, apart from some phase I studies. There were preclinical data published on a combination of a TRAIL receptor 1 agonist and panitumumab, as well as other combinations of panitumumab and new angiogenesis inhibitors. Preclinical data have shown some additive effect, and according to some data, a promising synergistic effect. Studies of panitumumab in combination with other biologics are ongoing and detailed results are awaited. There is a good rationale to combine EGFR and angiogenesis inhibitors, as well as other classes of drugs. Data from a phase I trial in recurrent non-small cell lung cancer were presented at the American Society of Clinical Oncology meeting in 2006 on the combination of cetuximab with gefitinib (Iressa, AstraZeneca), an anti-EGFR tyrosine kinase inhibitor. The combination of these two biologics acting on the same receptor was found to be feasible, with a suggestion of superior activity, which might suggest an additive effect.

H&O Could you discuss the side effects seen with anti-EGFR therapy?

EVC Rash is a side effect specific to the class of EGFR inhibitors. There has been no head-to-head comparison between agents to determine the intensity or frequency of this side effect for each, but using cross-trial comparisons, the rash seems to be similar in severity and frequency with each agent. Also, from my personal experience, the pattern of the rash is similar with panitumumab and cetuximab. Cytotoxics do not cause this rash, so the PACCE study did not show increased rash in patients treated with panitumumab.

There are many data showing a correlation between the degree of rash and activity of the entire class of anti-EGFR agents. Therefore, the more rash patients experience, the more activity panitumumab and cetuximab have. At present, with the information available in patients with chemorefractory metastatic colorectal cancer, clinicians will not stop administering the drug when there is no rash. In this setting, often there are no other good alternative therapies. Furthermore, even if rash does not occur, although the chance of having a beneficial response is lower, there is still a low chance of tumor growth control or response with no or minimal rash. Two questions that follow from the observations of rash in this setting are: what should the clinician do if a patient has no rash and should the dose be increased if there is no skin toxicity? These questions have been investigated with cetuximab in the EVEREST study, in which the dose of cetuximab was increased in patients with no rash or slight rash. It was found that some more response—and some more rash—could be induced with dose increases. Although this trial was nicely designed, it was not powered for a phase III study. As a result, at present, the recommendation cannot be given to clinicians that they should increase the dose if

there is no rash. For panitumumab, there has not yet been a similar study.

Another side effect that can occur with anti-EGFR antibodies is allergic reaction. This event is not frequent, but is slightly more frequent with cetuximab than with panitumumab because the latter is a human monoclonal antibody. More recently, it has been described that EGFR-inhibiting antibodies compromise renal magnesium retention capacity, leading to hypomagnesemia in many patients.

Anti-EGFR antibodies do not increase most of the typical side effects of chemotherapeutic agents with which they are combined. Diarrhea has, however, been observed to be increased in patients treated with a combination of chemotherapy and an anti-EGFR agent. For example, in a study of FOLFIRI with or without cetuximab, there was slightly more diarrhea seen in patients treated with cetuximab and FOLFIRI as opposed to FOLFIRI alone. In patients who received panitumumab in the PACCE study, diarrhea was also more pronounced. This finding is likely due to an effect of the EGFR antibody itself.

H&O What is the future of panitumumab in less advanced stages of colorectal cancer?

EVC This question is difficult to answer today, and my point of view may differ from that of Amgen, the manufacturers of panitumumab. The data from the PACCE trial were certainly disappointing; many researchers and clinicians expected that an additional positive effect with the combination of panitumumab, bevacizumab, and chemotherapy would be seen. I believe the fate of the combination of panitumumab and chemotherapy in colorectal cancer will be determined by two large phase III studies with FOLFOX with or without panitumumab in the first-line setting and FOLFIRI with or without panitumumab in the second-line, as well as by the possibility to find a predictive molecular marker for response. If these two randomized studies are positive and show an acceptable safety profile, then panitumumab will be integrated into the management of patients in earlier stages of metastatic colorectal cancer.

It will also be crucial in the future to discover molecular markers that help us to predict which patients are more or less likely to benefit. If the combination of chemotherapy and panitumumab with or without bevacizumab is associated with toxicity, then its use will be determined by the amount of benefit that can be seen. If there is no benefit, then no one will use the combination, but if future studies show a benefit, then the challenge will be to balance the toxicity with the benefit. It will become necessary to find patients who do benefit more than others, and I believe this will be the focus of translational research with molecular markers. Many research projects are focusing on this area. Our team in Leuven

is working on this challenge. Data from several studies with cetuximab (and it is expected that panitumumab will be the same) have shown that patients with a wild-type K-Ras tumor have a better outcome than patients with the K-Ras mutation in their tumor. The distinction is not black and white, but K-Ras mutations are likely to help identify patients who benefit more or less. It has indeed been shown that patients with a K-Ras mutation have no response after treatment with cetuximab or cetuximab plus irinotecan in chemorefractory metastatic colorectal cancer. Almost all objective responses are seen in the wild-type K-Ras group. Data elucidating the correlation of the K-Ras status and activity of panitumumab are not yet available. Whether K-Ras mutation status also plays a role in the prediction of response in first-line treatment when cetuximab or panitumumab is combined with chemotherapy is not known. The data we have with cetuximab now are in patients in the second, third, or fourth line, and whether this finding holds true for first-line therapy is unclear. Approximately 40% of patients with metastatic colorectal cancer have a K-Ras mutation.

Other markers need to be explored for their possible role in prediction of response. Possible candidates are the ligands. Additional markers that might help identify patients who benefit are epiregulin and amphiregulin. Data from a US study with cetuximab suggest that epiregulin and amphiregulin may help to predict for outcome. My coworkers also presented data recently, showing that patients receiving cetuximab who have high epiregulin and amphiregulin have better outcomes.

In the future we may therefore use a panel of different markers, including K-Ras and epiregulin and amphiregulin, as well as other yet-to-be-identified markers, for the selection of patients. If we can identify patients who will benefit, and if we can see some benefit in ongoing phase III studies, I am certain clinicians will be using panitumumab and cetuximab more widely in the future in less advanced stages of colorectal cancer.

Suggested Readings

Van Cutsem E, Peeters M, Siena S. 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;25:1658-1664.

Naret CL, Ramalingam S, Beattie L, et al. Total blockade of the epidermal growth factor receptor with the combination of cetuximab and gefitinib: a phase I study for patients with recurrent non-small cell lung cancer (NSCLC). *J Clin Oncol.* 2006;24(18S pt 1): Abstract 17045.

Hecht R, Chidiac T, Mitchell E et al. An interim analysis of efficacy and safety from a randomized controlled trial of panitumumab with chemotherapy plus bevacizumab in metastatic colorectal cancer. *Ann Oncol.* 2007;18(S7): Abstract O-0033.

Van Cutsem E, Peeters M, Gelderblom H et al. Cetuximab dose-escalation in MCRC patients with no or slight skin reactions on standard treatment (Everest). *Ann Oncol.* 2007;18(S7): Abstract O-0034.

Tejpar S, Peeters M, Humblot Y, et al. Dose-escalation study using up to twice the standard dose of cetuximab in patients with metastatic colorectal cancer (mCRC) with no or slight skin reactions on cetuximab standard dose treatment (EVEREST study): preliminary data. *J Clin Oncol.* 2006;24(18S pt 1): Abstract 3554.

Berlin J, Posey J, Tchekmedyian S, et al. Panitumumab with irinotecan/leucovorin/5-fluorouracil for first-line treatment of metastatic colorectal cancer. *Clin Colorectal Cancer.* 2007;6:427-432.