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ORIGINAL ARTICLE

Successful re-challenge with panitumumab in patients who developed hypersensitivity reactions to cetuximab: report of three cases and review of literature

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Abstract
Introduction Monoclonal antibodies (MAbs) targeting epidermal growth factor receptor (EGFR) are effective in treatment of metastatic colorectal cancer (mCRC). Cetuximab, a chimeric MAb targets EGFR. Even with premedication, cetuximab can cause a hypersensitivity reaction (HSR). In case of severe HSR, further therapy with cetuximab is contraindicated, thus preventing these patients from receiving potentially beneficial anti-EGFR therapy. Panitumumab is a fully human MAb also targets EGFR. To date, no human antihuman Ab have been detected, and unlike CET, HSR are infrequent, and no premedication is required. Safety of panitumumab in patients with a previous severe HSR with cetuximab is not fully known. We present three patients with GI cancers who tolerated panitumumab without HSR after experiencing severe HSR to cetuximab.
Patients and methods Three patients were challenged with standard dose of panitumumab (6 mg/kg) after experiencing grade 3 HSR to standard dose of cetuximab under strict observation and no premedication. First patient, a 58-year-old male with mCRC developed grade 3 HSR during 8th dose of cetuximab. Second patient was a 58-year-old female with mCRC developed grade 3 HSR during 12th dose of cetuximab. Third patient was a 61-year-old male with pancreatic cancer who experienced grade 3 HSR during loading dose of cetuximab. Charts were reviewed to find history of prior allergy, including H1 blocker use, drug allergy, bee sting allergy, eczema, allergic reactive airways disease, or food allergy.
Results All patients were Caucasians with an average age of 59 year with no history of prior allergy. No patient received any premedication. First patient received panitumumab for 2 months, second patient was treated for 6 months, and third patient who was rechallenged 1 week after HSR to cetuximab had a partial response following 6 months of therapy.
Conclusions HSR are serious complications associated with MAbs. Thanks to hybridoma technology that newer generations of MAbs contain less or no mouse-specific protein sequences, hence reducing the risk of HSR. Identification of individuals likely to develop severe and sometimes life-threatening HSR is challenging. Our report of three patients successfully treated with panitumumab after they had severe HSR to cetuximab warrant further investigation.

Keywords Panitumumab · Epidermal growth factor (EGFR) · Colorectal cancer · Cetuximab

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Introduction

Agents targeting the epidermal growth factor receptor (EGFR) pathway offer promise for the treatment of patients with advanced malignancies. EGFR is overexpressed in numerous types of solid tumors, including colorectal cancer (CRC) [1]. EGFR activation is associated with proliferation, anti-apoptosis and metastatic spread, making this pathway a particularly compelling target for rational drug design [2]. Currently, there are two classes of anti-EGFR agents; the monoclonal antibodies (MAbs) directed toward the extracellular EGFR domain (cetuximab, panitumumab) and small molecule tyrosine kinase (TK) inhibitors, which inactivate the receptor enzyme activity (gefitinib, erlotinib) [1].

EGFR is expressed on nearly all normal cells, particularly those of epithelial origin such as liver, skin, and gastrointestinal tract, but not on hematopoietic cells [3]. Cetuximab is a chimeric IgG_1 monoclonal Ab (MAb) that selectively binds EGFR. Immunologic effects, such as cell-dependent cytotoxicity (CDC) and antibody-dependent cell mediated cytotoxicity (ADCC) may contribute to cetuximab's mechanism of action [4]. A rash is the most common side effect of cetuximab. Allergic and anaphylactoid reactions have been reported with cetuximab administration [5–7].

Panitumumab, a fully human IgG_2 antibody (Fig. 1) has consistently shown to have less infusion reactions compared to cetuximab [8]. This presents panitumumab as a strong option to patients for use as monotherapy for patients with CRC. It is difficult to predict which individuals are likely to develop severe and sometimes life-threatening HSR. It has been proposed that some risk factors of HSR include repeated use of the agent and personal history of drug allergy [9]. Experience from rituximab suggests that gender, age, and primary tumor type may predispose patients to have severe HSR [10]. No data is yet available to identify patients who are more likely to have severe HSR to cetuximab infusion. With a lower incidence of life-threatening HSR in patients with CRC, we report three patients who were re-challenged with panitumumab after developing severe HSR to cetuximab.

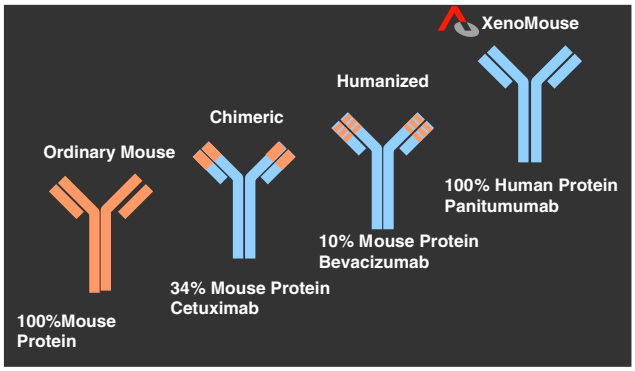

Fig. 1 Structure of monoclonal antibodies

Patients and methods

Patient # 1

A 58-year-old Caucasian male with mCRC initially received FOLFOX-4 and bevacizumab as first-line therapy. Due to progression of extrahepatic disease in the mediastinum and retroperitoneum, he was switched to single-agent irinotecan. Irinotecan therapy was complicated by grade 3 diarrhea and febrile neutropenia, which required inpatient admission to the hospital. After further progression of his disease, he subsequently began single-agent cetuximab (250 mg/kg) IV after receiving a loading dose (400 mg/kg). The patient was treated with cetuximab for a total of 4 months before developing symptomatic bronchospasm, urticaria, and hypotension consistent with grade 3 HSR (Tables 1, 2). Cetuximab treatment was stopped and supportive management was performed [11]. After further discussion and patient's consent, panitumumab (6 mg/kg) was administered 1 month later.

Patient # 2

A 58-year-old Caucasian female with rectal cancer and pulmonary metastases was treated with FOLFOX-6 and bevacizumab till progression. At the end of 8 months of previous therapy, she started irinotecan which she did not tolerate well due to grade 3 neutopenia and grade 3 diarrhea that required dose reduction to at a dose of 100 and then 75 mg/m^2. Therefore, she was switched to capecitabine and bevacizumab. Upon progression, she received cetuximab but, developed grade 3 HSR during her initial treatment. Therefore, cetuximab was discontinued.

Patient was referred to us for second opinion and different options including phase I studies and rechallenge with anti-EGFR therapy, such as panitumumab was offered. Patient opted to go for panitumumab.

Patient # 3

A 61-year-old Caucasian male with locally advanced unresectable pancreatic carcinoma was initially treated with gemcitabine/oxaliplatin plus cetuximab (GEMOX–CET), based on a phase II study showing a high response rate [12]. During the first dose (400 mg/kg), he developed grade

Table 1 Common toxicity criteria (ver. 3.0) of the National Cancer Institute

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Allergic reaction/hypersensitivity	Transient flushing or rash Drug fever <100.4°F	Rash; urticaria; dyspnea Drug fever >100.4°F and/or asymptomatic bronchospasm	Symptomatic bronchospasm with or without urticaria; parenteral medication(s) indicated; allergy-related edema/anigiodema	Anaphylaxis	Death

3 HSR to cetuximab manifested as bronchospasm, sweats, facial flushes, and diaphoresis. Cetuximab was stopped and the patient was treated with diphenhydramine 50 mg IV, famotidine 20 mg IV, and dexamethasone 20 mg IV. He later developed rigors and was again treated with diphenhydramine along with meperidine 25 mg IV. A second dose of meperidine was administered which stopped the rigors; however, the patient's blood pressure remained elevated. The patient was later hospitalized for continued observation and discharged 24 h later.

The patient was followed up 3 days later and further treatment options were discussed. Since patient had unresectable disease, surgery was the only potential cure if he has a significant response. Therefore, after discussion patient consented to be treated with GEMOX plus panitumumab.

Results

Summary demographics

All patients were Caucasians with an average age of 59 years. No patient has prior history of drug or food allergy, use of chronic intake of H1 blocker, bee sting allergy, eczema, or allergic reactive airways disease. No patient received any premedication (Table 3).

Table 2 Signs and symptoms of anaphylaxis

Neurological	Dizziness, headache, weakness, syncope, seizure
Psychiatric	Anxiety, "sense of impending doom,"
Respiratory	Nasal congestion, rhinitis, sneezing, oropharyngeal or laryngeal edema, bronchospasm, tachypnea, cyanosis, respiratory arrest
Cardiovascular	Tachycardia, hypotension, arrhythmias, chest pain, ischemia or infarction, cardiac arrest
Cutaneous	Flushing, erythema, pruritus, urticaria, angioedema, maculopapular rash
Gastrointestinal	Nausea, vomiting, cramping, diarrhea

Outcome

Patient # 1

The patient continued on therapy without any grade of HSR and without premedication for 8 weeks at which point therapy was discontinued due to disease progression.

Patient # 2

The patient received her first dose of panitumumab 3 months since her grade 3 HSR to cetuximab. She sustained stable disease with combination irinotecan and panitumumab for 6 months. She tolerated the therapy well requiring no premedication and no HSR. At the end of 6 month, CT scan showed progressive disease and of irinotecan and panitumumab were stopped.

Patient # 3

The patient received the first treatment of GEMOX–PAN on day 8 from the last dose of cetuximab and no premedication was given. Patient was observed for 4-h after finishing the cetuximab therapy and no HSR was observed. Two weeks later, he developed grade 2 acnieform rash on nose and scattered spots on chest and forehead which was treated with minocycline. Patient received a total of 11 treatments with GEMOX–PAN with partial response and was successfully resected for his tumor. Currently, he is receiving adjuvant therapy with gemcitabine–panitumumab based on his excellent response.

Discussion

Similar to other agents targeting the EGFR pathway, rash has been the primary toxicity with panitumumab [13–15]. The anti-tumor activity of panitumumab has been tested in vitro and in vivo, and inhibition of tumor growth has been observed in numerous cancer models, particularly lung, kidney, and colorectal [16]. It has been efficacious and well tolerated in combination with other chemothera-

Table 3 Summary of safety and response to re-challenge with PAN

Case	Age/sex	Diagnosis	Cetuximab dose (mg/kg)	Grade of HSR	Time interval between Cetuximab and Panitumumab	Panitumumab dose (mg/kg)	Tolerance	Duration of Panitumumab (months)
1	58/M	CRC	250	G3	1 month	6	No HSR	2
2	58/F	CRC	250	G3	3 months	6	No HSR	6
3	61/M	Pancreatic cancer	400	G3	1 week	6	No HSR	6

M male, *F* female

peutic agents as well as monotherapy [17–19]. Recent studies in pretreated and chemo-naïve mCRC colorectal cancer have shown very few, if any, HSR to panitumumab. Our cases provide further data to support the lower incidence of HSR with panitumumab. In addition, these data offer an alternative therapy with anti-EGFR when further therapy with cetuximab is contraindicated, especially when these patients can receive benefit from receiving anti-EGFR therapy. First patient received panitumumab for 2 months, second patient was treated for 6 months, and third patient who was rechallenged 1 week after HSR to cetuximab had a partial response following 6 months of therapy. This patient restarted panitumumab after Whipple's procedure.

Severe HSR is observed in approximately 3% of patients following cetuximab administration, with a fatal outcome in 0.1% of patients [20, 21]. Up to 90% of severe HSR are associated with first dose of cetuximab despite routine use of premedication. Needle et al. [22] reported that while majority of HSR occurred with the first infusion, 33% of patients who experienced grade 3/4 HSR developed after their second dose. Furthermore, all grade 4 HSR were observed within minutes of the first infusion indicating possible difference in mechanisms between mild and severe HSR. This issue gains more clinical significance after a recent finding indicated a high incidence of cetuximab-related infusion reactions in Tennessee and North Carolina [23]. Data for 88 patients treated with cetuximab on clinical trials and an additional 55 patients treated outside of trials were included in this analysis. For the clinical trial group ($n = 88$), the overall rate of grade 3–4 HSR was 22%, significantly higher than the rate noted in any large published trial (<3%). All HSRs occurred during the first dose. The investigators also found a strong relationship between prior allergy history and chance of HSR.

Pathophysiology of cetuximab-associated HSR is not completely understood. Chung et al. [24] analyzed serum samples from four groups of subjects for IgE antibodies against cetuximab: pretreatment samples from 76 case subjects who had been treated with cetuximab at multiple centers, predominantly in Tennessee, Arkansas, and North Carolina; samples from 72 control subjects in Tennessee; samples from 49 control subjects with cancer in northern California; and samples from 341 female control subjects in Boston. Among 76 cetuximab-treated subjects, 25 had a HSR to the drug. IgE antibodies against cetuximab were found in pretreatment samples from 17 of these subjects; only 1 of 51 subjects who did not have a HSR had such antibodies ($P < 0.001$). IgE antibodies against cetuximab were found in 15 of 72 samples (20.8%) from control subjects in Tennessee, in 3 of 49 samples (6.1%) from northern California, and in 2 of 341 samples (0.6%) from Boston. The IgE antibodies were shown to be specific for an oligosaccharide, galactose-α-1,3-galactose, which is present on the Fab portion of the cetuximab heavy chain.

Unlike most other MAbs, cetuximab is produced in the mouse cell line SP2/0, which expresses the gene for α-1,3-galactosyltransferase. It is now recognized that all humans have IgG antibodies specific for the oligosaccharide galactose-α-1,3-galactose, which is closely related to substances in the ABO blood group. This oligosaccharide is one of the major barriers to the transplantation of organs from other mammals in humans and has prompted the development of a strain of pigs in which the gene for α-1,3-galactosyltransferase has been knocked out. Natural exposure to galactose-α-1,3-galactose appears to induce the production of IgE antibodies against galactose-α-1,3-galactose in some people. The presence of such IgE antibodies before treatment may put patients who receive MAbs containing galactose-α-1,3-galactose at risk for HSR. The rapid reactions to cetuximab may be explained by intravenous injection, and the presence of galactose-α-1,3-galactose on both Fab segments of the cetuximab antibody allows for the efficient cross-linking of IgE on mast cells. Patients who have such antibodies do not report a rapid onset of allergic symptoms after the ingestion of beef, pork, or cow's milk. However, the same investigators claim to have identified a series of patients with IgE antibodies against galactose-α-1,3-galactose who reported having had episodes of anaphylaxis or severe angioedema 1–3 h after eating beef or pork (unpublished data). The explanation for such a delayed reaction is not clear, but a similar delay has been reported in patients with IgE antibodies against carbohydrate epitopes of plant proteins. In addition, it has recently been reported that some patients with cat allergy have IgE antibodies that bind to a carbohydrate epitope on cat IgA [25–28].

Severe HSR require immediate interruption of infusion followed by supportive care including appropriate use of vasopressors, corticosteroids, antihistamines, bronchodilators, and oxygen (Table 4). In cases of mild to moderate HSR, cetuximab infusion may be safely resumed with slowed rate of infusion [20].

Panitumumab is the first fully human MAb to EGFR that was constructed by introducing human immunoglobulin genes into genetically engineered mice without functional mouse immunoglobulin expression. Across clinical trials including 1,336 patients, only 3% of patients experienced HSR of all grades and severe reactions were extremely rare occurring approximately 1%. No fatal reactions have been reported yet [29]. The proposed low immunogenicity of panitumumab was also supported by immunoassays that detect anti-panitumumab antibodies. Approximately 1% of patients' serum was tested positive for neutralizing antibodies [29]. As with cases of earlier generation MAbs, exact mechanism of panitumumab HSR is not clear at this point. No reported case of re-challenging panitumumab after

Table 4 Pharmaceutical management of acute anaphylaxis in adults: recommendations from Joint Council of Allergy, Asthma and Immunology

Life-threatening signs and symptoms present	
Epinephrine	Initial dose: 0.2–0.5 mL of a 1:1,000 dilution (0.2–0.5 mg) SC or IM may repeat every 10–15 min up to 1 mg per dose If indicated, initiate IV epinephrine: use dilution of 1:10,000 (10 μg/mL) or 1:100,000 (1 μg/mL) Infuse initially at 1 μg/min; may increase to 2–10 μg/min
Oxygen	
Bronchodilators	When bronchospasm present: aerosolized beta-agonist (nebulized albuterol, 2.5–5 mg in 3 mL of saline
Vasopressors	When hypotension presents: may be used in concert with placing patient in recumbent position and infusion of large volumes of IV fluids/colloid.
Glucagon	When concomitant beta-blocker use complicates treatment (1–5 mg IV over 5 min, followed by infusion at 5–15 μg/min
Corticosteroids	May prevent protracted or recurrent anaphylaxis (methylprednisolone IV, up to 0.5 mg/kg every 6 h)
Life-threatening signs and symptoms absent	
Epinephrine	Initial dose: 0.2–0.5 mL of a 1:1,000 dilution (0.2–0.5 mg) SC or IM may repeat every 5 min up to 1 mg per dose
Diphenhydramine	1–2 mg/kg maximum to 50 mg IV
Corticosteroids	Oral prednisone 0.5 mg/kg may be considered

IM intramuscularly, *IV* intravenously, *SC* subcutaneously

severe HSR was published due to lack of clinical experience. A 50% reduction of infusion rate is appropriate with grade 1–2 HSR. Infusion must be stopped immediately with grade 3–4 HSR with appropriate supportive care regimen described above. Use of premedication was not standardized in clinical trials and it is not routinely recommended.

Scarce data is available on the safety of panitumumab in patients who developed HSR to cetuximab. One anecdotal report was published in May of 2007 describing a 53 year-old male with mCRC who was pretreated with diphenhydramine before receiving an infusion with cetuximab [30]. During the infusion, the patient developed HSR and infusion was stopped and the patient was treated with diphenhydramine 50 mg and dexamethasone 4 mg. The patient was switched to panitumumab 6 mg/kg and began treatment 5 weeks after his reaction to cetuximab. He received one dose every 2 weeks. He completed six doses of panitumumab without premedication and without incident before experiencing further disease progression. A decision was made by the patient and his family to cease active therapy and he was referred to hospice. A similar case also describes a 39-year-old white male with mCRC who received cetuximab monotherapy as third-line treatment and experienced an HSR with massive facial urticaria within 5 min despite premedication with dexamethasone, clemastine, and ranitidine [31]. A second attempt was made at a reduced infusion rate 90 min later with the same response. No subsequent cetuximab was given. The patient was then given panitumumab. The patient was premedicated with cetrizine. No HSR occurred and the patient received in total six infusions of panitumumab every 2 weeks. Our cases show a similar response demonstrating a decrease in the incidence of severe HSR to panitumumab requiring no premedication when switched from cetuximab. The most severe reaction to panitumumab presented as a grade II acneiform rash.

Though there is documentation of the low risk of HSR to panitumumab in the trials as mentioned above, these trials do not include patients with a previous reaction to cetuximab. Therefore, the actual risk of HSR to panitumumab in patients with a previously documented reaction to cetuximab is not known. Hypothetically, there should not be cross-over effect given most HSR are likely related to the murine component of cetuximab. However, this hypothesis has yet to be confirmed clinically in future trials of panitumumab in patients with previous cetuximab reactions.

Conclusions

It is important that clinicians treating patients with cetuximab, especially in the middle South region must obtain a thorough history of allergic reaction and be prepared to use an alternative drug, such as panitumimab, for patients with a history of HSR. Bristol-Myers Squibb is studying a screening test for the specific factor that leads to the reaction.

Based on the results of this study, UNC has a physician, physician assistant or nurse practitioner present for the first 30 min of all infusions of cetuximab. The Sarah Cannon Cancer Center halted all studies the drug. Panitumumab can be used safely in patients who previously developed HSR to cetuximab. No fatal HSR has not been reported with panitumumab to date. In case of severe HSR, stop the infusion and administer steroid and antihistamines. Consider to

discontinue the use of panitumumab in cases of the severie or persistent reaction. For prolonged severe reactions admission to hospital should be considered. These occurrences, however, are rare. Further clinical surveillance will be needed to help decide if panitumumab is a safe therapeutic alternative for patients who developed HSR to cetuximab.

References

1. Ritter CA, Arteaga CL (2003) The epidermal growth factor receptor—tyrosine kinase: promising therapeutic target in solid tumors. Semin Oncol 30:3–11
2. Mendelsohn J (2002) Targeting the epidermal growth factor receptor for cancer therapy. J Clin Oncol 20(18 Suppl):1S–13S
3. Ennis BW, Lippman ME, Dickson RB (1991) The EGF receptor system as a target for antitumor activity. Cancer Invest 9:553–562
4. Khazaeli MB, LoBuglio AF, Falcey JW et al (2000) Low immunogenicity of a chimeric monoclonal antibody (MAb), IMC-C225, used to treat epidermal growth factor receptor-positive tumors. Proc Am Soc Clin Oncol 19:207a Abs 808
5. Saltz L, Meropol N, Loehrer PJ et al (2004) Phase II trial of cetuximab in patients with refractory colorectal cancer that express the epidermal growth factor receptor. J Clin Oncol 22:1201–1208
6. Cunningham D, Humblet Y, Siena S et al (2004) Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. N Engl J Med 351:337–345
7. Baselga J, Pfister D, Cooper MR et al (2000) Phase I studies of anti-epidermal growth factor receptor chimeric antibody C225 alone and in combination with cisplatin. J Clin Oncol 18:904–914
8. Lynch DH, Yang XD (2002) Therapeutic potential of ABX-EGF: a fully human anti-epidermal growth factor receptor monoclonal antibody for cancer treatment. Semin Oncol 29(Suppl 4):47–50
9. Patel DD, Goldberg RM (2006) Cetuximab-associated infusion reactions: pathology and management. Oncology (Williston Park) 20(11):1373–1382
10. Kimby E (2005) Tolerability and safety of rituximab (MabThera). Cancer Treat Rev 31(6):456–473 Epub 2005 July 28
11. http://ctep.info.nih.gov/ctc3/ctc-manual.htm
12. Kullmann F, Hollerbach S, Dollinger MJ (2007) Cetuximab plus gemcitabine/oxaliplatin (GEMOXCET) in 1st line metastatic pancreatic cancer. First results from a multicenter phase II study. Gastrointestinal cancers symposium Abs 128
13. Lacouture ME, Melosky BL (2007) Cutaneous reactions to anticancer agents targeting the epidermal growth factor receptor: a dermatology-oncology perspective. Skin Therapy Lett 12(6):1–5
14. Saif MW, Kim R (2007) Incidence and management of cutaneous toxicities associated with cetuximab. Expert Opin Drug Saf 6(2):175–182
15. Cohenuram M, Saif MW (2007) Panitumumab the first fully human monoclonal antibody: from the bench to the clinic. Anticancer Drugs 18(1):7–15
16. Roskos L, Lohner M, Schwab G (2001) A biomathematical model of neoplastic cell growth and prediction on silico of effective doses of ABX-EGF in cancer patients. Proced Am Assoc Cancer Res 42:833 Abs 4471
17. Berlin J, Malik I, Picus J (2004) Panitumumab therapy with irinotecan, 5-fluorouracil, and leukovorin (IFL) in metastatic colorectal patients. Proc of the Eur Soc of Med Onc Abs 265PD
18. Malik I, Hecht JR, Patnaik A, Venook A, Berlin J, Croghan G, Navale L, MacDonald M, Jerian S, Meropol NJ (2005) Safety and Efficacy of panitumumab monotherapy in patients with metastatic colorectal cancer. Proc Am Soc Clin Oncol Abs 3520
19. Hecht JR, Berlin J, Malik I, Picus J, Glisson S, Kozloff M, Spitzer G, Arends R, Hollifield A, Yang B (2005) Panitumumab therapy with irinotecan, 5-fluorouracil, and leukovorin (IFL) in metastatic colorectal patients: a pharmacokinetic analysis. Program of the Am Soc Clin Onc. Gastrointestinal cancers symposium Abs 259
20. Lenz HJ (2007) Management and preparedness for infusion and hypersensitivity reactions. Oncologist 12(5):601–609
21. Melichar B, Cerman J Jr, Malírová E (2007) Successful management of infusion reaction accompanying the start of cetuximab therapy. Support Care Cancer 15(4):445–449
22. Needle MN (2002) Safety experience with IMC-C225, an anti-epidermal growth factor receptor antibody. Semin Oncol 29(5 Suppl 14):55–60
23. O'Neil BH, Allen R, Spigel DR, Stinchcombe TE, Moore DT, Berlin JD, Goldberg RM (2007) High incidence of cetuximab-related infusion reactions in Tennessee and North Carolina and the association with atopic history. J Clin Oncol 25(24):3644–3648
24. Chung CH, Mirakhur B, Chan E, Le QT, Berlin J, Morse M, Murphy BA, Satinover SM, Hosen J, Mauro D, Slebos RJ, Zhou Q, Gold D, Hatley T, Hicklin DJ, Platts-Mills TA (2008) Cetuximab-induced anaphylaxis and IgE specific for galactose-alpha-1, 3-galactose. N Engl J Med 358(11):1109–1117
25. Milland J, Sandrin MS (2006) ABO blood group and related antigens, natural antibodies and transplantation. Tissue Antigens 68:459–466
26. Paschinger K, Fabini G, Schuster D et al (2005) Definition of immunogenic carbohydrate epitopes. Acta Biochim Pol 52:629–632
27. van der Veen MJ, van Ree R, Aalberse RC et al (1997) Poor biologic activity of cross-reactive IgE directed to carbohydrate determinants of glycoproteins. J Allergy Clin Immunol 100:327–334
28. Adédoyin J, Gronlund H, Oman H, Johansson SG, van Hage M (2007) Cat IgA representative of new carbohydrate cross-reactive allergens. J Allergy Clin Immunol 119(3):640–645
29. Saif MW, Cohenuram M (2006) Role of panitumumab in the management of metastatic colorectal cancer. Clin Colorectal Cancer 6(2):118–124
30. Heun J, Holen K (2007) Treatment with panitumumab after a severe infusion reaction to cetuximab in a patient with metastatic colorectal cancer: a case report. Clin Colorectal Cancer 6(7):529–531
31. Helbling D, Borner M (2007) Successful challenge with the fully human EGFR antibody panitumumab following an infusion reaction with the chimeric EGFR antibody cetuximab. Ann Oncol 18(5):963–964