Monoclonal Antibodies in Colorectal Cancer: What We Know

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Monoclonal antibodies to the epidermal growth factor receptor (EGFR) are among the promising novel targeted therapies being explored in colorectal cancer. Two such agents that inhibit EGFR signaling by interfering with ligand-binding are cetuximab (Erbitux) and panitumumab (Vectibix). This review will address the use of cetuximab and panitumumab in chemotherapy-refractory colorectal cancer as well as in front-line therapy for the disease, consider predictors of response and resistance, and outline comparisons between these agents.

Dr. Burtness provides a thorough summary of the clinical experience with the monoclonal antibodies cetuximab (Erbitux) and panitumumab (Vectibix) in the treatment of patients with metastatic colorectal cancer. The following comments are intended to complement her review.

Antibodies consist of two identical heavy chains and two identical light chains that are held together by disulfide bonds. The N terminal of each chain possesses a variable domain that binds antigen through three hypervariable complementarity-determining regions. The C terminal domains of the heavy and light chains form the constant regions, which define the class and subclass of the antibody. The light chains are either of the kappa or lambda types. The amino acid sequence of the constant region of the heavy chains specifies the class of immunoglobulin (IgG in this case) and the subclasses (there are four subclasses of IgG), each of which have different functions. Both cetuximab and panitumumab are competitive inhibitors of the binding of epidermal growth factor (EGF) and other ligands, such as transforming growth factor-alpha, to the human epidermal growth factor receptor (EGFR). EGFR is expressed in normal epithelial tissues, including skin, hair follicles, and gastrointestinal mucosa, and is overexpressed in many human colorectal cancers. Antibody-binding prevents phosphorylation and activation of the EGFR-associated kinases, and interrupts transmission of various growth-promoting signals that regulate transcription of molecules involved with cellular growth and survival, motility, proliferation, and transformation.

Cetuximab

Cetuximab is a recombinant chimeric monoclonal antibody that binds specifically to the extracellular domain of the EGFR. Cetuximab contains the Fv regions of a murine anti-EGFR antibody with human IgG1 heavy and kappa light chain constant regions. Its molecular weight is approximately 152 kDa, and the antibody is produced in a murine myeloma cell culture system. The US Food and Drug Administration (FDA) approved cetuximab in February 2004 under the accelerated approval of biologics regulations based on the safety and efficacy from three studies.[1] Cetuximab was approved for use in patients with colorectal cancer whose tumors stained positive for EGFR using a test kit manufactured by DakoCytomation California, Inc (www.dakousa.com), in combination with irinotecan (Camptosar) in patients whose cancer had progressed on prior irinotecan-based therapy, and as monotherapy in patients who cannot tolerate irinotecan-based therapy.[2] With the recommended dose regimen (400 mg/m² initial dose followed by 250 mg/m² weekly), steady-state concentrations of cetuximab are reached by the third weekly infusion, and the mean half-life is about 4.7 days. In vitro, IgG1 antibodies elicit antibody-dependent cellular cytotoxicity, which can kill cancer cells and may contribute to their overall therapeutic effects. Information presented at the Spring 2007 American Association for Cancer Research meeting suggests that cetuximab administered to patients with metastatic colorectal cancer in a 500 mg/m² dose every 2 weeks shows a similar pharmacokinetic profile, and no increased toxicity compared to the weekly dosing regimen.[3]

Panitumumab

Panitumumab is a recombinant fully human IgG2 kappa monoclonal antibody that also binds specifically to the extracellular domain of the human EGFR. Its molecular weight is approximately 147 kDa, and the antibody is produced in a genetically engineered Chinese hamster ovarian cell culture system.[4] The FDA approved panitumumab in September 2006 for the treatment of patients with EGFR-expressing, metastatic colorectal carcinoma with disease progression on or following...
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fluoropyrimidine-, oxaliplatin (Eloxatin)-, and irinotecan-containing chemotherapy regimens. The
approval was made on the basis of the results of a single, open-label, randomized, multinational
study that enrolled 463 patients with metastatic colorectal cancer who were randomized to receive
either best supportive care alone or best supportive care plus panitumumab. This trial showed
improvement in progression-free survival with panitumumab [5]. With the recommended dose
regimen (6 mg/kg over 1 hour every 2 weeks), steady-state concentrations of cetuximab are reached
by the third weekly infusion, and the mean half-life is about 7.5 days.

Comparisons and Conclusions
It is unlikely that direct comparisons of these two antibodies will be pursued in randomized clinical
trials. There is greater clinical experience with cetuximab, since it has been available for evaluation
in clinical trials for a longer time than panitumumab. Emerging information on alternative schedules
may affect the relative costs of therapy. Panitumumab offers the advantage of a lower incidence of
serious hypersensitivity reactions, and anecdotal information suggests that some patients who
develop infusion-associated reactions with cetuximab may be treated with panitumumab. I agree
with Dr. Burtness that there is no evidence of therapeutic benefit for employing either anti-EGFR
antibody in patients who experience disease progression on the other antibody.

Ongoing studies are evaluating the worth of either cetuximab or panitumumab as a component of
first-line therapy for patients with metastatic colorectal cancer. The results of a randomized study of
irinotecan, 5-FU, and leucovorin with or without cetuximab in the first-line treatment of patients with
metastatic colorectal cancer were presented at the recent meeting of the American Society of
Clinical Oncology. Over 1,200 patients were randomized to receive either FOLFIRI alone or FOLFIRI
plus cetuximab. The addition of cetuximab was associated with a significant improvement in
progression-free survival (8.9 vs 8.0 months, \( P = .036 \)) and response rate (46.9% vs 38.7%, \( P =
.005 \)).[6] Amgen issued a press release in March 2007 regarding a preliminary preplanned interim
analysis of a randomized trial that explored the benefit of adding panitumumab to therapy with
bevacizumab (Avastin) given with 5-FU, leucovorin, and either oxaliplatin or irinotecan. The interim
analysis revealed a statistically significant difference in progression-free and overall survival in favor
of the control arm [7]. This surprising announcement raises a cautionary note regarding the
premature incorporation of multiple agents as initial therapy for patients with metastatic colorectal
cancer outside of a clinical trial setting. Given the high cost of the newer agents, it will be critical to
incorporate cost-effectiveness analysis into long-term clinical studies. This is particularly important
with the availability of multiple lines of therapy for patients with metastatic colorectal cancer.

Disclosures: Dr. Grem is a speaker and consultant for Amgen.

References:
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