Panitumumab, a Monoclonal Anti–Epidermal Growth Factor Receptor Antibody in Colorectal Cancer: Another One or the One?

Wells A. Messersmith and Manuel Hidalgo

Panitumumab (Vectibix, Amgen, Inc.) is a fully human IgG2 monoclonal antibody targeting the epidermal growth factor receptor (EGFR). Panitumumab, formerly called ABX-EGF, was initially developed by Abgenix using the XenoMouse transgenic technology. This methodology is based on inactivating the mouse immunoglobulin genes that are replaced by a megabase gene containing the human heavy and κ chains. The result is the generation of fully human antibodies that do not contain murine portions of the IgG molecule as chimeric antibodies do. This property avoids the formation of human antimouse antibodies, which may result in more frequent hypersensitivity reactions and shorter half-life (1).

Panitumumab binds specifically and selectively to the EGFR, preventing binding of activating ligands, such as the EGF and transforming growth factor-α. In preclinical studies, this action reduces EGFR signaling and causes cell cycle arrest. The panitumumab-coated receptor is rapidly internalized resulting in receptor down-regulation although it is not clear if the receptor is degraded or recycled to the plasma membrane. In selected studies, panitumumab reduces angiogenesis as well. The preclinical activity of the agent is more pronounced in cells expressing the EGFR at levels of ≥15,000 per cell and inactive in EGFR-negative tumors. As with most of the EGFR-targeting agents, preclinical studies do show synergistic effects when combined with chemotherapy and radiation therapy (2, 3).

The initial clinical development of panitumumab aimed to define the most effective and safe dose and schedule for patient treatment. Based on previous experiences with cetuximab, a chimeric anti-EGFR antibody, it was unlikely that an approach based solely on toxicity was appropriate to that end. Two important factors were considered in the design of these studies. First, it was expected that clearance of the antibody would be dose dependent, reflecting full saturation of EGFR binding sites because the principal mechanism of elimination of the agent is by degradation of antibody-occupied receptors (4). Second, it was already apparent that patients who developed skin rash after treatment with EGFR inhibitors had better treatment outcome. Thus, the phase I studies with the agent recommended a dose of 2.5 mg/kg based on saturation of elimination, frequency and severity of rash, and achievement of plasma levels above the levels needed for activity in preclinical models (5). Subsequent studies showed that a dose of 6 and 9 mg/kg resulted in equivalent exposure and that a loading dose was not needed to achieve the desired plasma levels (6). As discussed below, the dose of 6 mg/kg was selected for phase III studies.

It should be noted, however, that there are some limitations in the criteria used for dose selection. Although the hypothesis of the EGFR sink is appealing and pharmacokinetically intuitive, the notion that receptor saturation is the only and principal factor accounting for the observed saturation in clearance has not been shown experimentally. Second, although there is significant information supporting the association between skin rash and treatment outcome, including both response rate and survival with EGFR-targeting agents, and that the frequency and severity of rash is dose related, there is not direct information to indicate a dose-dependant antitumor effect of these agents (7, 8). The underlying reason why rash is related to outcome is indeed not known and it could be that the development of rash could just indicate a state of vulnerability to EGFR inhibition that could be genetically based and not pharmacologic (9). Thus, the significance of the rash may not be the same at the different doses and schedules tested. Studies are in progress to address these questions. Importantly, there are not comparative pharmacodynamic studies among the different doses and schedules tested. These studies are difficult to do (paired tumor biopsies) and are limited by methodologic aspects but eventually they will be the “gold standard” for dose selection in early clinical trials with targeted anti-cancer agents.

Notwithstanding the above-mentioned limitations, the dose of 6 mg/kg every other week was selected for definitive clinical trials. This dose is convenient and very well tolerated. As expected, 89% of patients developed cutaneous rash, which was grade 3 in 16% of the patients, typical of EGFR inhibitors when used with this dose schedule. Other frequent toxicities (>20% of patients) included fatigue, abdominal pain, nausea, diarrhea, constipation, and nail abnormalities. Up to 40% of patients developed hypomagnesemia with prolonged administration; therefore, close follow-up of electrolyte levels and proper replacement is recommended. Only 4% of the patients developed hypersensitivity reactions, which were serious in 1% (10). This is in contrast to the 19% and 3%, respectively, reported for cetuximab, a chimeric anti-EGFR antibody approved for clinical use (Table 1). This suggests that the humanized nature of panitumumab may indeed reduce the occurrence of this toxicity event. A pooled safety analysis in 920 patients treated with panitumumab...
showed that the agent was generally well tolerated with a consistent toxicity profile across the studies. Less than 20% of patients developed grade 3 to 4 toxicity and only 4% discontinued treatment because of toxicity events. The most common toxicities mild to moderate were skin related, gastrointestinal, and hypomagnesemia. Importantly, grade 3 to 4 infusion reactions were rare (0.05%) and the drug can be safely administered without premedication. Less than 5% of patients formed anti-panitumumab antibodies post-dose with no discernible effects in drug pharmacokinetics or toxic events (11).

Disease-oriented studies with panitumumab have focused on metastatic colorectal cancer (mCRC). Phase II single-agent studies have shown an ~10% response rate in patients with chemotherapy-resistant mCRC who expressed the EGFR. Subsequently, the safety and efficacy of panitumumab were studied in an open-label, multinational, randomized, controlled trial of 463 patients who expressed EGFR (>1+ in ≥1 cell by the DAKO EGFR pharmDX test kit; ref. 10). Patients were randomized 1:1 to receive panitumumab at a dose of 6 mg/kg given once every 2 weeks plus best supportive care (n = 231) or best supportive care alone (n = 232) until investigator-determined disease progression. Patients allocated to best supportive care were allowed to cross-over to panitumumab on disease progression. Patients treated with panitumumab had a significantly longer progression-free survival rate (90 versus 64 days; P = 0.0001). No differences in overall survival were noted but, as mentioned above, best supportive care–treated patients had the option to receive panitumumab progression. Based on these results, the U.S. Food and Drug Administration—approved panitumumab for treatment of EGFR-positive refractory mCRC patients.

Despite being a targeted agent, panitumumab reaches the clinic without a clear answer as to which patients to target. The agent has been developed and is approved for EGFR-expressing tumors as determined by immunohistochemistry. Patients with EGFR expression in >1% of cells were enrolled in the studies. Is the EGFR expression indeed important? The most logical answer is that for an agent that targets the EGFR, its expression should be important. An interesting observation is that an assessment of outcome as a function of receptor expression failed to identify a relationship between level of expression, either by staining intensity or proportion of positive cells, and outcome (12). Notwithstanding the retrospective and exploratory nature of this analysis, the lack of a level of expression-outcome relationship argues against the importance of EGFR expression per se as a predictor of patient outcome. A recently reported phase II study with cetuximab in which 346 patients with EGFR-positive mCRC were treated with the agent also failed to identify a relationship between levels of EGFR and outcome (13). Because patients lacking any EGFR expression were not enrolled, however, the question cannot be answered definitively. In other words, the possibility of a dichotomy threshold between no expression and any expression cannot be ruled out.

The biological plausibility of this observation is, however, far from obvious. How can it be that a tumor with just 1% of cells expressing low levels of EGFR has the same likelihood of response to an agent that supposedly only targets that population than a tumor where 90% of cells express high levels of the target? It is reasonable to think that other factors may be involved. Two pieces of information are pertinent to this discussion. One is the observation that patients with allegedly EGFR-negative tumors respond to cetuximab, an agent with virtually the same mechanism of action as panitumumab (14). Another is the differences in EGFR expression observed between primary tumors and corresponding liver metastasis (15). These observations have important implications. One is that tumors are indeed heterogenous with regards to expression of the EGFR and that reliance on expression based on archival material sometimes remote in time and location from the lesion to be treated to assess EGFR expression may be misleading. Indeed, our ability to classify tumors with regards to EGFR expression may need to be based on sampling of multiple lesions right before treatment. This type of assessment is not realistic unless nuclear medicine or imaging techniques are developed that permit the noninvasive assessment of the receptor expression for widespread clinical use.

Another explanation is that the methods used to determine receptor expression (i.e., immunohistochemistry) are just not reproducible and do not provide reliable information (16, 17). Very few studies have compared the results of immunohistochemistry with other measures of receptor expression and lacking a “gold standard” to compare, it is not possible at the present time indeed to determine if a tumor is truly EGFR negative or not. To complicate the matter further, a study that evaluated EGFR mRNA expression found an inverse association between levels of the messenger and the activity of cetuximab (18). At the present time, therefore, the link between receptor expression and the activity of EGFR-targeting antibodies is, at best, weak. This has important practical applications as clinicians often face patients with EGFR-negative tumors for

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<th>Table 1. Comparison between Food and Drug Administration–approved EGFR-targeted antibodies</th>
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<td><strong>Property</strong></td>
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<td>Combination with chemotherapy studies</td>
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<tr>
<td>FDA “black-box” labeling</td>
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<td>Cardiopulmonary arrest*</td>
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Abbreviations: ADCC, antibody-dependent cell-mediated cytotoxicity; FDA, Food and Drug Administration; H1, histamine receptor type 1.

*For head and neck cancer patients treated with radiation and cetuximab.

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whom this class of drugs are the best palliative option. In our opinion, as well as many others, these patients should not be excluded from treatment based only on this point (16).

It is clear that better predictors of EGFR-targeted agents are needed. What are the suspects? A retrospective study evaluated the association between EGFR gene amplification and response to panitumumab (9 patients) or cetuximab (22 patients). Patients with EGFR amplification with a ratio of EGFR to nucleolus greater than 3 were more susceptible to the agent as shown by a higher response rate (19). An interesting aspect of this study is the demonstration of heterogeneity across tumor areas with regard to EGFR amplification with tumor areas showing normal genome versus other areas showing clear amplification. A larger study with cetuximab, however, failed to show an association between gene copy number and response or progression-free survival (13). A difficult-to-explain relationship was found between gene copy number and survival. Although there are methodologic differences between these two studies that could influence the observations, it is clear that prospective, well-designed studies are needed to address this question. The frequency of EGFR tyrosine kinase mutations is very low or absent in mCRC and it is not clear if these mutations really confer a greater susceptibility to EGFR-targeted antibodies (13, 20). Mutations in other genes in the EGFR pathway, such as PI3K, KRAS, and BRAF, are more frequent in CRC but their relationship with response to EGFR-targeted antibodies is less well studied and also conflicting. In particular, although some studies suggest that patients with KRAS mutations may be resistant to these agents, other studies do not show such a relationship (19, 21). Finally, other groups have focused on studying the expression of genes related to the EGFR pathway by PCR (18). An initial report from this work suggests that levels of expression of EGFR, cyclooxygenase-2, and vascular endothelial growth factor may be relevant. Additional prospective studies with well-validated methodologies are needed to determine which patients are best candidates for this agent.

The importance of immunoglobulin subtype of the EGFR-targeting antibodies is controversial. Cetuximab is an IgG1 antibody and therefore can activate the antibody-dependent cell-mediated cytotoxicity mechanism. The ability of cetuximab to induce antibody-dependent cell-mediated cytotoxicity has been documented in vitro with esophageal squamous cell carcinoma cell lines. Theoretically, as an IgG2 antibody, panitumumab does not have this property (22). The clinical relevance of this difference remains a significant unknown. Given the similar single-agent activity, it is doubtful that the difference is important in monotherapy, but the combination studies with panitumumab are still pending.

In summary, panitumumab increases our repertoire of agents to treat mCRC. The available clinical data are the strongest for a single-agent anti-EGFR monoclonal antibody in this disease at the present time. The principal clinical feature of the agent is the potential for less hypersensitivity reactions in clinical practice. The every other week schedule, lack of loading dose, and cost are not necessarily clinically relevant differential features with cetuximab. It is likely that these two drugs have very similar clinical efficacy although head-to-head trials have not been performed. The PACCE trial, which showed (via press release only) worse progression-free survival of panitumumab/FOLFOX/bevacizumab compared to FOLFOX/bevacizumab alone in untreated mCRC patients, complicates the picture and demonstrates that assumptions regarding additive efficacy of combinations are incorrect. Future directions with panitumumab treatment will include the incorporation of the agent in combination with other chemotherapy in multiple settings, combinations with other targeted agents, and exploitation of the agent in curative settings such as in patients with resectable liver metastases.

References
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