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ORIGINAL ARTICLE

Successful desensitization with cetuximab after an infusion reaction to panitumumab in patients with metastatic colorectal cancer

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Abstract
Background Cetuximab and panitumumab are chimeric and fully human monoclonal antibodies, respectively, against epidermal growth factor receptor used in the treatment of metastatic colorectal cancer (mCRC). Incidence of documented infusion reaction (IR) is more common with cetuximab (all grades [g]: 15–21%, g 3/4: 2–5%) than panitumumab (all g: 4%, g 3/4: 1%). Anecdotal reports suggest successful challenge with panitumumab following IR with cetuximab (Saif et al. in Cancer Chemother Pharmacol 63(6):1017–1022, 2009). However, safety of cetuximab after IR with panitumumab is not known. We report two patients successfully desensitized with cetuximab after IR with panitumumab.
Patients and methods A 42-year-old female with mCRC received panitumumab as a third-line agent. She developed severe chest tightness, pain, and shortness of breath (SOB), 5 min after first panitumumab infusion. A second 70-year-old male with mCRC developed severe facial flushing, back pain, SOB, tachycardia and hypotension, 5 min after second dose of panitumumab plus irinotecan as a second-line therapy. These two patients received desensitization protocol for cetuximab after a test dose of 20 mg IV over 10 min followed by a slow infusion 10% of original rate in 0–2 h, 25% of original rate in 2–2.5 h, 50% reduced rate in 2.5–3 h, and then 100% infusion rate after 3 h. Patients were observed 4 h after completion of infusion.
Results First patient received a total of 12 cycles of cetuximab with stable disease, no recurrence of IR, and grade 1–2 acniform rash that first developed after third cycle. Second patient received a total of eight cycles uneventfully without IR.
Conclusions To our knowledge, this is the first report of two patients with documented IR with panitumumab being desensitized successfully with cetuximab. Though anecdotal reports suggest safety of panitumumab in patients following IR with cetuximab, panitumumab can also cause severe IR. Our experience suggests that in case of limited options, such patients can be successfully challenged with cetuximab in a hospital after appropriate desensitization and premedication. Further studies focusing on desensitization and identifying hypersensitivity profile of different anti-epidermal growth factor receptor antibodies are warranted.

Keywords Cetuximab (Erbitux) · Panitumumab · Epidermal growth factor receptor (EGFR) · Colorectal cancer · Hypersensitivity reaction · Infusion reaction · Desensitization

Introduction

Epidermal growth factor receptor (EGFR) is a subclass of the receptor tyrosine kinase (RTK) superfamily. EGFR is implicated in many human cancers. Tumors with alterations in EGFR receptors are found to have a more aggressive disease and hence a poorer prognosis. So, epidermal growth factor receptors have been pursued intensely as therapeutic targets. There are two major classes of anti-EGFR therapeutics: antibodies binding to the extracellular ligand-binding

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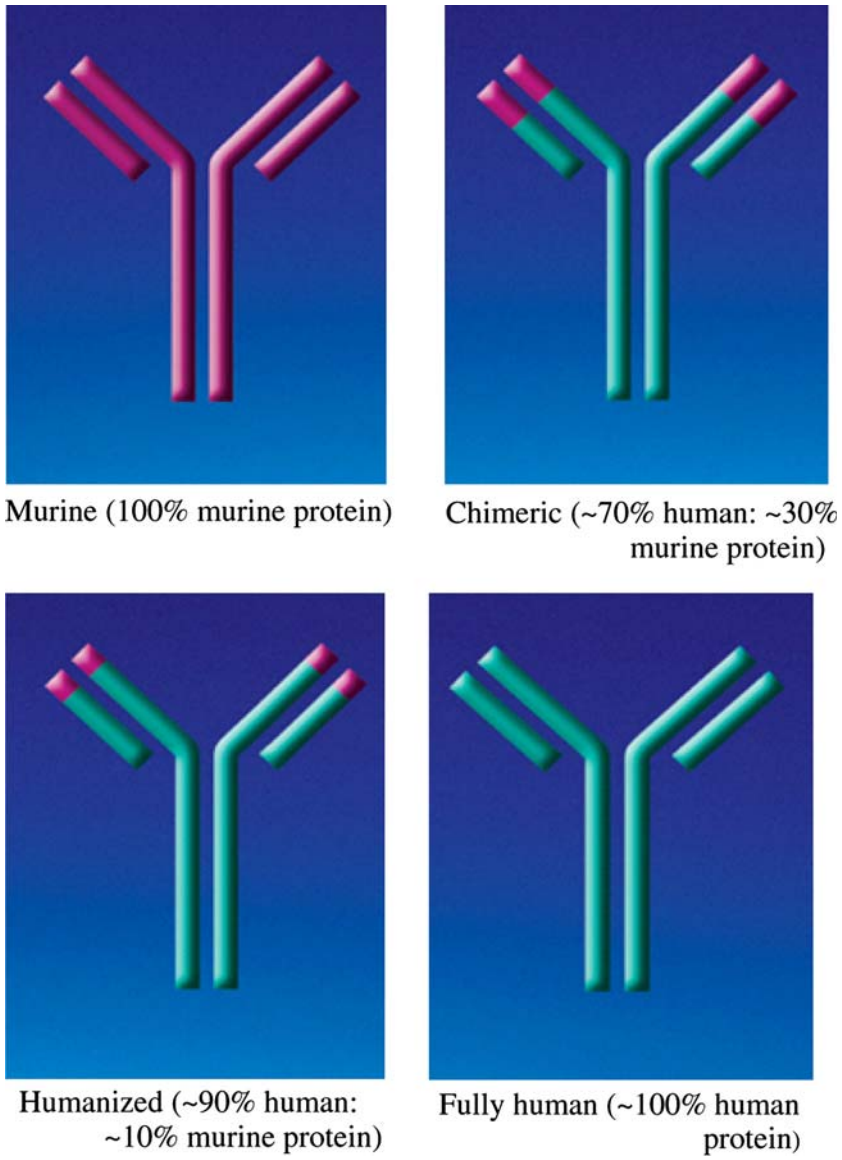

Fig. 1 Classes of therapeutic antibodies: there are four types of therapeutic monoclonal antibodies

region and the small-molecule tyrosine-kinase inhibitors (TKIs) that compete with ATP in the tyrosine-kinase domain [1]. The Food and Drug Administration (FDA) has approved two monoclonal antibodies against EGFR, Cetuximab (Erbitux) and Panitumumab (Vectibix), for treatment of colorectal and/or head-and-neck cancer [2].

Cetuximab is a chimeric antibody (Fig. 1) from the murine fraction variable regions of the myeloma cell line 225, a mouse monoclonal antibody that blocks the ligand-binding site of the EGFR, and a human immunoglobulin G constant region gene segment [3]. Panitumumab is the first complete human monoclonal antibody (Fig. 1). Similar to cetuximab, it is also directed against the extracellular binding domain of EGFR and inhibits apoptosis, proliferation and differentiation of EGFR expressing (normal and neoplastic) cells. In clinical trials, it has been found to be less immunogenic than other antibodies [4].

These EGFR inhibitors are well tolerated in most patients. Skin toxicity (acneform rash) is the most common adverse effect. Other common side effects are asthenia/malaise, fever, nausea, constipation, diarrhea, and hypomagnesaemia [4, 5]. Cetuximab has been associated with severe (grade 3–4) allergic reactions/infusion reactions (IR) in 3–5% of the patients. Fatal outcomes have occurred in 0.1% of the patients. Reactions of all grades occurred in 25% of the patients [5–8]. Panitumumab was significantly less immunogenic than cetuximab and extremely few IR have been reported with its uses [9–11]. In clinical trials, 4% patients suffered from IR of which 1% was reported to be severe [12].

Anecdotal reports have suggested a possibility of treating patients who have experienced a severe infusion reaction due to cetuximab with panitumumab [13–15]. However, little is known about infusion reactions to

Table 1 Desensitization Protocol for Cetuximab infusion

Time	Rate of infusion (%)	Rate of infusion (ml/h)	Comment
Test dose/ Pre-treatment	Cetuximab test dose of 20 mg IV over 10 min	Cetuximab test dose of 20 mg IV over 10 min	Observe for 30 min
0–2 h	10% of original rate	13.0 ml/h	Observe and vitals every 30 min
2–2.5 h	25% of the original rate	33.0 ml/h	Observe and vitals every 30 min
2.5–3 h	50% of the original rate	66.0 ml/h	Observe and vitals every 30 min
After 3 h	Original rate of infusion	133.0 ml/h	Observe and vitals every 30 min

Premedicated with prednisone 50 mg 24 h, 12 h, 3 h, and 30 min before treatment. She also received diphenhydramine 50 mg IV and famotidine 20 mg IV prior to cetuximab infusion

panitumumab and further treatment options. We present two cases with severe IR to panitumumab who were successfully challenged with cetuximab and describe a desensitization protocol adapted from Nielsen et al. [16].

Patients and methods

Patient 1

A 42-year-old female with an unremarkable past medical history presented with intermittent dizziness, nausea, anemia, and acute onset of shortness of breath in June 2004. A computed tomography scan of the chest revealed multiple pulmonary lesions and liver lesions. A subsequent CT chest angiogram showed pulmonary embolism. A CT abdomen/pelvis revealed a rectosigmoid mass and a carcinoembryonic antigen (CEA) done at that time was 1,200 mg/ml. Surgical excision of the mass was performed and the biopsy revealed adenocarcinoma. Liver biopsy also showed metastatic disease and 3 of the 12 lymph nodes were positive for metastases. In July 2004, the patient was started on FOLFOX-6 with bevacizumab. After six cycles, chemotherapy regimen was changed to FOLFIRI in October 2004 because of worsening nausea/vomiting/diarrhea with oxaliplatin. Bevacizumab was reintroduced. In March 2006, the patient's disease had stabilized, CEA level was 9 mg/ml and chemotherapy was held. She underwent chemoembolization of hepatic lesions. However, in September of 2006, the disease progressed with CEA levels trending upwards of 117 mg/ml, and FOLFIRI with avastin was restarted. Because of the increasing levels of CEA, the previous regimen was stopped and in June 2007, the patient was started on panitumumab.

Within 5 min of the first infusion, the patient developed severe chest tightness, shortness of breath, and wheezing. The infusion was immediately stopped, and intravenous (IV) diphenhydramine (25 mg) and dexamethasone (10 mg) were given. The patient's symptoms resolved with treatment after a few hours. She was hospitalized for 24 h and discharged in a stable condition with no further events.

She had further progression of disease with progressive metastases to the lungs and liver. Because of disease progression and limited treatment options, it was decided to start her on cetuximab treatment.

Given the history of a previous severe reaction to panitumumab, it was decided to give a test dose of cetuximab prior to a slow infusion reaction. The patient understood the risk of undergoing cetuximab infusion and an informed consent was signed. Patient was premedicated with 50 mg of prednisone 24 h, 12 h, 3 h, and 30 min before treatment. She also received diphenhydramine 50 mg IV and famotidine 20 mg IV prior to cetuximab infusion. Cetuximab test dose of 20 mg IV was given over 10 min and the patient was observed for 30 min. In the absence of any IR, IV cetuximab infusion was given over 3–4 h as detailed in Table 1.

Patient 2

A 70-year-old male with metastatic colorectal cancer received panitumumab plus irinotecan as a second-line therapy. First administration was uneventful. However, few minutes after the second dose of panitumumab, he developed severe facial flushing, back pain, dyspnea, tachycardia, and hypotension. The infusion was immediately stopped and he was treated with oxygen, fluid replacement, and dexamethasone. His symptoms subsequently resolved within a few hours.

Because of lack of available treatment options and in view of the successful experience with the previous patient, a therapeutic regimen with cetuximab was considered. The patient was explained the risks and benefits, and an informed consent was obtained. He was premedicated with prednisone 50 mg PO 24 h, 12 h, and 3 h from receiving cetuximab, diphenhydramine 50 mg IV and famotidine 20 mg IV prior to cetuximab. Then, he received desensitization protocol for cetuximab after a test dose of 20 mg IV over 10 min followed by a slow infusion 10% of original rate in 0–2 h, 25% of original rate in 2–2.5 h, 50% reduced rate in 2.5–3 h, and then 100% infusion rate after 3 h (as detailed in Table 1).

Desensitization protocol

The treatment protocol is exemplified using the dose calculation of the first patient as below:

Drug dose and administration

BSA was calculated as 2.14 m, based on height of 160 cm and weight of 103.7 kg [2].

Drug dose	Administration
Cetuximab test dose 20 mg	IV over 10 min and observe for 30 min on day 1 only
Cetuximab 250 mg/m^2 (535 mg)	IV infusion over 3–4 h as detailed below, observe for 2 h post dose
Infusion instructions were as follows:	
0–2 h	10% of original rate (13.0 ml/h)
2–2.5 h	25% of original rate (33.0 ml/h)
2.5–3 h	50% of original rate (66.0 ml/h)
After 3 h, proceed with initial plan of infusion (133 ml/h)	
Preparation of Cetuximab	
Undiluted cetuximab was administered (2 mg/ml). Cetuximab 100 mg in 50 ml begin with test dose infusion of 20 mg in 10 ml and infuse over 10 min at 60 ml/h stop after 10 ml and cetuximab 535 mg in 267.5 ml	
Premedication	
Patients were premedicated with prednisone 50 mg PO 24 h, 12 h, and 3 h prior adminsitration of cetuximab. In addition, patients were premedicated with diphenhydramine 50 mg IV and famotidine 20 mg IV infusion prior to infusion of cetuximab	
Emergency medications were immediately available next to the patient	
Diphenhydramine 25 mg IV infusion prn IR	
Epinephrine 1/1,000 0.5 mg SC prn IR	
Hydrocortisone 100 mg IV infusion over 20 min prn IR	
Meperidine 25 mg IV infusion over 20 min prn IR	
Albuterol dose: 2 puffs prn bronchospasm	
Subsequent cetuximab dose	
Dosage	250 mg/m^2
Administration	IV infusion over 2 h, observe for 2 h post dose
Frequency	Weekly
Akin to first dose, patients were premedicated in a similar fashion for subsequent dosages.	

Results

Patient #1 tolerated the treatment well and she was monitored closely for a day without any adverse events. She received a total of 12 treatments of cetuximab with stable disease, no recurrence of IR and grade 1–2 acneform rash that first developed after the third cycle.

Patient #2 was observed for 4 h after the completion of the first infusion and no untoward complications were observed. The patient received a total of eight cycles of cetuximab with no recurrence of IR.

Discussion

Cetuximab and panitumumab have an extremely important anti-tumor activity in the treatment of metastatic colorectal cancer and head and neck cancer. The overall safety profile of these anti-monoclonal antibodies is favorable because they do not elicit many of the adverse effects traditionally elicited by the cytotoxic agents. However, the occurrence of IR poses a problem in the treatment of such patients. IR may be defined as "any signs or symptoms experienced by patients during the infusion of pharmacologic, or biologic agents or any event occurring on the first day of drug administration" [17]. Currently, our understanding of IR associated with monoclonal antibodies is very limited.

The terms hypersensitivity, allergic or anaphylactoid have been used interchangeably to describe acute infusion reactions although there is no convincing evidence that they have an allergic etiology [18]. The fact that 90% of the infusion reactions occurred with the first cetuximab infusion despite premedication with antihistamines, suggests that these reactions are not IgE mediated. Also, patients who experienced moderately severe reactions to cetuximab tolerated a rechallenge with either cetuximab or panitumumab without severe reactions; supporting a lack of IgE-mediated reactions [18]. However, Needle et al. reported that although most infusion reactions with cetuximab occurred with the first infusion reaction, 33% of grade 3–4 reactions occurred with the second infusion. They suggested a possible difference in mechanisms between mild and severe infusion reactions [19].

Theoretically, infusion reactions to monoclonal antibodies may be a result of their ability to elicit human antichimeric antibodies (HACAs) and human anti-human antibodies (HAHAs), respectively. Approximately, 1.4% of the people demonstrated HAHA's in their serum after panitumumab treatment [11]. However, a correlation between infusion reactions and the above antibodies has not been demonstrated as yet.

Another hypothesis of monoclonal antibody-associated infusion reactions is derived from infusion reactions secondary to rituximab. A role of complement activation and release of pro-inflammatory cytokines has been described in the latter case [20]. In addition, an association of infusion reactions is noticed due to rituximab and increased number of circulating tumor cells (tumor burden) [21]. A similar mechanism could account for the infusion reactions with first dose of cetuximab or panitumumab. The

Table 2 Grading of hypersensitivity reactions and acute infusion reactions according to the National Cancer Institute (NCI) criteria for adverse events (version 3.0) [22]

Grade	Hypersensitivity reaction (IgE mediated)	Acute infusion reaction (cytokine release syndrome)
I	Transient flushing or rash, drug fever ≥ 38°C	Mild reaction, infusion interruption not indicated
II	Rash, flushing, urticaria, dyspnea, drug fever ≥ 38°C	Requires interruption of infusion and prompt symptomatic treatment (i.e., antihistamines, non steroidal anti-inflammatory drugs, narcotics, intravenous fluids)
III	Symptomatic bronchospasm, urticaria, hypotension, and angioedema. Parenteral medications indicated	Symptoms are prolonged, do not respond rapidly to symptomatic medication and/or brief interruption of infusion, recurrence of symptoms following initial improvement, hospitalization indicated for treatment of sequelae
IV	Anaphylaxis	Life threatening, pressor and/or ventilatory support indicated
V	Death	Death

interaction between monoclonal antibodies and EGFR expression on the tumor cells can result in the rapid activation of complement system and inflammatory cytokines. In addition, since the tumor burden in patients with metastatic colorectal cancer is frequently extensive, a high incidence of infusion reactions could occur during the first exposure [18].

Despite the different possible mechanisms underlying hypersensitivity/infusion reactions, the clinical signs and symptoms associated with these reactions overlap (Table 2) [22]. Mild-to-moderate reactions (grades 1 and 2) are characterized by flushing, rash, fever, rigors, chills, dyspnea, and mild hypotension. Severe reactions (grades 3 and 4) are associated with bronchospasm and hypotension requiring treatment, cardiac dysfunction, anaphylaxis, and other symptoms.

When IR do occur, there are few options which allow the continuation of monoclonal antibody-based therapy. Nielsen et al. [16] described two cases with grade 2 IR with cetuximab who were rechallenged with cetuximab under controlled conditions. They were premedicated with prednisone and antihistamines prior to treatment, and were started on a low-infusion rate of cetuximab with gradual titration to the goal rate without any further adverse events.

To our knowledge, this is the first report of two patients with documented infusion reaction with panitumumab being treated with cetuximab. Both the cases were being treated for metastatic colorectal cancer with panitumumab. The first case developed a grade 3 infusion reaction 5 min after the first dose of panitumumab. The second patient tolerated the first dose but developed severe reaction few minutes after the second infusion of panitumumab. Both patients were then successfully rechallenged with cetuximab. A test dose of cetuximab was followed by a prolonged infusion time and a gradual dose escalation along with additional premedications.

Thanks to hybridoma technology, IR are less frequent with fully human and humanized antibodies. Panitumumab-associated reaction is rare and for severe reaction, re-exposure is not indicated. The exact mechanism of such a reaction is unknown and hence no recommendations on desensitization have been made. Based on our clinical experience, we conclude that patients with moderate–severe infusion reactions with panitumumab can be rechallenged with cetuximab under supervised conditions. Patients should be premedicated with prednisone and antihistamines, and observed for several hours after the cetuximab infusion to monitor for delayed reactions. Future studies are warranted for determining the pathogenesis of monoclonal antibody-mediated infusion reactions and the safety of rechallenging with the same or different anti-EGFR therapies.

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