Journal of Case Reports in Practice (JCRP) 2013; 3: 73-75

CASE REPORT

Cetuximab induced acute cardiotoxicity, a rare but severe side effect

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ABSTRACT

Cetuximab is a monoclonal antibody that treats malignant disease by inhibiting epidermal growth factor receptors. Cetuximab has many common adverse events have been reported including infusion reactions, skin rashes, headache and gastrointestinal disturbances. Cardiactoxicity and cardiac complications such as heart failure (HF), myocardial ischaemia, arrhythmias, hypertension, and thromboembolism are some types of side effects of anticancer agents, cardiovascular complications are one of the most feared side-effects as they can increase mortality which interferes with the gain in life expectancy due to anticancer therapy. Up till now, cetuximab associated cardiotoxicity has been rarely reported in the literature.

In this paper we are reporting a case of 89-year-old male diagnosed to have laryngeal squamous cell carcinoma with a history of hypertension but no history of coronary artery disease; he developed non-ST elevation myocardial infarction (NSTEMI) after receiving the loading dose of cetuximab; his case was deteriorated to develop heart failure and atrial fibrillation and required admission to cardiac intensive care unit (CCU) on mechanical ventilation.

Assessment of cardiac toxicity remains a critical issue in cancer management; physicians should be aware of the potential for cardiotoxicity associated with the administration of cetuximab. Before treatment with monoclonal antibodies; caution and baseline assessment are suggested for patients aged >60 years, or with cardiovascular risk factors such as hypertension, hypercholesterolaemia, diabetes, obesity, or with a history of coronary artery disease, congestive heart failure, or arrhythmias,critical monitoring of serum electrolytes (including magnesium, potassium and calcium) should be monitored during and after treatment.

Key words: cetuximab, cardiotoxicity, monoclonal antibody, laryngeal carcinoma

INTRODUCTION

Cetuximab is a monoclonal antibody (IgG1 Mab) it inhibits the function of epidermal growth factor receptor (EGFR, HER1, c-ErbB-1) which is a molecular structure expressed on the surface of normal and tumor cells.[1, 2] EGFR is part of a signaling pathway that is linked to the growth and development of many human cancers, including those of the head and neck, colon and rectum. Binding of cetuximab to the EGFR blocks phosphorylation and activation of receptor-associated kinases and this was shown in in-vitro assays and in-vivo animal studies resulting in inhibition of cell growth, induction of apoptosis, and decreased matrix metalloproteinase and vascular endothelial growth factor production. In vitro, cetuximab has activity mediating antibody-dependent cellular cytotoxicity (ADCC) against certain human tumor types. The in-vivo mechanism of cetuximab anti-tumor effect(s) is unknown; however all of these processes may contribute to the overall therapeutic effect of cetuximab.[3]

Cardiopulmonary arrest and/or sudden death have been reported in 2% of patients treated with concurrent radiation in squamous cell carcinoma of the head and neck[4], with fatal events reported 1-43 days following the last treatment.[8]

In a post marketing surveillance study done on 1800 patients; cardiotoxicity was observed in 17 patients (0.9%) and cardiotoxicity ≥ grade 3 was reported in 0.2% (n=5). Cardiotoxicity included myocardial infarction, right and left heart failure and coronary spastic angina. All five patients with cardiotoxicity ≥ grade 3 were treated with cetuximab plus irinotecan or FOLFIRI (FOL-folinic acid, F-fluorouracil, IRI-irinotecan), and four patients died.[9]

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An 89-year-old male patient known to have hypertension but no history of coronary artery disease, he was admitted to National Centre for Cancer Care and

Table 1, Naranjo causality scale for adverse drug reactions[11]

Question	Scoring			
	Yes	**No**	**Do Not Know or N/A**	**Score**
1. Are there previous conclusive reports on this reaction?	+1	0	0	+1
2. Did the adverse event appear after the suspected drug was given?	+2	+1	0	+2
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?	+1	0	0	+1
4. Did the adverse reaction appear when the drug was re-administered?	+2	-1	0	0
5. Are there alternative causes that could have caused the reaction?	-1	+2	0	+2
6. Did the reaction reappear when a placebo was given?	-1	+1	0	0
7. Was the drug detected in any body fluid in toxic concentrations?	+1	0	0	0
8. Was the reaction more severe when the dose was increased/ increasing, or less severe when the dose was decreased?	+1	0	0	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	+1
Total				+6

Scoring: > 9: definite adverse drug reaction (ADR), 5-8: probable ADR, 1-4: possible ADR, 0: doubtful ADR[11]

Research with hoarseness of voice and upon investigations he was found to have laryngeal squamous cell carcinoma, he was not fit for surgery so the decision of the multidisciplinary team meeting was to consider chemo/ radiotherapy, patient has ECOG score 3, so based on patient's clinical conditions it was decided to consider cetuximab as single agent concurrently with radiation, patient was evaluated by radiation oncologist but based on the patient performance and poor condition it was decided to postpone radiation till the patient's condition improves and start cetuximab as 400 mg/m2 IV loading dose for one dose starting on day1, followed by 250 mg/m2 IV weekly. Patient was started on the loading dose of cetuximab as 400 mg/m2, patient tolerated the infusion very well, but on day 2 he developed chest discomfort and palpitation, ECG and cardiac enzymes showed abnormalities, cardiology team was consulted and patient was diagnosed with Non-ST elevation myocardial infarction (NSTEMI), patients condition deteriorated and developed heart failure and atrial fibrillation. Patient was transferred to CCU on mechanical ventilation for 5 days. Based on the current poor performance condition of the patient he was not fit for any further oncologic management, and his treatment plan was changed to only best supportive care.

DISCUSSION

Cetuximab is a recombinant chimeric monoclonal antibody that binds to the human epidermal growth factor receptor (EGFR) with high affinity.[1], Cetuximab also induces internalization and degradation of EGFR, with resulting down regulation of cell surface receptors and reduced EGFR signaling.[6] Mutation of the K-ras gene, a part of the EGFR signalling cascade, may affect response to cetuximab, in that mutated K-ras in the tumour cell may render EGFR inhibitors ineffective.[5] Cetuximab is cell cycle phase-specific, arresting cells in the G1 phase.[4]

Cetuximab is an indicated treatment for locally advanced squamous cell carcinoma of the head and neck stage III and IV, squamous cell carcinoma of the hypopharynx, oropharynx, oral cavity, supraglottic or larynx including head and neck primary unknown with cervical lymphadenopathy. Cardiotoxicity has also been reported following fluorouracil treatment and it is important to pay close attention when administering cetuximab in combination with these drugs.[9]

New anticancer therapies have led to a long life expectancy for many patients; however, treatment-related comorbidities have become an issue for long-term cancer survivors.[10] Cardiovascular complications are one of the most feared side-effects as they can increase mortality which interferes with the gain in life expectancy due to anticancer therapy.[1, 2]

The report describes a patient with cardiotoxicity secondary to administration of cetuximab (monotherapy). Our case have hypertension but no history of coronary artery disease prior to the administration of cetuximab, after receiving the loading dose of cetuximab; patient developed non-ST elevation myocardial infarction (NSTEMI), who deteriorated to develop heart failure and atrial fibrillation and required admission to cardiac intensive care unit (CCU) on mechanical ventilation.

The incidence of cardiotoxicity depends on different factors related to oncological therapies (type of drug, dose administered during each cycle, cumulative dose, schedule of administration, route of administration, combination of other cardiotoxic drugs or association with radiotherapy) and to patient [age, presence of cardiovascular (CV) risk factors, previous cardiovascular disease (CVD), prior mediastinal radiation therapy]. Detection of cardiac injury is crucial since it may facilitate early therapeutic measures. Naranjo scale for adverse drug reactions we obtained a score of 6 (probable adverse drug reaction), table 1.[11] Based on that and on the clinical and investigation findings we considered a possibility of cardiotoxicity induced after the first cycle of cetuximab.

CONCLUSION

Clinicians should be aware that in patients treated with cetuximab cardiotoxicity can occur as an adverse reaction of this drug. Assessment of baseline systolic and diastolic cardiac function with baseline Doppler echocardiogram (DEcho) might be conducted before treatment with monoclonal antibodies in patients aged >60 years,with cardiovascular risk factors such as hypertension, hypercholesterolaemia, diabetes, obesity or previous treatment with 5-hydroxytryptamine-2B agonists (in Parkinson or obese patients) potentially inducing cardiac valvulopathy, or documented cardiopathy or previous thoracic radiotherapy.[2]

Critical monitoring of serum electrolytes (including magnesium, potassium and calcium) should be monitored during and after treatment. Caution is suggested for patients with a history of coronary artery disease, congestive heart failure, or arrhythmias.[3]

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