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Case Report

5-Fluorouracil Induced Cardiotoxicity in a Young Patient with Colon Cancer: An Unusual Finding

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Abstract

Cardiotoxicity is a common side effect associated with some chemotherapeutic agents especially anthracyclines such as doxorubicin. It can however be associated with some antimetabolites such as 5-fluorouacil and methotrexate though in lesser degree. Our presentation is a case of 33-year-old female patient with colon cancer treated with 5-fluorouracil and oxaliplatin. She developed bradycardia (pulse rate 39bpm) while on 5-fluorouracil infusion necessitating discontinuation of the infusion. Subsequent 5-FU therapy was carried out with bolus intravenous injection in three dived daily doses and this was well tolerated. In cases of bradycardia following continuous infusion of 5-fluorouracil, bolus intravenous injection in divided doses might be tolerated

Keywords: Bradycardia; Cancer; 5-Fluorouracil

Introduction

5 Fluorouracil (5FU) is a fluoropyrimidine antimetabolite chemotherapeutic agent, which is widely used in the treatment of various solid cancers such as colorectal, breast, head and neck, stomach, and pancreatic carcinoma. It is a cell cycle-specific agent with activity in the S-phase. It inhibits the enzyme thymidylate synthase resulting in inhibition of DNA synthesis and function. The most common adverse effects of 5-FU include diarrhea, mucositis, myelosuppression, and thrombophlebitis of peripheral veins [1].

Cardiotoxicity is a frequent side effect associated with administration of chemotherapeutic agents to cancer patients, mostly in the case of anthracycline such as doxorubicin. Cardiotoxicity can also be induced by antimetabolites like 5-fluorouracil, but in far less proportion [2,3]. The first reported case of 5-FU induced cardiotoxicity appeared in 1975 [4]. Since then large prospective studies have demonstrated an incidence of 5-FU induced cardiotoxicity ranging from 1.6-8% [3,5]. Cardiotoxicity appears to be dose and schedule dependent since its frequency is lower with bolus regimens than with continuous infusion over 2-4 days [6]. With shorter bolus regimens, the incidence of cardiotoxicity ranges from 1.6%-3% of cases [7] while with continuous infusion regimens the incidence of cardiotoxicity ranges between 7.6%-18% of cases [8].

Chest pain with projection to the left arm or neck appears to be the most frequent symptom of 5-FU induced cardiotoxicity; others are arrhythmias, myocardial infarction, cardiogenic shock or heart failure. In many patients, Electrocardiography (ECG) may reveal ST segment depressions or transient bradycardia [9]. Patients with history of cardiac disease, particularly coronary artery disease, are at a higher risk of developing 5-FU induced cardiotoxicity than patients without cardiac disease [10]. Therefore 5-FU induced cardiotoxicity is assumed to be rare in young cancer patients without prior cardiac disease. We present a case of a 33-year-old female patient with colon cancer who developed bradycardia while on 5-FU infusion as part of FOLFOX regimen.

Case Report

A 33-year-old single, female textile trader presented at the University College Hospital (UCH) Ibadan Nigeria for oncology treatment following a referral from her primary physician after abdominal surgery. She had a nine months history of abdominal pain and passage of bloody watery stool prior to presentation to the primary physician. She was not a known hypertensive nor diabetic patient. Barium enema revealed a mass in the caecum. She was then planned for surgery but 5 days later she re-presented with features of acute intestinal obstruction on account of which she had an emergency exploratory laparotomy. Intraoperative findings

revealed intussusception involving the terminal ileum, ceacal mass and 2 mesenteric (regional) lymph nodes enlargement. She had a right hemicolectomy and ileotransverse anastomosis. Histological examination of the caecal mass described moderately differentiated infiltrating adenocarcinoma of the colon AJCC stage IIIA (T2N1M0) She was subsequently referred to the Radiation Oncology clinic, University College Hospital (UCH) Ibadan for further management.

At presentation at the referral center, she was clinically stable with a healed mid line abdominal scar. Her pulse rate was 84 Beats Per Minute (BPM) while the blood pressure was 130mmHg. The chest was clinically clear and other systems were essentially normal. An assessment of locally advanced colorectal carcinoma post-surgical excision was made. Computed Tomography (CT) scan of the abdomen and pelvis did not describe any abnormal findings and the chest x-ray was normal. Carcinoembronic Antigen (CEA) level was within normal range (0.9ng/ml) while HIV screening, electrolyte urea and creatinine and the full blood counts were all within normal ranges. She was subsequently scheduled to receive chemotherapy with FOLFOX 4 regimen. Pre-chemotherapy assessment on day 1 of chemotherapy was normal with a pulse rate of 78 BPM and a blood pressure of 120/80mmHg. She then had intravenous infusions of oxaliplatin (170mg), leucovorin (400mg) each over 2 hours and bolus 5FU (800mg) without any symptoms. Continuous intravenous infusion of 5-FU (1200mg) was then set up. However, 4 hours after the commencement of intravenous 5-fluorouracil continuous infusion, she started complaining of chest pain, dizziness and headache. On examination, Pulse rate reduced to 60 BPM and the blood pressure was 100/70mmHg. Other systems were essentially normal.

She was reassured then and rate of infusion of the 5-FU was reduced to 10 drops per minute but with close monitoring of her vital signs every 15 minutes. Two hours later the chest pain became worse and a Pulse rate of 39 BPM with associated missed beats was noted while the blood pressure was 90/60mmHg. The chemotherapy was immediately discontinued and replaced with normal saline infusion and she was given 1mg of intravenous atropine. She was reviewed by the cardiologist who requested for an Electrocardiography (ECG) and echocardiography. The ECG described sinus bradycardia while the echocardiography was essentially normal. Hence symptoms were attributed to 5-FU induced cardiotoxicity.

She was reviewed 2 weeks later and there were no abnormalities noted. Her chemotherapy was recommenced but with modification of the FOLFOX-4 regimen. Her initial chemotherapy plan was continuous 5-FU infusion of 1200mg over 22 hours daily for 2 days while the bolus 5-FU was 800mg daily for 2 days. The 'modification' entailed the complete removal of continuous 5-FU infusion with the dose added to bolus 5-FU making it 1000mg daily for 4 days. The dosage for oxaliplatin and leucovorin remained the same. She received the first course of 'modified' FOLFOX-4 without any symptoms. She subsequently completed 4 additional courses of the 'modified' FOLFOX-4 without any symptoms of cardiotoxicity. The patient has good disease control and is without any cardiac symptoms two years post treatment as at the time of this report.

Discussion

Cardiotoxicity is a rare adverse effect associated with 5-FU chemotherapy. The precise aetiology and pathophysiology of 5-FU induced cardiotoxicity is still unknown and few insights are based primarily on limited animal studies, case reports, and small clinical studies. However, there are several proposed mechanisms of this phenomenon, which include coronary vasospasm [11], toxicity on myocardium [12,13], activation of autoimmune response [14], or production of fluoroacetaldehyde generated in the alkaline solution of 5-FU vials during storage, which undergoes conversion in vivo into the cardiotoxic fluoroacetate [15]. In a study by Sudhoff and colleagues (2004), 5-FU was shown to induce brachial artery vasocontraction in 50% of patients treated with 5-FU based chemotherapy compared with none in patients treated with non-5--FU based chemotherapy [13]. However, in another report, many patients who had coronary angiography performed during symptomatic attacks of cardiotoxicity did not reveal spasm of coronary arteries [16]. Another possible mechanism is the direct toxic effect on coronary endothelial cells, Electron microscopy evaluation of rabbit arterial endothelium following infusion of 5-FU revealed significant degradation of endothelial cells often accompanied by platelet accumulation and fibrin formation [17]. In a study by Kinhult and colleagues (2003), administration of probucol, which possesses strong antioxidant properties, prevented 5-FU mediated endothelial injury [18]. It has also been reported that toxic myocarditis is responsible for the pathological findings associated with 5-FU infusion [19]. Myocarditis may thus explain the observed clinical symptoms such as chest pain, reversible ST segment depression, left ventricular dysfunction and elevation of cardiac enzymes observed in some studies [19].

Pre-existing cardiac disease is one of the several risk factors for occurrence of 5-FU induced cardiotoxicity. In a study, 390 patients were evaluated after receiving 5-FU based chemotherapy, 13 adverse cardiac events were observed. The incidence of cardiotoxicity was higher in patients with previous cardiac disease than in otherwise healthy counterparts (15.1 vs 1.5%) [20]. In another study, silent ischaemia-like ECG changes occurred at higher frequency in patients with cardiac disease [10]. A study by Jensen and Sorensen showed that impaired renal function may also be an associated risk factor, which increases susceptibility to chemotherapy-induced cardiotoxicity [21]. However, some other studies have not confirmed a causal relationship between renal function and 5-FU induced cardiotoxicity [11,22,23].

Cardiotoxicity with 5-FU infusion tends to occur most com-

monly during the first cycle of administration [23]. The median time to symptoms is 12 hours following initiation of the infusion with a range between 2 hours and 18 hours [24], although a study suggests earlier onset and increased severity of symptoms with higher dose regimens or repeat of drug administration [25]. The patient under review noticed symptoms 4 hours after the commencement of 5-FU infusion. Prevention of recurrence of 5-FU induced cardiotoxicity involves dose reduction during subsequent chemotherapy courses, administration of calcium channel blockers, B-blockers and long-acting nitrates. In some studies, up to 70-90% of patients responded to such conservative therapy [23,26] while in other studies there was less than 50% response [21,27].

Several studies have utilized oral capecitabine, an oral prodrug of 5-FU, as an alternative agent to mitigate the adverse effect of 5-FU. Unfortunately, several reports still demonstrate drug induced cardiotoxicity, albeit delayed until significant metabolite accumulation occurred [6,28]. Overall, most investigators suggest decrease in drug dose as the most effective strategy [26, 27] or complete withdrawal of 5-FU in high risk patients with administration of alternative chemotherapy such as raltitrexel as an option [29]. Raltitrexel is a thymidylate synthase inhibitor that thus far does not show cardiotoxic effect that 5-FU seems to have [30].

The patient in review had her 5-FU continuous infusion converted to 5-FU bolus with the dose spread over 4 days instead of the usual 2 days but with the same total dosage. This mitigated the cardiotoxicity related symptoms and also ensured the stability of her pulse rate during subsequent chemotherapy. This strategy may be adopted to ensure completion of chemotherapy although further studies are needed to confirm the efficacy of this method in terms of patients' safety and efficacy compared with continuous infusion

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