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Panitumumab: An Arrow on Target

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Abstract Several options are available today in the treatment of advanced colorectal cancer: traditional chemotherapeutic regimens, targeted therapies, and their combinations. Panitumumab is a new, fully human anti-EGFR monoclonal antibody, what is well-tolerated, effective as a single agent in chemotherapy refractory patients and in different combinations. The clinical response is restricted to tumors with wild-type RAS, therefore the RAS status should be checked before treatment.

Keywords Panitumumab · Colorectal cancer · Anti-EGFR therapy

EGFR1/EGFR (epidermal growth factor receptor), a transmembrane glycoprotein that is a member in a subfamily of type I receptor tyrosine kinases (including EGFR1/HER1/ERBB1, −2, −3, −4), is an important target for cancer therapy, because its activation stimulates key actions in tumor growth and progression. Monoclonal antibodies and small-molecule tyrosine kinase anti-EGFR inhibitors are new treatment options for various solid tumors. Cetuximab (ER-K0034, Erbitux) was the first anti-EGFR monoclonal antibody to be approved for clinical use for metastatic colorectal cancer. While cetuximab is a chimeric (mouse-human), panitumumab (ABX-EGF, Vectibix, Amgen Inc, Thousand Oaks, CA) is a fully human (immunoglobulin G2) antibody, showing efficacy as monotherapy in chemotherapy-refractory patients and in different combinations against metastatic colorectal cancer.

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Mechanism of Action

Panitumumab targets human epidermal growth factor receptor (EGFR) [1, 2]. The strategy is obvious: EGFR promotes cell proliferation in a variety of normal and transformed cells and its overexpression has been observed in several types of human malignancies. Panitumumab binds with high affinity and specificity to the ligand binding domain in the extracellular part of EGFR inhibiting receptor dimerisation [3]. The receptor-antibody complex will be internalised preventing the ligand induced autophosphorylation of the receptor and activation of downstream signaling pathways.

It was initially believed that panitumumab, as an IgG2 antibody would not provoke ADCC (antibody dependent cell-mediated cytotoxicity), but it has beeen demonstrated recently in squamous cell head and neck carcinomas in vitro at concentrations analogous to therapeutic doses [4].

Preclinical Results

Panitumumab was developed using XenoMouse strains, decided to be deficient in mouse antibody production but to contain integrated fragments from human heavy and kappa light chain loci. It showed high affinity to EGFR and neutralised the ligand-binding (EGF, TGFα) to EGFR expressed on human carcinoma cell lines. Besides

inhibiting EGFR signaling panitumumab showed anti-angiogenic effect by inhibiting VEGF, interleukin-8 and matrix metalloproteases.

Predicting Markers

It was expected that the response to an anti-EGFR drug is associated with the expression of EGFR. As a surprise, the immunohistochemically determinded EGFR-expression had no correlation with clinical efficacy. This finding initiated an intensive search for alternative markers [5].

Rapidly growing amount of evidences indicated the role of constitutive activated signaling pathways downstream of the EGFR in tumor growth and progression. Moreover the crosstalks between these pathways may provide escape routes for the tumor cells to circumvent a pathway which was pharmacologically targeted. EGFR can activate several signaling routs, most frequently these are RAS/RAF/MEK/ERK- or PI3K/AKT/mTOR-mediated. A recent study of 586 colorectal cancer found that KRAS is the most commonly mutated gene (35–45%), followed by mutations in PIK3CA (<20%, encodes the p110 catalytic subunit of PI3K) and BRAF (<15%) [6]. The mutations of KRAS and BRAF are mutually exclusive, but mutations in PIK3CA and KRAS or BRAF may coexist. The KRAS mutation status is usually concordant in primary and in its metastatic lesions [7].

The prognostic value of KRAS mutation is controversial. The RASCAL study seems to support the association of KRAS mutation with increased risk of death [8], but other studies on the effect of panitumumab monotherapy found no correlation between the KRAS mutation and outcome of patients receiving only best supportive care [9, 10]. Similarly, KRAS mutations did not appear to have a stage-specific prognostic value [11].

KRAS Mutations Several studies made retrospective testing of KRAS status in metastatic colorectal cancer receiving cetuximab or panitumumab, with or without chemotherapy [5]. It turned out that KRAS mutations are the major predictors of resistance to these monoclonal antibodies. In general, the progression-free survival (PFS) in patients with tumors carrying mutant KRAS seems to be approximately half that of those with wild-type KRAS treated with anti-EGFR antibodies [12–14].

The negative predictive value of KRAS mutation was clearly demonstrated in the pivotal randomized phase III study (427 patients) of panitumumab monotherapy in the relapsed or refractory setting [9]. Among the 208 patients assigned to panitumumab 17% in the wild-type KRAS group showed objective response, but none in the mutant group (84 patients), while the PFS was 12.3 weeks and 7.4 weeks, respectively. As a consequence, 77% of the 219 KRAS evaulable patients initially assigned to the control group crossed over to receive panitumumab after disease progression; this crossover confounded the estimation of overall survival.

It is also a fact, that the proportion of the patients with wild-type KRAS tumors, who failed to make objective response or disease stabilization with panitumumab or cetuximab differs considerably between studies. (Table 1).

KRAS mutations in colorectal tumors can be detected by different molecular methods; most commonly (a) by DNA sequencing (Sanger sequencing or pyrosequencing), or (b) by real-time polymerase chain reaction using fluorescent probes or dyes (allele-specific real-time PCR, post-PCR fluorescent melting-curve analysis with specific probes, PCR clamping method). All of these seem to have adequate sensitivity to select patients unlikely to respond to anti-EGFR monoclonal antibodies. However, there is no consensus on the required sensitivity (percentage of the mutant allele) for KRAS mutant analysis. Since KRAS mutation are usually acquired at the early stage in colon carcinogenesis, therefore the mutant KRAS is probably present in the majority of the tumor cells. Until clinical evidence for correlation with response is validated, highly sensitive methods may not be necessary [15]. The main factor essential to quality testing is the expertise of pathologists (or who makes the test)!

BRAF Mutations A retrospective analysis of 113 tumors where the patients received panitumumab or cetuximab in second or subsequent lines showed that tumors carrying BRAF mutations (V600E) did not respond to these agents and had significantly shorter PFS than tumors with wild type BRAF. In vitro experiment proved that introduction of BRAF V600E allele into wild-type BRAF colorectal cancer cells could result resistance to either cetuximab or panitumumab. Furthermore, sorafenib (a multitarget drug inhibiting e.g. BRAF) may restore the sensitivity to anti-EGFR therapy in BRAF mutated colorectal cancer lines [16].

PTEN and PI3K Colorectal tumors with PIK3CA mutations and PTEN loss associated with lack of response to panitumumab (0/15 patients) or cetuximab (1/32 patients) [17]. It was suggested that a combined mutational analysis for KRAS and PIK3CA (loss of PTEN and/or PIK3CA mutation) could identify up to 70% of patients with metastatic colorectal cancer who are unlikely respond to anti-EGFR monoclonal antibodies. Another report provided contradictory results questioning the use of PIK3CA mutations as single marker to predict sensitivity to cetuximab [18]. It also needs further evidences that concordant inhibition of EGFR and PIK3CA pathway will

Table 1 Clinical response of colorectal cancers to panitumumab with wild-type or mutant RAS

Treatment	*No patients/ % mutKRAS*	*CR or PR (mut/wild %)*		*Stabil disease (mut/wild %)*		*Progression (mut/wild %)*		*Ref*
Panitumumab (phase III chemotherapy refractory)	208 / 40	0 / 17		12 / 34		70 / 36		[19]
Panitumumab crossover (phase III extension, chemotherapy refractory)	168 / 46	0 / 22		26 / 38		48 / 25		[19]
Panitumumab (patient cohort, chemotherapy refractory)	62 / 39	0 / 11		21 / 53		79 / 37		[24]
Cetuximab ± CT or Panitumumab (patient cohort, chemotherapy naive and refractory)	48 / 33	6 / 31		31 / 25		63 / 44		[22]
		PFS (months) wild / mutant		*OS (months) wild / mutant*		*RR (%) wild / mutant*		
Panitumumab + FOLFOX4	1183 / 40	9.6	7.3	23.9	15. 1	55	40	[32]
FOLFOX4		8.0	8.8	19.7	18.7	48	40	
Panitumumab + FOLFIRI	1083 / 45	5.9	5.0	14.5	11.8	35	13	[33]
FOLFIRI		3.9	4.9	12.5	11.1	10	14	

achieve clinical advantage. Besides, in colorectal cancer BRAF and PIK3CA mutations (but not KRAS mutations) showed gender bias with a higher frequency occurring in women which suggest that female patents have less benefit from treatment with anti-EGFR antibodies [19]. However, most clinical data disagree with this hypothesis [10, 20].

EGFR Several reasons could explain the lack of association between EGFR detection by *immunohistochemistry* (IHC) and response to EGFR-targeted treatment, e.g. disparity between the form or epitope of EGFR recognized by IHC and by the anti-EGFR monoclonal antibodies, difference in processing and handling of tumor samples. IHC is a semiquantitative method without standardized scoring system, and different EGFR expression in the primary and metastatic lesion can also contribute to the inappropriate prediction. Another problem comes from the inability of IHC to make a distinction between low- and high-affinity binding sites. Only EGFR phosphorylation status may reflect the level of receptor activity and predict the clinical response. *Activating mutations* are rare or absent in colorectal tumors in contrast to lung cancer. Amplification of EGFR gene resulting overepression and detected by FISH or CISH was likely not reflected by IHC. However, an increase in EGFR *gene copy number* evaluated by PCR is more promising, although contraversies are existing. In a supporting study a mean EGFR gene copy number threshold of less than 2.5 copies per nucleus or fewer than 40% of tumor cells with chromosome 7 polysomy selected patients with shorter PFS and OS after treated with anti-EGFR antibodies. In the group receiving only best supportiv care such association was missing suggesting that EGFR copy number and chromosome 7 polysomy are not prognostic in colorectal tumors [21].

Clinical Results

Single Agent Therapy Phase 1 and 2 studies have evaluated different panitumumab doses and schedules in patients with previously treated advanced solid tumors. The doses and schedules ranged between 0.01 mg/kg to 5 mg/kg weekly, or 6 mg/kg in every 2 weeks, or 9 mg/kg in every 3 weeks. The most frequent side effect was skin toxicity [22–25]. Further phase 2 and 3 studies examined the safety and efficacy of panitumumab used in monotherapy in previously treated metastatic colorectal cancer. Surprisingly, but similarly to cetuximab, the level of EGFR (measured by immunohistochemistry) in the tumor usually showed no association with the response rate [9, 26–28].

Panitumumab is appoved by FDA as a single agent for the treatment of metastatic colorectal carcinoma with diseases progression on or following fluoropyrimidine, oxaliplatin, and irinotecan chemotherapy. The indication approved by EMEA is very similar: Panitumumab is indicated as monotherapy for the treatment of patients with EGFR expressing metastatic colorectal carcinoma with non-mutated (wild-type) KRAS after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens. The recommended dose is 6 mg/kg body weight given once every two weeks.

It is known that the response to anti-EGFR treatment (small molecular-weight inhibitors) could be different in asian and non-asian patients with NSCLC (probably due to the different mutational status of EGFR). In an open-label, phase I study the safety and pharmacokinetics of panitumumab was investigated in Japanase patients with advanced solid tumors [29]. Although the number of patients were low the authors concluded that panitumumab was well tolerated, the pharmacokinetic and safety profiles (adverse events, changes in laboratory values, appearance of anti-panitumumab antibodies) were similar to those observed

previously in non-Japanase patients, and they considered the antitumor activity encouraging in colorectal cancer.

It could be a question, whether cetuximab and panitumumab are interchangable or not. [30]. Compared with cetuximab, panitumumab seems to have a more favourable interaction with oxaliplatin, at least in patients with wild-type KRAS. The reason is unclear, but it is true, that none of the panitumumab trials used capecitabine as basic therapy. Nevertheless it is early to consider these two drugs as equivalents.

Combination Therapy Combination of panitumumab and FOLFOX4 versus FOLFOX4 alone was studied in PRIME-trial (open label, randomized, global, phase 3) as first line treatment in patients with metastatic colorectal cancer [31]. In patients with wild-type KRAS the PFS was 9.6 months in the combination group versus 8.0 months in FOLFOX only group. Response rate was improved in patients with wild-type KRAS (55% vs 48%). Similar to the OPUS data (cisplatin based regiment with or without cetuximab) the patients with KRAS mutation who received panitumumab did worse in terms of PFS and OS compared to standard FOLFOX (PFS: 7.3 versus 8.8 months). It is important, that panitumumab was well-tolerated when administered with FOLFOX.

Another randomized phase 3 study compared the effect of panitumumab with FOLFIRI versus FOLFIRI alone as second-line treatment in patients with metastatic colorectal cancer. The objective response rate was 35% in the combined arm and 10% in the FOLFIRI only, the PFS 5.9 months versus 3.9 months, the overall survival 14.5 months versus 12.5 months, respectively. These results support the beneficial effect of panitumumab in patients with wild-type KRAS tumors. There was no evidence of improvement in patients with mutant KRAS. The panitumumab plus FOLFIRI combination was well tolerated [32].

Both panitumumab and cetuximab were evaluated in combination with bevacizumab, a monoclonal antibody targeting VEGF (vascular endothelial growth factor), plus first-line chemotherapy. The increased toxicity and shorter PFS proved the failure of this combination [33, 34]. In the PACCE (Panitumumab Advanced Colorectal Cancer Evaluation) study, a randomised, open label, controlled clinical trial, the median PFS in the panitumumab/chemotherapy (oxaliplatin or irinotecan)/bevacizumab group was 10.1 months compared to 11.4 months in the chemotherapy/bevacizumab group, the median overall survival (OS) 19.4 and 24.5 months, respectively [33].

The important message from these trials, that the selection of the combination with chemotherapy and EGFR-inhibitors should be made cautiously, because adverse interactions can happen. An example on that was provided by the combination of oxaliplatin-based therapy with EGFR-antibodies in KRAS mutant tumors.

Side Effects

Cetuximab and panitumumab produce similar clinical effect, an objective response rate of approximately 10% used as monotherapy against chemotherapy refracter EGFR-expressing metastatic colorectal cancer. It is expected, that panitumumab as a fully human antibody is less immunogenic than the chimeric cetuximab. Indeed, panitumumab seldom causes severe infusion reactions, [9] while such events may appear in up to 22% of cetuximab-treated patients.

Dermatological Reactions In most patients treated with EGFR-inhibitors the “acneiform” skin rash was suggested as a potential marker of efficacy. If a patient has dermatological rections that are grade 3 (NCI-CTC/CTCAE) or higher, or can be considered as intolerable, drug administration should be withhold until the reactions have improved (≤grade 2). The skin toxicity has been related to higher response rate and longer survival in patients with metastatic colorectal cancer treated with panitumumab, whereas patients without skin reaction seems to have poor outcome [9, 35]. In patients (n=231) who were progression free for 28 days the PFS in the panitumumab study showed significant benefit for patients with grade 2–4 toxicity compared to grade 1. However, rash frequently developes in patients without obvious benefit from anti-EGFR treatment, and conversely, benefit can occur without rash. Skin rash could reflect the local receptor saturation, the high-affinity EGFR, or immune status of the patient. Therefore, the use of rash as an early physical marker of efficiency has several limitations.

Pulmonary Complications If the symptoms of interstitial lung diseases develop the treatment should be interrupted.

Electrolyte Changes In some patients the decrease in serum magnesium level can lead to severe (grade 4) hypomagnesemia accompanied by hypocalcaemia. The electrolyte levels should be periodically monitored.

Infusion Related Reactions In clinical studies such reaction occurred in 3–4% of patients, and of which was considered as severe (grade 3–4) in <1% of patients.

Future Trends

Panitumumab proved to be a very effective agent in the tratment of advanced colorectal cancer. The main task now is to enhance the activity (a) by knowing more about the reasons of primary or acquired resistance, and (b) find the

most useful biomarkers to predict the clinical response by selecting the potentially sensitive patients' population. Besides, there an increasing interest into the value of circulating tumor cells as prognostic indicators and as predictive value in advanced colorectal cancer under panitumumab or chemotherapy plus panitumumab treatment [36, 37, 38]. Furthermore, the usefulness of panitumumab in other tumor-types should also be considered.

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