

Successful treatment with the fully human antibody panitumumab after a severe infusion reaction with cetuximab

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ABSTRACT

Aims and background. There are only limited data on the safety and efficacy of panitumumab in patients who experienced severe infusion reactions during cetuximab antibody therapy.

Case report. We report the case of a 69-year-old woman with chemotherapy-refractory metastatic colorectal cancer who received single-agent cetuximab treatment but experienced a severe reaction during the first infusion, despite premedication with corticosteroids/antihistamines. Cetuximab was discontinued and treatment with panitumumab initiated approximately 14 days later (without premedication); no infusion reactions occurred and there was a rapid improvement in her general condition. She experienced a partial response that was sustained for 7 months before progression.

Conclusions. This case supports the use of panitumumab in patients with chemotherapy-refractory metastatic colorectal cancer and suggests that panitumumab may be used in some patients with prior infusion reactions to cetuximab. Free full text available at www.tumorionline.it

Introduction

The epidermal growth factor receptor (EGFR) signalling pathway is known to play a key role in promoting the growth of colorectal tumors. Two monoclonal antibodies (mABs) targeting EGFR are currently approved for the treatment of colorectal cancer. Cetuximab (Erbix[®], Merck KGaA, Darmstadt, Germany), a chimeric immunoglobulin G (IgG) 1 mAB, is indicated in combination with chemotherapy or as monotherapy in patients with metastatic colorectal cancer (mCRC) who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan¹. Panitumumab (Vectibix[®], Amgen Europe B.V., Minerva, Breda, The Netherlands) is a fully human IgG 2 mAB that is approved as monotherapy for the treatment of patients with mCRC with disease progression during or following fluoropyrimidine-, irinotecan-, and oxaliplatin-containing chemotherapy regimens². Both agents are used in the treatment of patients with EGFR-expressing, *KRAS* wild-type tumors.

Skin rash is the most common side effect associated with EGFR therapy. Cetuximab is also associated with mild to moderate infusion reactions during the first infusion in 16-19% of patients, and severe reactions in $\leq 5\%$ ^{1,3}. More recent observations in the clinical setting and in specific patient populations suggest that severe reactions may actually occur much more frequently, with 22% of patients in a Tennessee and North Carolina study experiencing grade 3/4 reactions⁴. Most reactions occur during the first or second cetuximab administration, although these can be delayed in up to a third of cases⁵. It is difficult to predict those who are most at risk of experiencing an infusion reaction but it has been suggested that a history of drug allergy may be a factor⁶. Panitumumab treatment is associated with a much lower incidence of infusion

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reactions than cetuximab, with 3% of patients experiencing any-grade reactions and grade 3 reactions observed in approximately 1%⁷⁻¹⁰. There are also limited data to suggest that panitumumab can be successfully used in patients who experienced severe infusion reactions during cetuximab treatment¹¹⁻¹⁴.

Results from a recent phase III randomized trial demonstrated that panitumumab plus best supportive care significantly reduced the rate of disease progression by 46% compared with best supportive care alone and no grade 3/4 infusion reactions occurred in this or the subsequent open-label extension study^{8,9}. However, this trial did not include patients who had experienced reactions to cetuximab and therefore the risk of infusion reactions occurring in response to panitumumab in those with previous reactions to EGFR-targeted therapies could not be reported. Here we report the clinical course of a patient with mCRC who showed disease progression after being treated in the control arm of a randomized, phase III study comparing FOLFIRI (folinic acid/5-fluorouracil/irinotecan) with FOLFIRI plus panitumumab as second-line therapy¹⁵. She experienced a severe infusion reaction during cetuximab treatment and was subsequently successfully treated with panitumumab.

Case report

In May 2006, a 69-year-old female patient presented with defecation problems (but no bleeding) and pain in her left lower abdomen. Following an initial computerized tomography (CT) scan, she was diagnosed with mCRC with multiple inoperable metastases in both lobes of her liver. She had no comorbid conditions (no history of diabetes, hypertension or cardiac problems) and a World Health Organization performance status of 0. Prior to surgery, her carcinoembryonic antigen level was 8.6 ng/mL and her levels of lactic acid dehydrogenase (422 U/L) were elevated above normal (<250 U/L and <35 U/L, respectively). The blood counts as well as liver and renal function tests were within the normal range. She underwent laparoscopic hemicolectomy with lymph node dissection, and histology of the sigmoid tumor showed a poorly differentiated grade 3 adenocarcinoma with lymphangiosis and hemangiosis carcinomatosa. The primary tumor was 4 cm in diameter with ulceration, and had infiltrated 5 out of 11 biopsied lymph nodes. Initial tumor stage was pT3 pN2 pL1 pV1 G3 M1. DNA was extracted from microdissected tumor slides taken from the primary tumor and sequenced by polymerase chain reaction to determine the *KRAS* mutation status. The primary tumor was found to be wild-type for *KRAS*. The target lesions in her liver were 3.1 cm, 4.3 cm and 2.0 cm at baseline.

Prior to first-line treatment with folinic acid/5-fluorouracil/oxaliplatin (FOLFOX) plus bevacizumab, the patient's CEA levels had risen to 13.6 ng/mL (normal range: 0-4.5 ng/mL). After 3 months of treatment, a CT

scan showed a partial response (based on the Response Evaluation Criteria in Solid Tumors [RECIST]); lesions in her liver had decreased in size and CEA levels had dropped to 5.6 ng/mL (Figure 1). Her response remained stable over the next 3 months, after which point treatment was stopped temporarily to allow the patient to take a trip abroad. Four months later a routine CT scan during an off-treatment phase revealed progression of the liver metastases, which was also confirmed by ultrasound.

At this point the patient was entered into a phase III second-line trial (20050181) of FOLFIRI ± panitumumab and was randomized into the control arm¹⁵. The patient showed no response after 8 cycles of FOLFIRI and developed new lesions in her liver and so was withdrawn from the trial. FOLFOX plus bevacizumab was restarted as third-line treatment and the patient's disease stabilized after 3 months, after which she had another treatment break, in line with a "stop-and-go" strategy as previously utilized. At 3 months' follow-up she had symptomatic progression of the liver metastases, which took the form of weight loss and abdominal pain in the upper right quadrant. Progression was subsequently confirmed by CT scan and ultrasound.

The oxaliplatin- and irinotecan-refractory patient was then subjected to anti-EGFR antibody therapy. At this

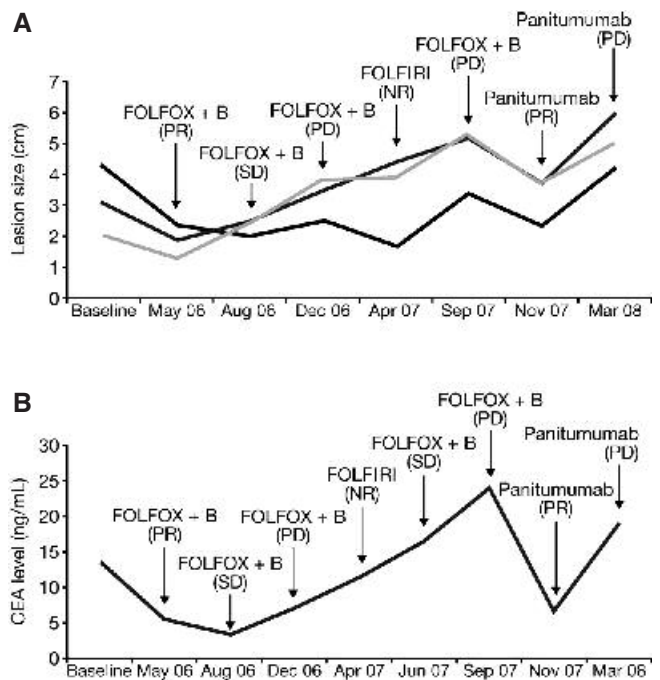


Figure 1 - A) Target lesion response and B) CEA response during treatment.

FOLFOX, folinic acid + 5-fluorouracil + oxaliplatin; B, bevacizumab; FOLFIRI, folinic acid + 5-fluorouracil + irinotecan; CEA, carcinoembryonic antigen; PR, partial response; SD, stable disease; PD, progressive disease; NR, no response.

time, the patient was 70 years old, her performance status had deteriorated to 1 and she was experiencing symptoms of general weakness as well as continuing occasional pain in the region of the liver. She was premedicated with corticosteroids (dexamethasone) and antihistamines (ranitidine and dimethindene maleate) – a treatment requirement with cetuximab to reduce risk of infusion reaction – and cetuximab monotherapy (400 mg/m² initial loading dose administered as a 120-minute intravenous infusion) was administered as fourth-line treatment. Within minutes after the start of the first cetuximab infusion, a severe grade 3 infusion reaction occurred (whole body erythrodermia, swelling of the tongue, dyspnea, fever, chills, hypotension, and bronchospasm) and cetuximab was discontinued. During the reaction the patient became very anxious and required close monitor surveillance, oxygen, intravenous prednisone (250 mg), fluids (saline 0.9%, 1 L), antihistamines, benzodiazepines, and bronchodilators. Clinic staff were well prepared for the potential occurrence of an infusion reaction, although they had not previously encountered one during cetuximab therapy. Intensive care treatment of this patient was not required because of their quick and appropriate response to the reaction.

Following stabilization of the patient's condition, fourth-line treatment with panitumumab monotherapy (6 mg/kg every 14 days as a 60-minute intravenous infusion) was initiated approximately 14 days later, with no premedication. No infusion reaction occurred and there was a rapid improvement in her general condition and performance status within days after the first infusion. A routine CT scan after 4 infusions revealed a partial response (Figure 2), with the 3 target lesions each reducing

in size by 30-32%. This response was sustained for 7 months with the patient receiving a total of 11 panitumumab infusions. Her quality of life was generally improved during this period, with no diarrhea or infusion reactions. She did, however, experience nail and cutaneous toxicities for which she received local antibiotic therapy and used gloves. It took several months for these symptoms to resolve following discontinuation of panitumumab therapy. Disease progression in her liver metastases was noted at a routine follow-up after 8 months and panitumumab treatment was discontinued.

The patient subsequently received another 7 months of FOLFOX chemotherapy; however, she did not respond. Her disease continued to progress, she developed lung metastases and her performance status deteriorated to 2. She received steroid treatment for symptomatic relief of fever and night sweats and best supportive care was initiated. The patient was still requesting additional therapy and therefore was retreated with a total of 3 infusions of panitumumab (1 infusion every 2 weeks), but no response occurred. The following month the patient was retreated with panitumumab. She finally died in December 2008.

Discussion

This case demonstrated that single-agent panitumumab was effective and well tolerated by a patient with mCRC who had experienced a severe infusion reaction during prior cetuximab therapy. No premedication was required prior to panitumumab administration and the lack of infusion reaction during treatment is consistent with clinical data where the incidence of in-

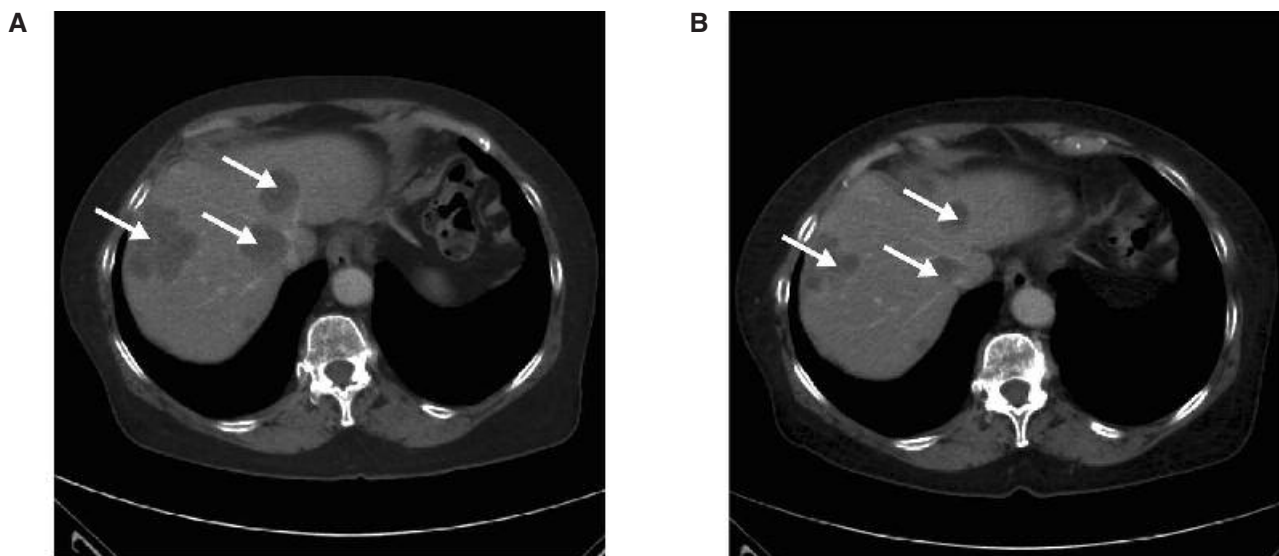


Figure 2 - Computed tomography scans of the patient's liver (A) before and (B) after 2 months of panitumumab therapy, showing response to treatment.

fusion reactions has been rare^{8,9}. The patient's tumor in this case study was *KRAS* wild-type and responded well to panitumumab, in concordance with previous reports that only patients with *KRAS* wild-type respond to treatment with panitumumab¹⁶. The response was particularly rapid and the patient had only received 8 weeks' treatment with panitumumab monotherapy when it was first documented. Cutaneous side effects of panitumumab and other EGFR-targeted therapies have also been reported previously^{8,9,17} but are generally manageable¹⁸, as was seen here. Of note, the presence and intensity of acneiform rash may be a marker of response to therapy in some patients^{19,20}.

The etiology of infusion reactions is not fully understood, although it appears they can arise through both IgE-mediated and non-IgE-mediated mechanisms²¹. Theoretically, with chimeric antibodies such as cetuximab, they could be due to the mAb's ability to elicit human antichimeric antibodies²². This is supported by the observation that the fully human mAb, panitumumab, appears to be associated with a lower incidence of infusion reactions than cetuximab^{8,9}.

Only limited data are currently available on the safety and efficacy of panitumumab in patients who experienced severe infusion reactions during cetuximab treatment. Four reports have been published to date including 6 cases, 5 of which were patients with mCRC and 1 patient had pancreatic carcinoma¹¹⁻¹⁴. These patients all experienced severe infusion reactions between their first and twelfth cetuximab infusions; reactions were noted as grade 3 in 3 cases and grade was not reported in the remainder. All 6 patients later successfully tolerated subsequent panitumumab therapy, mostly without receiving premedication, suggesting that there are no complications when panitumumab is given following an infusion reaction to cetuximab. The most severe reaction to panitumumab was grade 2 acneiform rash, occurring in a patient who experienced a partial response of 6 months' duration¹⁴.

This case report adds to the growing body of evidence suggesting that panitumumab offers a valuable treatment option for patients who have experienced severe infusion reactions during cetuximab therapy. As such, panitumumab may allow these patients to continue potentially beneficial anti-EGFR therapy when further cetuximab treatment is contraindicated. This case also demonstrates that retreatment with panitumumab is probably not beneficial since most of the tumor cells might be resistant to both chemo- and EGFR-directed therapy at this stage in a patient's clinical course.

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