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Successful Treatment with Panitumumab and Irinotecan in a Colorectal Cancer Patient with a Severe Hypersensitivity Reaction to Cetuximab

Leila R Mohassel[1], Andrew Whitman[2], Kara Zacholski[3] and William B Ershler[4]

[1]*Inova Fairfax Hospital, Virginia, USA*
[2]*University of Virginia Health System, Virginia, USA*
[3]*Detroit Receiving Hospital, USA*
[4]*Hematology-Oncology Division, Institute for Advanced Studies in Aging, USA*

Abstract

Infusion-related reactions resulting from administration of monoclonal antibodies targeting the epidermal growth factor receptor (EGFR) are well defined in the literature. Although these reactions occur more frequently with earlier generation antibodies such as cetuximab, which contains 34% murine protein, the risk of immunogenicity is still present with fully human and humanized antibodies. Panitumumab is the first fully human monoclonal antibody approved by the US Food and Drug Administration for the treatment of patients with metastatic colorectal cancer. It is associated with a lower risk of hypersensitivity reactions and premedications are not routinely required. Because of the inherent differences in protein sequence between the two agents, patients who experience infusion reactions with cetuximab may tolerate panitumumab administration. There are however limited data on the safety of panitumumab in patients with prior infusion reactions to cetuximab. We report a case of a 62-year-old patient with metastatic colorectal cancer who was treated successfully with panitumumab and irinotecan after developing a grade 4 infusion reaction to cetuximab therapy. Treatment with panitumumab was initiated approximately five weeks after the single dose of cetuximab resulted in respiratory failure, cardiac arrest and intensive care management. The patient was premedicated prior to first and all subsequent doses. To date, the patient has not experienced any hypersensitivity reactions and continues to receive panitumumab in combination with chemotherapy with objective improvement in his overall condition. This case suggests that panitumumab maybe safely administered in patients with prior infusion reactions to cetuximab.

Keywords: Panitumumab; Cetuximab; Hypersensitivty reaction

Abbreviations: mCRC: Metastatic Colorectal Cancer; EGFR: Epidermal Growth Factor Receptor; Fab: Fragment Antigen Binding; HSR: Hypersensitivity Reactions; Cmab: Cetuximab; Pmab: Pantitumumab; PET/CT: Positron Emission Tomography-Computed Tomography; CEA: Carcinoembryoinc Antigen

Background

There are currently two monoclonal antibodies approved for the treatment of patients with metastatic Colorectal Cancer (mCRC): cetuximab (Erbitux©) and panitumumab (Vectibix©) [1]. Both of these agents target the extracellular domain of the epidermal growth factor receptor (EGFR), a known signaling pathway involved in the pathogenesis of colorectal cancer. Cetuximab is a chimeric IgG1 monoclonal antibody that is composed of approximately 34% mouse protein and is used in combination with chemotherapy or as monotherapy for patients with mCRC. In comparison, panitumumab is a fully human IgG2 monoclonal antibody that is indicated for patients with disease progression who have received fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens [1]. The development of an acneiform skin rash is the most common toxicity reported with these agents, and both cetuximab and panitumumab carry boxed warnings for severe infusion reactions [2]. Grade 1 or 2 hypersensitivity reactions occur in about 19% of patients treated with cetuximab and 3% of those treated with panitumumab. The majority of infusion reactions develop with the first or second dose; premedication with an antihistamine is recommended prior to cetuximab but not with panitumumab administration.

Severe infusion reactions (grade 3 or 4) are rare with an overall incidence of 3% for cetuximab and less than 1% for panitumumab [2]. Recent data, however, suggest that patients who live in the mid-southeast region of the United States, such as North Carolina or Tennessee, are at greater risk of developing severe infusion reactions when undergoing treatment with cetuximab [3]. The reason for such regional variability is unclear but may be due to pre-existing serum IgE antibodies prior to treatment [3,4]. According to prescribing information, the further use of cetuximab therapy in patients with severe hypersensitivity reactions is contraindicated because of the significant risk for subsequent adverse outcomes. Because of differences in rates of life-threatening hypersensitivity reactions, panitumumab appears to be a viable alternative in patients who might benefit from anti-EGFR therapy but are intolerant to cetuximab. Herein, we report a patient that was treated successfully with panitumumab after developing a severe hypersensitivity reaction following cetuximab therapy.

Case Report

A 62-year-old male was diagnosed with locally advanced colon cancer in 2006. He was initially managed with surgical resection of the colon and adjuvant capecitabine. In April 2012, he was found to have a single pulmonary nodule which, upon resection proved to be carcinoma with immunostaining characteristics of colon carcionoma. He was treated with six cycles of capecitabine and oxaliplatin and upon completion a Positron Emission Tomography-Computed Tomography (PET/CT) scan revealed post surgical changes without evidence for active disease. However, approximately a year later, the patient

***Corresponding author:** Leila R Mohassel, Inova Fairfax Hospital, 3300 Gallows Road, Falls Church, Virginia 22042, USA, E-mail: leila.mohassel@inova.org

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he presented with symptoms of bronchitis which did not improve with antibiotics. A repeat CT demonstrated innumerable bilateral pulmonary nodules most consistent with metastatic disease. A right lower lobe nodule was biopsied once again revealing changes consistent with adenocarcinoma of the colon and tumor tissue revealed wild type *K-ras* expression.

Treatment was begun with cetuximab and irinotecan. Premedications with acetaminophen and diphenhydramine were administered prior to the cetuximab infusion. Within a few minutes after initiation of the loading dose, the patient became unresponsive and suffered a cardiopulmonary arrest. The infusion was stopped immediately and hydrocortisone, atropine, and epinephrine were administered. Patient was intubated and transferred to the intensive care unit. The following day, his condition stabilized, he was extubated and as planned received single-agent irinotecan 350 mg/m^2 over 90 minutes.

Due to rapid progression of his tumor after two cycles of irinotecan, alternative options including cetuximab desensitization and use of other anti-EGFR therapies were discussed. Based on previously published case reports and after thorough discussions with the patient and his family, a decision was made to challenge with panitumumab. Two months after the severe hypersensitivity reaction to cetuximab, the patient was admitted to the hospital to receive his first dose of panitumumab (6 mg/kg over 60 minutes) in the intensive care unit. He was premedicated with acetaminophen, dexamethasone, diphenhydramine, and famotidine. He reported drowsiness after the administration of diphenhydramine but no hypersensitivity reactions were observed during or after the panitumumab infusion. He remained in the ICU for close monitoring for 24 hours and was transferred the oncology unit on the following day. All subsequent doses have been administered on an outpatient basis without any symptoms suggestive of an infusion reaction. To date, he has received a total of 16 doses of panitumumab in combination with irinotecan. In addition to a subjective improvement in his sense of well-being, there have been objective indicators of durable disease response including chest CT and near normalization of Carcino Embryoinc Antigen (CEA) level.

Discussion

Infusion reactions are a well-known side effect of monoclonal antibodies that occur commonly in patients receiving chimeric antibody therapy [5]. Most reactions are mild to moderate in severity and develop during or shortly after the first or second infusion. Severe hypersensitivity reactions characterized by hypotension, bronchospasms, urticaria, and/or cardiac arrest are rare but can lead to potentially life-threatening complications [6]. The underlying mechanisms involved in infusion-related reactions as a result of targeted therapies have not been fully elucidated. Chimeric immunoglobulins that contain a small amount of murine protein are more likely to induce an immune response when compared to fully human antibodies such as panitumumab. The lower incidence of hypersensitivity reactions with panitumumab has been documented in a number of colorectal cancer studies. In a phase III trial that included a total of 463 mCRC patients randomized to panitumumab monotherapy versus best supportive care, infusion-related reactions were observed in only 4% of treatment group with no grade 3 or 4 reactions reported [7]. When combined with chemotherapy upfront or in the second-line setting, rates of infusion-related reactions remained low, occurring in about 1% of patients with mCRC. Because of the lack of murine sequences and the resultant lower immunogenicity, panitumumab appears to be a viable option in patients who are intolerant to other anti-EGFR therapy such as cetuximab.

There is a growing literature base for patients who are treated successfully with panitumumab after developing a severe hypersensitivity reaction to cetuximab [1-3,8-13]. Table 1 summarizes some of the existing reports of patients treated with panitumumab after a reaction to cetuximab [1-3,8-13].. The first report, published in 2007, describes a 53 year-old male with mCRC who despite premedication with diphenhydramine developed a grade 3 hypersensitivity reaction during cetuximab loading dose. Five weeks after this reaction, the patient was challenged with panitumumab 6mg/kg administered on an every two week schedule. He received a total of six doses without any complications before he was diagnosed with disease progression. A subsequent case reported similar findings in a 55 year-old male with metastatic rectal cancer. Approximately five weeks after experiencing a grade 4 hypersensitivity reaction to cetuximab, the patient was given panitumumab every 2 weeks and tolerated all infusions without any symptoms indicative of infusion reactions. A series of four case reports published by Langerak and colleagues provides further support for using panitumumab in patients intolerant of cetuximab. All patients had mCRC previously treated with 5-flourouracil-based regimens and bevacizumab. Three of the four patients experienced grade 4 infusion reactions within 15 minutes after initiation of cetuximab. The patient with atypical presentation developed a delayed reaction 18 months after cetuximab exposure. Subsequent therapy with panitumumab 6 mg/kg repeated every other week was tolerated in all patients. Panitumumab was given as early as eight days in one patient without incident. A report of six patients with grade 3 or 4 hypersensitivity reactions post-cetuximab administration also demonstrated a lack of cross reactivity with panitumumab. All patients had metastatic colorectal cancer with the majority receiving treatment in the third-line setting. Panitumumb was given in combination with chemotherapy and patients tolerated all doses without evidence of hypersensitivity reactions. The most

Reference	n	Cancer diagnosis	Cmab dose # at time of HSR	Grade of HSR	Time interval between Cmab and Pmab	Pmab premeds	Tolerance to Pmab	Duration of Pmab treatment
Heun et al. [2]	1	Colon	Dose #1	Grade 3	5 weeks	None	No reaction	6 doses
Cartwright et al. [8]	1	Rectal	Dose #1	Grade 4	5 weeks	Hydrocortisone and lorazepam	No reaction	16 doses
Langerak et al. [10]	4	3 Colon 1 Rectal	Dose #1 in 3 pts After 18 months in 1 pt	Grade 3 and 4	8 days – 5 months	No premeds in 2 pts Premeds with diphenhydra + methypred +/- cimetidine in 2 pts	No reaction	1-11 doses
Nielsen et al. [11]	6	5 Colon 1 Rectal	Unknown	Grade 3 and 4	Unknown	No premeds in 5 pts	No reaction	Unknown
Saif et al. [12]	3	1 Colon 1 Rectal 1 Pancreas	Dose #1 in 2 patients After 4 months in 1 pt	Grade 3	8 days-3 months	No premeds	No reaction	2-6 doses
Resch et al. [13]	20	Colorectal	Unknown	Unknown	Unknown	Unknown	No reaction	1-32 doses

Table 1: Summary of patient cases successfully re-challenged with panitumumab after cetuximab therapy.

common adverse event reported was dermatologic toxicities grade 2 or 3 observed in all six patients. The lower incidence of infusion reactions with panitumumab is also evident by a report published in 2009 in which three patients with severe hypersensitivity reactions to cetuximab were successfully re-challenged with panitumumab. Grade 3 infusion reactions occurred during initial treatment with cetuximab in two patients and after 4 months in one patient. No premedications were administered and all three patients tolerated multiple doses of panitumumab. A recent publication which included twenty heavily pretreated mCRC patients in a compassionate use program yielded similar results, indicating safe use of panitumumab in patients with previously documented infusion reactions to cetuximab. In the majority of cases reported here, no premedication was used before the initiation of panitumumab. When administered, patients received one or more of the following agents: methylprednisolone, diphenhydramine, cetirizine, lorazepam, or cimetidine [10]. In addition, there is currently no consensus on the appropriate interval between cetuximab infusion reaction and subsequent trial of panitumumab. In the case reports the time frame ranged from eight days to five months with the average being around 49 days [2,8,10]. Our patient received panitumumab 2 months after his severe reaction to cetuximab therapy and was given premedications with each dose which may have contributed to the prevention of an infusion reaction with panitumumab.

Conclusion

Discontinuation of potentially beneficial anti-EGFR therapy because of infusion reactions has been reported in approximately 1-3% of patients enrolled in cetuximab studies. Results from several case reports and case series suggest that panitumumab is a safe therapeutic alternative in patients who are intolerant to cetuximab. Most likely explanation for the lack of cross-reactivity is the absence of murine proteins in the panitumumab antibody structure. Although the reported risk of grade 3 or 4 infusion reactions with panitumumab is low, none of the trials included patients with a prior history of infusion reactions to cetuximab. Therefore, the actual incidence of severe hypersensitivity reactions in patients with documented reactions to cetuximab is not known and panitumumab should be used cautiously. In our case, the patient was successfully rechallenged with panitumumab after a grade 4 reaction to cetuximab. Although premedications are not routinely recommended with the use of this agent, we took a more conservative approach in light of the severe reaction to cetuximab and heavily premedicated the patient prior to panitumumab. Our case adds to the existing literature suggesting that patients unable to tolerate cetuximab because of severe hypersensitivity reactions can benefit from subsequent panitumumab therapy. Further studies are warranted to confirm these clinical findings.

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