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Panitumumab

Prop INN

Oncolytic
Anti-EGFR Human Monoclonal Antibody

ABX-EGF
E7.6.3

Immunoglobulin, anti-(human epidermal growth factor receptor) (human monoclonal ABX-EGF heavy chain), disulfide with human monoclonal ABX-EGF light chain, dimer

CAS: 339177-26-3

EN: 276195

Abstract

The epidermal growth factor receptor (EGFR) is a transmembrane glycoprotein associated with autonomous cell growth, invasion and angiogenesis, which are key features of cancer. Inhibition of the extracellular ligand-binding domain of EGFR has been pursued as a therapeutic strategy in the treatment of cancers overexpressing EGFR, and monoclonal antibodies targeting this site have been developed, including panitumumab (ABX-EGF), a fully human IgG_2 monoclonal antibody directed against EGFR. In preclinical studies, panitumumab resulted in significant inhibition of the growth of a variety of human tumor xenografts, and completely prevented the formation of human epidermoid carcinoma A-431 tumors in nude mice. It also completely eradicated established tumors. The antitumor activity of panitumumab was further demonstrated in mice bearing human prostate and renal cell cancer xenografts, with significant inhibition of tumor growth in these models. Clinical studies in patients with advanced cancers have shown a low pharmacokinetic variability, allowing consistent exposure to the drug. Phase II studies in patients with colorectal and renal cell carcinoma have shown that panitumumab is well tolerated and has encouraging clinical activity as monotherapy in patients refractory to standard chemotherapeutic regimens. Panitumumab has also been evaluated in patients with non-small cell lung cancer, and pivotal phase III studies have been initiated in third-line colorectal cancer.

Introduction

The epidermal growth factor (EGF) family of membrane receptors has been well characterized in cancer research. Conclusive evidence from studies in the last two decades has demonstrated that dysregulation of the epidermal growth factor receptor (EGFR, also known as HER1, ErbB1) is associated with the principal characteristics of cancer, including autonomous cell growth, invasion and angiogenesis. The EGFR is a transmembrane glycoprotein with an extracellular ligand-binding domain and an intracellular domain with tyrosine kinase activity for signal transduction. Ligand binding activates the receptor and its signaling pathways, leading to the activation or modulation of cellular processes. The receptor is expressed on healthy cells originating from all three germ cell layers, particularly those of epithelial origin, as well as on malignant tissues, and EGF and transforming growth factor-α (TGF-α) are the most important stimulatory ligands for EGFR. Overexpression of EGFR has been demonstrated in a wide variety of malignant cells, and this increase in receptor levels has been associated with a poor clinical prognosis. Thus, therapeutic strategies to inhibit EGFR and EGFR-related pathways have been pursued, including the development of monoclonal antibodies against the extracellular ligand-binding domain of EGFR. This targeted approach to the treatment of cancer limits the toxicity to healthy tissues associated with traditional cytotoxic therapies, and potentially allows the opportunity for synergistic activity when combined with these therapies (1, 2).

Panitumumab (ABX-EGF) is a fully human IgG_2 monoclonal antibody directed against EGFR. It was developed from a panel of such antibodies using XenoMouse™ technology, whereby human immunoglobulin genes were introduced into mice genetically engineered to lack functional mouse immunoglobulin expression (1-6).

Pharmacological Actions

In vitro studies were conducted with the human cervical epidermal carcinoma cell line A-431, which expresses

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more than 1 million EGFRs per cell. Panitumumab bound to EGFR with high affinity (K_D = 50 pM; IC_{50} = 3 nM). It blocked the binding of both EGF and TGF-α to the EGFR, resulting in inhibition of EGF-activated tyrosine phosphorylation of the EGFR. This effect was concentration-dependent, as demonstrated in A-431 cells cultured overnight and incubated with or without EGF, in the presence or absence of concentrations of panitumumab ranging from 0.2 to 133 nmol/l. The highest concentration resulted in almost total inhibition of EGFR phosphorylation. Cell activation and cell proliferation were correspondingly inhibited at the G_0/G_1 interphase, in a concentration-dependent manner, with a maximal inhibition of 50-60% in A-431 and MDA-MB-468 breast cancer cell lines. Inhibition of the tyrosine phosphorylation of EGFR is mediated by rapid internalization of the receptor, as well as blockade of the EGF binding site on the receptor (3-8).

The effect of panitumumab on human tumor xenografts expressing different levels of EGFR was studied in nude mice. The numbers of EGFRs expressed on human breast, epidermal, renal, pancreatic, prostate, ovarian and colon carcinoma cell lines were quantitated by analytical flow cytometry of immunofluorescently stained cells. The cells expressed between 0 (colon SW707) and 1.6 million copies per cell (breast MDA-MB-468). The cells were inoculated into mice, which were then treated with panitumumab at a dose of 1 mg i.p. twice a week for 3 weeks. Panitumumab treatment resulted in significant growth inhibition of all tumors expressing 17,000 or more EGFRs per cell, supporting the concept that blocking the EGFR pathway in cancer cells overexpressing the receptor leads to tumor growth arrest. A variety of tumors were inhibited with EGFR expression ranging from 17,000 to 1.6 million per cell, indicating that panitumumab activity is not restricted to tumors expressing extremely high levels of EGFR (3, 4, 6).

The effect of panitumumab on established tumors *in vivo* was investigated in mice. Athymic mice were injected subcutaneously with A-431 human tumor cells. Panitumumab was administered twice a week for 3 weeks for a total dose of 1.2 mg or 6 mg. None of the mice treated with panitumumab developed tumors for more than 8 months after the last antibody injection, whereas all mice in the control groups had developed tumors by day 10. The effect of panitumumab on established tumors was also investigated by treating mice with 1 mg twice a week once the tumors had reached a defined size. Continuous tumor regression was observed, which resulted in complete tumor eradication in all mice treated with panitumumab. The effect of the antibody was long lasting, in contrast to untreated mice or mice treated with control antibody, in which aggressive growth of the tumors continued. The profound effect of panitumumab was observed in established tumor xenografts up to 1.2 cm^3 in size. Panitumumab was also effective when given by different administration routes and the elimination of tumor cells was supported by histopathological analysis (3-6).

The role of panitumumab in angiogenesis was investigated by measuring vascular endothelial growth factor (VEGF) and IL-8 production in cultured A-431 cells, transformed endothelial cells (ECV304) and breast carcinoma cells (MDA-MB-468). Basal VEGF production was inhibited by more than 75% in A-431 cells compared with controls. In all cells, basal and EGF-stimulated VEGF and IL-8 production was inhibited by over 70%, suggesting that blockade of angiogenesis may contribute to the effects of panitumumab on tumor growth. Inhibition of tumor angiogenesis by panitumumab was also demonstrated indirectly in prostate cancer DU 145 cells *in vitro*, by inhibition of spontaneous and EGF-induced VEGF and IL-8 production (7, 9).

The efficacy of panitumumab in suppressing the metastasis of human breast cancer MDA-MB-231 cells was demonstrated in SCID mice, and additive antitumor activity was evident when panitumumab was administered as combination therapy with doxorubicin, cisplatin or docetaxel in models of human epidermoid, prostate and lung carcinomas (8).

The potential antitumor activity of panitumumab against prostate cancer was investigated in three human prostate cancer cell lines – DU 145, LNCaP and PC-3 – expressing approximately 100,000, 80,000 and 30,000 copies of EGFR per cell, respectively. The cells were treated in culture for 7 days with panitumumab 5 μg/ml. Following an additional 14 days' culture without treatment, tumor cell colony formation was inhibited by 38% for DU 145 cells and by 13% for LNCaP and PC-3 cells. Administration of panitumumab 0.5 mg twice weekly for 3 weeks to nude mice also resulted in significant growth inhibition of DU 145 and PC-3 xenografts. When panitumumab was administered in combination with doxorubicin, the tumor growth inhibition was greater than with panitumumab alone (9).

The correlation of panitumumab tumor penetration and EGFR saturation with pharmacokinetic, pharmacodynamic and antitumor activity was studied in an A-431 xenograft model system. Immunohistochemical analysis demonstrated a dose- and time-dependent tumor penetration, with 33%, 80% and 100% immunoreactivity, respectively, after 96 h in mice administered 20, 200 and 500 μg panitumumab. Double-labeling for EGFR and panitumumab showed a progressive replacement of EGFR staining until the majority of viable tumor tissue stained predominantly for panitumumab. This was correlated with antitumor activity, with dose-dependent tumor regressions at lower doses (5 and 20 μg) and complete regressions at higher doses (200 and 500 μg) in mice bearing established A-431 tumor xenografts (10).

Panitumumab was also investigated for its antitumor activity in three renal cell cancer cell lines – SK-RC-29, Caki-1 and Caki-2 – expressing approximately 77,000, 69,000 and 258,000 copies of EGFR per cell, respectively. Pretreatment with panitumumab 5 μg/ml for 7 days resulted in inhibition of tumor cell colony formation by 63% for Caki-1 and 20% for Caki-2 cells. Treatment with panitumumab 1.0 mg twice weekly for 3 weeks also

resulted in significant growth inhibition of well-established SK-RC-29, Caki-1 and Caki-2 tumor xenografts in nude mice (77%, 31% and 48%, respectively) (11).

Dosing regimens for the administration of panitumumab to patients were predicted using a biomathematical model of A-431 tumor growth. The serum level of panitumumab producing 50% suppression of mitosis (IC_{50}) was calculated, and simulations of weekly dosing in humans indicated estimates of IC_{90} values at a dose of 1 mg/kg/week and complete tumor eradication at a dose of 3 mg/kg/week. The simulations supported twice-weekly dosing and provided a strong rationale for combination therapy with cytotoxic chemotherapeutic agents (12).

Clinical Studies

A phase I clinical trial was conducted to estimate the optimum clinical dose and evaluate the pharmacokinetics, pharmacodynamics and safety of panitumumab in 46 patients with advanced cancer. Patients with renal, prostate, non-small cell lung (NSCLC), pancreatic, esophageal or colorectal cancer received weekly doses of panitumumab of 0.01-3.5 mg/kg for 4 weeks. Pharmacokinetic modeling demonstrated that saturation of EGFR clearance was achieved at a dose of 2 mg/kg. Transient acneiform rash was also observed in over 90% of patients who received at least one dose at this level, a clinical response that correlates with EGFR blockade. There was a low pharmacokinetic variability and no human anti-human antibodies (HAHA) were detected in any patient. Stable or responding patients could continue treatment every other week for a further 6 months or until disease progression. Panitumumab was well tolerated, with no allergic reactions, infusion-related or serious adverse events. Biological activity was observed at low doses. One patient with colorectal cancer treated at the 2.5 mg/kg dose had a partial response lasting for over 7 months and 6 patients had a minor response/stable disease (13-15).

In a two-part phase II study in patients with metastatic renal cell cancer, patients were treated at each of 4 dose levels with panitumumab: 1.0, 1.5, 2.0 and 2.5 mg/kg (part 1). Patients who had failed or were unable to receive IL-2/interferon alfa therapy were administered 8 weekly infusions of panitumumab. Stable or responding patients could continue to receive weekly treatment for a further 8 months or until disease progression. In part 1 of the study, 88 patients received at least one dose of panitumumab, with approximately 22 patients being treated at each of the dose levels. Overexpression of EGFR was documented in 95% of patients. All patients completed an 8-week cycle of panitumumab and were evaluable for response, 3 of whom achieved a partial response and 2 a minor response. Disease stabilization was achieved by 50% of patients. Grade 2/3 adverse events attributable to panitumumab, in addition to skin rash, included pruritus, dyspnea, fatigue, abdominal pain, nausea and vomiting. Pharmacokinetic variability was very low, and trough concentrations in patients receiving 2.0 mg/kg or greater consistently exceeded the predicted IC_{90} values. Low intrapatient variability and consistent drug exposure throughout the initial 8-week treatment period were consistent with the absence of HAHA formation. This study provided preliminary evidence of antitumor activity in heavily pretreated renal cancer patients (15-18).

In another phase II study to assess the efficacy and safety of panitumumab in refractory metastatic colorectal cancer, 148 patients stratified by tumor cell EGFR expression were treated with panitumumab 2.5 mg/kg weekly. Patients had previously failed therapy with a fluoropyrimidine and irinotecan or oxaliplatin, or both. In patients evaluated after 8 weeks (primary endpoint), there was a 10% overall response rate (15 patients with a confirmed partial response) and 56 patients had stable disease (38%). Median overall survival was 7.9 months and median overall time to progression was 2 months. Panitumumab was well tolerated. The most frequently reported adverse event was reversible skin rash. Grade 3 or 4 fatigue was reported in 9 patients. No accumulation of panitumumab was observed for up to 4 cycles. The study demonstrated encouraging antitumor activity for panitumumab monotherapy in this group of patients (19, 20).

An open-label, dose-escalating phase II study enrolled patients with advanced NSCLC (stage IIIb or IV) expressing EGFR, who received weekly doses of panitumumab of 1.0, 2.0 or 2.5 mg/kg in a sequential design. Panitumumab was administered in combination with standard paclitaxel and carboplatin every 3 weeks. Of 19 patients enrolled in part 1 of this study, 5 had objective responses after 6 weeks (1 complete, 4 partial). The median time to progression was 6 months and the median overall survival was 17 months. Four patients had dosing interrupted or reduced because of skin toxicities. Panitumumab was well tolerated in combination with paclitaxel and carboplatin in NSCLC patients. In part 2 of the study, the clinical activity of panitumumab will be further assessed in 175 patients (20, 21).

In the first quarter of 2004, two pivotal trials of panitumumab were initiated in patients with colorectal cancer. One is for third-line monotherapy in this group of patients, and the other is being conducted outside the U.S. in third-line colorectal cancer patients. The studies are part of a comprehensive global development program for panitumumab, and their initiation follows the receipt of a special protocol assessment (SPA) letter from the U.S. FDA (22).

Sources

Abgenix, Inc. (US); Amgen, Inc. (US).

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