CASE REPORT

Cetuximab desensitization protocol in two patients with metastatic colorectal cancer after grade 3 infusion reaction to cetuximab

Augusto T. Akikubo Rodrigues Pereira[1], Ludmilla T. Domingos Chinen[2], Flavio A. Ismael Pinto[1], Debora de Melo Gagliato[3], Elizabeth Santana dos Santos[4], Joyce M. Lisboa Maia[5], Ronei J. Feitosa de Assis[5], Rafael Costa Lessa[5], Adriana R. Gonçalves Ribeiro[5], Maria Nirvana da Cruz Formiga[1], Vladmir Claudio Cordeiro de Lima[6], Celso A. Lopes Mello[6]

Abstract

Targeted monoclonal antibodies have become an important therapeutic option for patients with cancer. Cetuximab, a chimeric mouse-human (30:70) immunoglobulin G1 monoclonal antibody against epidermal growth factor receptor, has been approved by the US Food and Drug Administration for the treatment of head and neck and metastatic colorectal cancer (mCRC). Severe (grade 3/4) hypersensitivity-infusion reactions (HIRs) occur in 2-3% of the patients, with fatal outcomes in 0.1%. It is recommended that patients showing severe HIRs to cetuximab should avoid further exposure to it, but in some cases there is no alternative treatment. Two options are currently available for patients with HIRs to cetuximab: desensitization protocol and panitumumab. We describe here two patients with mCRC who successfully underwent a cetuximab desensitization protocol following a severe HIR to cetuximab.

Keywords: cetuximab, colorectal neoplasms, infusions, intravenous/adverse effects, neoplasm metastasis.

INTRODUCTION

Epidermal growth factor receptor (EGFR), a member of the transmembrane receptor tyrosine kinase family, is overexpressed in many human malignancies and usually linked to poor prognosis and more advanced disease[1]. EGFR has become an important therapeutic target since several clinical trials demonstrated that blocking it has direct antitumor activity[2-5].

Cetuximab (CTX) is a chimeric mouse-human (30:70) immunoglobulin (Ig) G1 monoclonal antibody that binds specifically to the extracellular domain of human EGFR and competitively inhibits the binding of EGF and other ligands, blocking the phosphorylation and activation of receptor-associated kinases[6-7]. It has been approved by the US Food and Drug Administration (FDA) for the treatment of head and neck[2-3] and metastatic colorectal cancer (mCRC)[4,5].

The primary collateral effects of CTX include skin rash, headache, fever, chills, nausea, constipation, diarrhea and hypomagnesemia[7-8]. Severe (grade 3 and 4) hypersensitivity-infusion reactions (HIRs) occur in 2-3% of the patients, with fatal outcomes in 0.1%[7]. There is a broad range of geographical variation in incidence of severe HIRs, ranging from less than 1% to up to 22%[9-11].

It is recommended that patients showing a severe HIR to CTX should avoid further exposure to it, but in some cases there is no alternative treatment. In this situation, patients may be retreated with the same agent under controlled conditions[12,13] or receive panitumumab[14-18], a fully human IgG2 monoclonal antibody against the extracellular domain of human EGFR[18].

We describe here two patients with mCRC who successfully underwent a CTX desensitization protocol (DP)[12] following a severe HIR to CTX.

Case 1: A 60-year-old man with mCRC received 12 cycles of FOLFOX-6 followed by 10 cycles of FOLFIRI plus bevacizumab (BVZ). Because of peritoneal

[1] MD - Medical Doctor of A.C. Camargo.
[2] PhD - Researcher - São Paulo - SP. Brazil.
[3] MD - Medical Doctor of Hospital Sirio Libanes.
[4] MD - Medical Doctor.
[5] MD - Resident Medical Doctor of A.C. Camargo.
[6] MD, PhD - Medical Doctor of A.C. Camargo.

Send correspondence to:
Fundação Antônio Prudente - Hospital A. C. Camargo.
Augusto T. Akikubo Rodrigues Pereira,
Rua Professor Antônio Prudente, nº211, Liberdade. São Paulo - SP. Brazil.
CEP: 01509-010
Phone: +55 11 2189-1231
E-mail: augustopereira68@gmail.com

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carcinomatosis, he started on FOLFIRI plus CTX. After 15 min of infusion, he experienced hypotension (80/40 mmHg), tachycardia (120 beats/min), shortness of breath without decreased O_2 saturation, hoarseness, and generalized urticaria (grade 3 HIR). Because of limited options, we suggested a DP with CTX. He agreed and signed an informed consent form. The DP consisted of dose escalation every 15 min, with each dose representing a doubling of the prior dose. The drug was infused at a constant rate of 5 mL/min, while varying the time of infusion and the concentration of the solution (12). He was admitted to the medical intensive care unit (ICU) and pre-medicated with prednisone (PDN) 20 mg 12 h and 1 h before DP and diphenhydramine (DPH) 50 mg IV 30 min before DP. A total CTX dose of 732.4 mg (400 mg/m^2) was calculated and he tolerated the infusion with no symptoms until the completion of bag 3. After 30 min infusion of bag 4, he developed hoarseness, rash and shortness of breath. The infusion was stopped for 1 h and he received DPH 50 mg and hydrocortisone (HYD) 100 mg. After symptoms resolution, we decided to continue the DP at half the infusion rate (2.5 mL/min). No symptoms were observed until the completion of bag 5 and FOLFIRI was administered uneventfully (Table 1). Twenty days later, he was re-challenged with CTX in the ICU with bags 4 and 5 infused at a rate of 2.5 mL/min following intravenous premedication with HYD 100 mg and DPH 50 mg. Cycle 2 was completed without any allergic reactions. Although the DP was successful, he continued to show symptoms of intestinal occlusion and infectious complications, interrupting subsequent cycles. He died 2 months later.

Case 2: A 54-year-old woman with mCRC, treated with 9 cycles of FOLFOX6 plus BVZ, received FOLFOX6 plus CTX due to liver disease progression. In cycle 2, within 5 min of CTX infusion, she experienced hypotension (60/40 mmHg), tachycardia (114 beats/min), dyspnea with decreased O_2 saturation (78%), diaphoresis and generalized urticaria (grade 3 HIR). Owing to persistent thrombocytopenia, we suspended FOLFOX6 and suggested DP with single agent CTX. She agreed and signed an informed consent form. After premedication with PDN, DPH and ranitidine (RAN), a total CTX dose of 372 mg (250 mg/m^2) was administrated according to the same protocol. The first four bags were administered without symptoms. After 10 min infusion of bag 5, she experienced nausea, emesis, fever and rash. The infusion was stopped and she received DPH 50 mg, HYD 100 mg and RAN 50 mg. After reversal of symptoms, the infusion rate was modified to 2.5 mL/min and no symptoms were observed until completion of bag 5. We decided to maintain the same protocol with the modified infusion rate of 2.5 mL/min for the last bag. She tolerated 3 more cycles and then, we added FOLFIRI despite the thrombocytopenia. She underwent 3 cycles of FOLFIRI plus CTX before presenting disease progression.

Table 1. Cetuximab desensitization protocol of patient 1. Adapted from Jerath et al.[12].

Bag 1: 0.0002 mg/ml (SC 0.9% 1000 ml + cetuximab 0.2 mg)

Dose nº	Cumulative dose	Dose of cetuximab (mg)	Volume of infusion (mL)	Time of infusion (min)
1	0.001	0.001	5	1
2	0.003	0.002	10	2
3	0.007	0.004	20	4
4	0.015	0.008	40	8

Bag 2: 0.002 mg/ml (SC 0.9% 1000 ml + cetuximab 2 mg)

Dose nº	Cumulative dose	Dose of cetuximab (mg)	Volume of infusion (mL)	Time of infusion (min)
1	0.03	0.015	7.5	1.5
2	0.06	0.03	15	3
3	0.12	0.06	30	6
4	0.25	0.13	65	13

Bag 3: 0.02 mg/ml (SC 0.9% 250 ml + cetuximab 5 mg)

Dose nº	Cumulative dose	Dose of cetuximab (mg)	Volume of infusion (mL)	Time of infusion (min)
1	0.5	0.25	12.5	2.5
2	1.0	0.5	25	5
3	2.0	1.0	50	10
4	4.0	2.0	100	20

Bag 4: 0.2 mg/ml (SC 0.9% 300 ml + cetuximab 60 mg)

Dose nº	Cumulative dose	Dose of cetuximab (mg)	Volume of infusion (mL)	Time of infusion (min)
1	8.0	4.0	20	4
2	16.0	8.0	40	8
3	32.0	16.0	80	16
4	64.0	32.0	160	32

Bag 5: 2 mg/ml (cetuximab 668.4 mg)

Dose nº	Cumulative dose	Dose of cetuximab (mg)	Volume of infusion (mL)	Time of infusion (min)
1	129.0	65	32.5	6.5
2	259.0	130	65	13
3	519.0	260	130	26
4	732.4	213.4	106.7	21.5

Premedication: prednisone 20 mg 12 hours and 1 hour before desensitization, diphenhydramine 50 mg intravenously 30 minutes before desensitization. Infusion rate of 5 mL/min unless otherwise specified. Successive doses are 15 minutes apart unless otherwise specified.

DISCUSSION

Target monoclonal antibodies have been used as a promising treatment option for patients with cancer, despite the minimal risk of infusion reaction.

The mechanisms underlying HIRs to CTX remain unclear, although the immediate and severe nature of these reactions indicates a pre-existing IgE-based immune reaction directed at the antibody itself[2]. Up to 90% of severe HIRs occurred with the first CTX infusion despite premedication, suggesting that these reactions are not IgE-mediated[7]. However, in another study, 33% of grade 3-4 HIRs required a second infusion of CTX[8]. All grade 4 HIRs occurred a few minutes after infusion, indicating a possible difference in mechanism between mild and severe HIRs. Chung et al. reported that most early HIRs to CTX were observed in patients with pre-existing IgE antibodies against the galactose-a-1,3-galactose (GaG) portion of the CTX molecule[4]. In addition, cross-reactive responses may be due to exposure to mouse antigens, particular plants or tree pollen[2-3]. There is no data in the literature describing cross-reaction between CTX and BVZ.

Two options are available for patients with HIRs to CTX: DP and panitumumab[14], a fully human IgG2 monoclonal antibody against EGFR. Successful DP was reported by Jerath et al.[12]. in a metastatic breast cancer patient with confirmed IgE-mediated HIR and by Nielsen et al.[13] in CRC patients with grade 2 HIR. Some case reports described successful treatment with panitumumab in patients who experienced HIRs to CTX infusion, suggesting a non-cross reactive IgE hypersensitivity (Table 2).

Based on our report, re-treatment with cetuximab desensitization protocol after grade 3 HIR to the same agent is feasible and may be considered in selected patients due to limited therapeutic options in cases of progressive mCRC. Even during DP, HIR can occur and should only be tried in a monitored environment, such as an Intensive Care Unit, and the entire medical and nurse staff should be trained to recognize and treat the initial signs and symptoms of HIR.

CONCLUSION

Desensitization protocol with cetuximab is a reasonable and safe option in patients with HIR to the same agent.

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Table 2. Case reports of treatments after infusion reactions to cetuximab and panitumumab.

Authors	Patients	Sex	Age	Diagnosis	Drug exposure	Grade	Treatment
Heun et al.[14]	1	M	53	mCRC	CTX (3rdL)	3	PNT
Nielsen et al.[13]	1	F	68	mCRC	CTX (3rdL)	2	CTX DP
	2	M	57	mCRC	CTX (3rdL)	2	CTX DP
Cartwrigh et al.[16]	1	M	55	mCRC	CTX (3rdL)	3	PNT
Jerath et al.[12]	1	F	60	mBC	CTX	3	CTX DP
Saif et al.[18]	1	F	42	mCRC	PNT (3rdL)	3	CTX DP
	2	M	70	mCRC	PNT (2ndL)	3	CTX DP
Saif et al.[18]	1	M	58	mCRC	CTX (3rdL)	3	PNT
	2	F	58	mCRC	CTX (4thL)	3	PNT
	3	M	62	mPC	CTX (1stL)	3	PNT
Langerak et al.[15]	1	F	52	mCRC	CTX	4	PNT
	2	M	48	mCRC	CTX	4	PNT
	3	F	59	mCRC	CTX	4	PNT
	4	M	58	mCRC	CTX	3	PNT

mCRC: metastatic colorectal cancer; mPC: metastatic pancreatic cancer; mBC: metastatic breast cancer; L: line of treatment, PNT: panitumumab; CTX: cetuximab; DP: desensitization protocol.

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