Case Report-II

5-FLUOROURACIL CARDIO TOXICITY-REVISITED

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ABSTRACT

Background: 5-fluorouracil (5-FU) is a frequently administered chemotherapeutic agent in various malignant neoplasms. Its adverse side effects involving bone marrow, skin, mucous membranes, gastrointestinal, and CNS, are well known, where as its cardiotoxicity is uncommon occurs in 1.2–18%.

Methods:

We report 3 cases of breast cancer patients in whom exposure to 5-FU resulted in a myocardial infarction (MI) pattern in two and reversible left ventricular (LV) dysfunction in the other.

Results:

The first case patient had life threatening reversible left ventricular dysfunction and recurrent ventricular arrhythmia. In this, coronary artery spasm was postulated as a possible mechanism for cardio toxicity. In the second case patient had angina after first cycle of 5FU and on re-exposure to the same drug she had non Q wave myocardial infarction. In the third case patient developed acute myocardial infarction following 5 FU. All these cases had no prior history to suggest ischaemic heart disease and were evaluated prior to administration of drugs.

Conclusions:

Cardio toxicity is an important, relevant but underestimated problem in 5-fluorouracil treatment. Patients with pre-existing coronary heart disease, electrolyte imbalance, and prior radiation exposure to heart are at significantly increased risk. After a cardio toxic event, fluorouracil should definitely be withdrawn and replaced by an alternative antineoplastic agent.

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INTRODUCTION

5-FU is a commonly used chemotherapeutic agent as a part of many cancer treatment protocols, particularly in breast cancer. Its cardio toxicity potential is known but considered uncommon and usually not life threatening. We report 3 cases of breast cancer patients in whom exposure to 5-FU resulted in a myocardial infarction (MI) pattern in two and reversible left ventricular (LV) dysfunction in the other.

METHODS

Case-1

A 35-year-old female was diagnosed to have right sided breast cancer $T_xN_2M_0$ in August 2001 and was on combined modality treatment. She completed 40 Gy RT to right breast, five cycles of CMF protocol chemotherapy, right patey's mastectomy and bilateral oopherectomy on 02 July 2002. There was no history of chest pain, palpitation, syncope and her effort tolerance had been normal till the previous day. There was no history of smoking and had never consumed alcohol.

On 24 July 2002, she received sixth cycle of chemotherapy in form of CMF (Cyclophosphamide 600 mg/mt^2, Methotrexate 50mg/ mt^2 and 5FU 600mg/mt^2) as IV bolus at

1200 hrs. Next day at 0700 hrs she developed sudden onset dyspnea (NYHA class IV), orthopnea, and recurrent vomiting.

When she was received in our ICU, she was found to be in a state of cardiogenic shock. She was orthopnoeic, her heart rate was 160 beats per min, irregular, systolic BP was 70 mmHg and her limbs were cold and clammy. Cardiac auscultation revealed normal S_1 and S_2, a LVS_3 and no murmurs. There were basal rales in both the lungs. An ECG taken in the emergency room revealed sinus tachycardia with <2 mm ST depression in inferior leads and unifocal ventricular ectopics. Serial estimation of serum glutamic oxaloacetic acid transaminase (SGOT) and CKMB1 did not show any rise in the levels. X-ray chest revealed cardiomegaly and bilateral opacities consistent with pulmonary edema.

A bedside echocardiogram was performed. It revealed dilatation of the ventricles, normal wall thickness and global hypokinesia, with an ejection fraction of 35%. There was no mitral regurgitation or thrombus. Doppler study revealed dilatation of IVC. She was managed with dopamine infusion and dobutamine was added when BP did not improve. Cardiac monitor revealed runs of ventricular tachycardia after one hour. She had two episodes of cardiac arrest and was resuscitated with IV Xylocard (bolus & infusion) followed by DC shock. She continued to get intermittent ventricular tachycardia which responded to IV Amiodarone infusion. Within 2 days of admission, she was relieved of her symptoms, ECG, X-ray and echocardiogram revealed normal LV function. She is asymptomatic and on follow up.

Case-2

A 45 year old female was diagnosed to have right sided breast cancer $T_3N_1M_0$ and was planned for combined modality treatment. Prechemo-therapy echo and ECG were normal. In July 2002, she received first cycle of FAC (Cyclophosphamide 600 mg/mt^2, Adriamycin 40mg/ mt^2 and 5FU 600mg/mt^2) as IV bolus. Next day after discharge to home she developed transient chest pain for which she took no treatment. The same was not disclosed to the treating physician.

After 3 weeks she received 2nd cycle of FAC of same dose. She developed chest pain, palpitation and syncope. When she was received in our ICU, she was found to be orthopnoeic, her heart rate was 110 beats/min and her BP was 110/70 mmHg. Cardiac auscultation revealed a LVS3 and no murmurs. There were basal rales of both lungs. An ECG revealed sinus tachycardia, transient left bundle branch block and minimal ST–T wave changes. Serial estimation of serum glutamic oxaloacetic acid transaminase (SGOT) and CKMB1 was raised in the levels. Serial ECG revealed anterior-wall Non Q wave MI.

An echocardiogram was performed which revealed hypokinesia of distal IVS and left ventricle apex. LVIDD 4.9, LVIDS 3.2, LVPWD 0.9, FS 35% and an ejection fraction of 65%. There was no mitral regurgitation or thrombus. No further 5FU or Adriamycin was given.

Case-3

A 65-year-old female without any co morbid illness, was diagnosed to have left sided breast cancer $T_{4b}N_2M_0$ in Feb2004. All preche-motherapy investigations including ECG, X –ray chest were normal and she was planned for combined modality treatment.

On 29 Mar 2004, she received chemo-therapy in form of CMF as IV bolus. Next day at 1000 hrs she developed acute onset pain in chest with sweating and recurrent vomiting. When she was received in our ICU after 6 hours, she was orthopnoeic, she was normotensive. Cardiac auscultation was normal. There were basal rales in both the lungs. An ECG taken in the emergency room revealed hyperacute changes of anterior myocardial infarction with transient RBBB. Serial estimation of serum glutamic oxaloacetic acid transaminase (SGOT) and CKMB1 (100 U/L) were significantly raised. An echocardiogram was performed. It revealed hypokinesia of IVS, LV apex and lateral wall, with an ejection fraction of 41%. There was no mitral regurgitation or thrombus She was managed at a on standard line of treatment and made uneventful recovery. In view of this episode, ER/PR positivity plan is to give only anti estrogen as systemic therapy.

DISCUSSION

The metabolite fluorouracil (5-FU) is a frequently administered chemotherapeutic agent used in various malignant neoplasms. Its adverse side effects including diarrhea, mucositis, neurotoxicity, palmoplantar dysesthesias and myelosuppression are well known, where as its cardiotoxicity is less familiar to physicians.

The first case of an adverse cardiovascular event due to 5FU was described by Roth et al in 1975. Cardiotoxicity due to 5-FU is known to occur in 1.2–18% of patients in different studies.[1] 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, angina like pain chest,[2] myocardial infarction,[3] cardiomyopathy, cardiac failure (left ventricle failure) and congestive heart failure.[4] These may occur during or shortly after treatment as was seen in our first patient, but occasionally delayed for 3 to 18 hours. Though commonly seen with 5FU infusion, cardiotoxicity can occur with IV bolus also. Robben et al[5] had analyzed the syndrome of cardio toxicity due to 5-FU. Of the 135 patients described to have had this phenomenon, angina was encountered in 89%, ST–T wave changes of ischemia on ECG in 75%, echocardiographically documented LV dysfunction in 24%. In one-fourth of them, the LV dysfunction reverted to normal as was seen in our first patient. Myocardial infarction by clinical means and ECG is diagnosed in 10%of patients as were seen in both case 2 & case 3. Cardiac arrhythmias are also seen[6] as it occurred in our first patient. In some patients, therapeutic re-challenge was attempted and in majority, the syndrome was reproduced as it happened in our second patient.

The pathophysiology of 5FU induced cardiotoxicity is controversial and conclusions are based on clinical studies and case reports more than on solid experimental evidence. 5-FU cardiotoxicity is suspected to be mediated by coronary vasospasm (explaining the occurrence of angina and Myocardial infarction and rapid normalization of the ST segment) and free radical damage to the myocardium.[7] Other histomorphological and biochemical studies indicate a more direct drug mediated cytotoxic action. Recent studies support the hypothesis that 5FU has direct endothelial toxicity resulting in thrombogenic effect and release of vasoactive substances.

We have presented three cases of severe cardio toxicity occurring in a patients receiving 5-FU chemotherapy for carcinoma of breast. In the first case coronary artery spasm has been postulated as a possible mechanism for cardio toxicity. It is based mainly on the finding of clinical and electrocardiographic evidence of reversible ischemic heart disease in the absence of coronary atherosclerosis on angiography in various studies. Furthermore, coronary artery spasm has been documented angiographically following intravenous 5FU administration[7], and prophylaxis with calcium channel antagonists has been successfully employed in preventing recurrence.[8] An alternative suggested mechanism is that 5-FU may cause metabolic changes producing hypoxia within myocardial cells, therefore imitating ischemic heart disease.[9] Though the echo in the emergency room suggested a dilated cardiomyopathy a rapid resolution of the symptoms and normalization of LV function (confirmed by echocardiography) supported the diagnosis that this phenomenon could be due to chemotherapeutic agents.

Chemotherapeutic drug-induced dilated cardiomyopathy (DCM) is one of the few forms of reversible DCM, the others being alcoholic DCM, peripartum DCM, DCM due to deficiency of selenium, hypocalcaemia, hypophosphatemia and hyperthyroidism.

In the second case patient had transient chest pain following first cycle of 5 FU based chemotherapy, it was not revealed by the patient prior to the next chemotherapy. Repeated exposure to 5-FU following an episode of cardio toxicity carries a risk of relapse of between 82

and 100% of case and therefore it is advised that the drug should not be re-administered in this group of patients[10] and this also was seen in this patient. Though Adriamycin can also be implicated in cardiotoxicity, she did not receive the drug in adequate dosages and for a long enough duration. Radiation-induced cardio toxicity was unlikely because it was low dose with right-sided lesion. Moreover, just prior to admission she had received 5-FU.

The majority of cardiac adverse events occur during the first cycle of 5-FU as it occurred in our third case. Management consists of discontinuation of the drug, conventional measures for cardiac failure and nitrates. Calcium-channel blockers could have a role if the LV function is normal. Antioxidants also have a potential role in the prevention and management of the condition. Recent study by Kinhult et al indicated that antithrombotic treatment by LMW heparin can protect against the thrombogenic effect of 5FU.[11] Recently a study by Sudhoff et al demonstrated that none of the 15 positive for 5FU – induced vasoconstriction had a symptomatic cardiotoxic event during study period. They stressed the importance of continuous ECG monitoring during 5FU infusion.[13]

In conclusion, cardiotoxicity is an important, relevant but underestimated problem in fluorouracil treatment. Patients with pre-existing coronary heart disease, electrolyte imbalance, and radiation exposure to heart are at significantly increased risk. Routine periodic echocardiography evaluation during 5-FU therapy may not be of value because cumulative toxicity in contrast to other drugs such as doxorubicin is unlikely to occur with this agent, but patients may benefit from continuous ECG monitoring. After a cardiotoxic event, fluorouracil should definitely be withdrawn and replaced by an alternative antineoplastic agent.

REFERENCES :

1. *Roth A, Kolari C, Popovic S. Cardiotoxicity of 5-FU. Cancer Chemother Rep 1975;59:1051-1062*

2 *DL Keefe, N Roistacher, MK Pierri: Clinical cardiotoxicity of 5-fluorouracil. J Clin Pharmacology 1993;33: 060-1070.*

3 *RG Dent, I McColl: 5 Fluorouracil and angina. Lancet 1975;1:347-348*

4. *A Pottage, S Holt, S Ludgate, AO Langlands. Fluorouracil cardiotoxicity. Br Med J 1978;1:547*

5. *DL Stevenson, DP Mikhailaidis, DS Gillet: Cardiotoxicity of 5 fluorouracil. Lancet 1977;2:406-407*

6. *Robben NC, Pippas AW, Moore JO. The syndrome of 5-fluorouracil cardiotoxicity. An elusive cardiomyopathy. Cancer 1993;71:493–509*

7. *JF Ensley, B Patel, R Kloner, JA Kish, J Wynne, M Al-Sarraf: The clinical syndrome of 5-fluorouracil cardiotoxicity. Invest New Drugs 1989;7:101-9.*

8. *RJ Luwaert, O Descamps, F Majois, JM Chaudron, M Beauduin: Coronary artery spasm induced by 5-fluorouracil. Eur Heart J 1991;12:468-470.*

9. *NS Kleiman, DE Lehane, CE Geyer, CM Pratt, JB Young: Prinzmetal's angina during 5-fluorouracil chemotherapy. Am J Med 1987;82:566-568.*

10. *Y Mizuno, Y Hokamura, T Kimura, Y Kimura, K Kaikita, H Yasue. A case of 5-fluorouracil cardiotoxicity simulating acute myocardial infarction. Jpn Circ J 1995;59:303-307*

11. *K Becker, JF Erckenbrecht, D Haussinger, T Frieling: Cardiotoxicity of the antiproliferative compound fluorouracil. Drugs 1999;57:475-484.*

12. *Kinhult S, Albertsson M, Eskilsson J, Cwikiel M. Antithrombic treatment in protection against thrombogenic effects of 5FU on vascular endothelium. Scanning. Jan-Feb 2001;23:(1):1-8.*

13. *T.Sudhoff, M.D Enderle, M Pahlke, C Petz: 5Fluorouracil induces arterial vasoconstrictions. Annals of Oncology 2004;15:661-664.*