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CASE REPORT

Cardiotoxicity associated with 5-flurouracil – A case series

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ABSTRACT

5-flurouracil (5-FU) is a frequently administered chemotherapeutic drug in various malignant neoplasms. We report four cases of cancer patients who were exposed to 5-FU and which resulted in cardio toxicity. Patients developed supraventricular tachycardia, sinus bradycardia, cardiomyopathy, and acute coronary vasospasms. In all cases, the events were reversible. Except in case of cardiomyopathy the chemotherapy was continued without any further issues. All the observed adverse drug reactions (ADR) were carefully studied and the causality was assessed using Naranjo ADR probability scale.

KEY WORDS: 5-Flurouracil; Cardiotoxicity; Cardiomyopathy

INTRODUCTION

5-flurouracil (5-FU) is a chemotherapeutic drug which comes under the category of antimetabolite agents or pyrimidine analogs, commonly used in the treatment of gastrointestinal tract carcinomas (CA), breast cancer, head and neck, cervical CA, etc.[1] Diarrhea, myleosuppresion, and thrombophlebitis of peripheral veins are the common toxicities associated with 5-FU.[2] The common cardiotoxicitis reported with the 5-FU administration are angina, myocardial infarction, QTc prolongation, congestive heart failure, cardiomyopathy, ventricular tacchycardias, cardiogenic shock, and sudden cardiac death.[3,4] The proposed mechanism of 5-FU-induced cardiotoxities are coronary artery spasm, endothelial damage, autoimmune mediated damage of the myocardium, thrombogenic effects or thrombus formation, direct myocardial toxicity causing necrosis, global dysfunction, and accumulation of metabolites.[5,6] The clinical manifestation of cardiac toxicities were observed as chest discomfort, palpitations, dyspnea, tachypnea, hypotension, and chest pain. The electrocardiogram (ECG) could showed signs of myocardial ischemia supraventricular tachycardia (SVT) and bradycardia.[7,8]

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CASE REPORTS

Case 1

A 33-year-old female was diagnosed with hilar cholangiocarcinoma and received three cycles of chemotherapy with FOLFOX regimen. The chemotherapy consisted of 5-FU 400 mg slow IV push and 5-FU 1000 mg over 22 h. On the 2nd day of fourth cycle, 30 min after the start of 5-FU, she developed chest discomfort and palpitations which lasted for 5-10 min and was associated with one episode of vomiting. ECG report was SVT with nonspecific ST and T wave abnormality and CK-MB was 22.8 U/L with troponin I of 0.0012 ng/ml. Carotid message was given and was shifted to intensive care for stabilization. Repeat ECG done was normal. She was treated with supportive measures and a stat dose of metoprolol 5 mg. She was symptomatically better and was discharged.

Case 2

A 33-year-old male was diagnosed with nasopharynx CA. He was admitted for 1st cycle chemotherapy (cisplatin+5-FU)

Table 1: Case assessment

Case	Age	Sex	Diagnosis	Chemotherapeutic agents	ECG test	Echo test	Cardiac markers	Naranjo score
1	33	F	Hailer cholangiocarcinoma CA	OXALIPLATIN 5-FU	SVT	Not done	Trop I: 0.0012 ng/ml CK-MB: 22.8 U/L	7 (probable)
2	33	M	CA nasopharynx	Cisplatin 5-FU	SVT	Severe LV dysfunction	Not done	6 (probable)
3	34	M	CA esophagus	Cisplatin 5-FU	Sinus bradycardia	Not done	Not done	6 (probable)
4	63	M	CA esophagus	Cisplatin 5-FU	Ischemic changes	Grade I diastolic dysfunction	Not done	6 (probable)

ECG: Electrocardiogram, SVT: Supraventricular tachycardia, CA: Carcinomas, 5-FU: 5-flurouracil, LV: Left ventricular

as per the protocol. At the time of chemotherapy, the patient developed sudden onset dyspnea and tachypnea, and his oxygen saturation dropped. Clinical examination showed tachycardia, tachypnea, and hypotension. The patient was shifted to intensive care unit and mechanically ventilated. The patient was evaluated by cardiologist and diagnosed as cardiomyopathy. ECG showed intermittent SVT. Two-dimensional (2D) echo was done and it showed severe left ventricular (LV) dysfunction. The patient was treated with provisional diagnosis of LV dysfunction secondary to chemotherapy (5-FU). He was managed with IV and subsequently oral digitalis, angiotensin-converting enzyme inhibitors and low-dose beta blockers. He was also administered antibiotics, bronchodilators, and supportive care. The patient responded to the above line of management, and he was weaned off the ventilator. Repeat 2D echo showed normal LV function.

Case 3

A 34-year-old patient male patient was diagnosed with CA esophagus well differentiated keratinizing cell CA, he was admitted for the chemotherapy with cisplatin and 5-FU. He tolerated the treatment well, with no major complaints. During the 3rd cycle, he developed sinus bradycardia for which cardiology consultation was sought. Echo done was normal. Cardiotoxicity probably due to 5-FU was suspected and chemotherapy discontinued from day 3. Advised follow-up in cardiology outpatient department for repeat echo. Holter done showed normal report. He recovered without any intervention.

Case 4

A 63-year-old male patient with the case of CA esophagus moderately differentiated squamous cell CA on concurrent cardiotoxicity of radiation therapy with 5-FU-cisplatin cycle one. He was admitted for first cycle, the patient developed chest pain, and ECG showed ischemic changes. Cardiology consultation was sought and their advice was followed. Echo was advised which showed good LV systolic function, Grade I diastolic dysfunction. He recovered without any intervention. Chemotherapy was restarted, he completed four fractions of radiation therapy. He tolerated the treatment with no major complaints. The comparative assessment of cases is described in Table 1

DISCUSSION

5-FU has been found to be an agent that may cause direct reversible cardiac toxicity or exacerbate the cause of myocardial dysfunction. The risk factor for the toxicity may be the continuous intravenous (IV) administration and coronary artery disease.[1] The incidence of cardiotoxicity lies between 1.6 and 3%. A pattern of increasing incidence rate has been seen in Indian population. The incidence is higher (4-6%) in those with pre-existing heart disease and in those who receive higher doses (6-7%). Cardiac events include mild blood pressure changes, thrombosis, and angina such as pain chest, myocardial infarction, cardiomyopathy, cardiac failure, and congestive heart failure.[9,10] These may occur during or shortly after treatment as was seen in our first patient but occasionally delayed for 3-18 h.[11]

Although commonly seen with 5-FU infusion cardiotoxicity can occur with IV bolus also. We have presented four cases of cardio toxicity occurring in patients receiving 5-FU chemotherapy for CA. Two patients had arrhythmias (one SVT and one bradycardia), one had reversible cardiomyopathy, and one had acute coronary vasospasm. Two patients were treated for CA esophagus and one patient for CA nasopharynx and the other for cholangiocarcinoma. The cardiac risk factors were not seen in these four cases. The majority of the observed reaction was reversible with the discontinuation of drug and by conservative management. De-challenge resulted normalization of investigational parameters.[12] The cardiomyopathy associated with the 5-FU was the only case which was not reversible. The most common intervention done was the discontinuation of the implicated drug.

CONCLUSION

Cardiotoxicity is a relevant, important, and underestimated problem in 5-FU treatment. The observed reactions were carefully studied and assessed and scored in between 6 and 8 which is probable for the drug as per Naranjo scale. The most common intervention done was the discontinuation of the drug and the effective symptomatic management. Here, we conclude that the cardiotoxicity can be expected at any time of therapy with 5-FU for the treatment of gastrointestinal malignancies. The cardiotoxicity can be prevented by modifying the factors associated for the toxicity, monitoring the clinical signs, and symptoms of the patient during the infusion and the continuous follow-up after the therapy. On the basis of changes in the monitoring parameters before the exhibition of clinical symptoms modification or discontinuation of the implicated drug can be considered.

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