REPORT

Capecitabine induced cardiotoxicity: A case report and review of literature

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Abstract: Capecitabine is an oral prodrug of 5-fluorouracil (5-FU) which is converted in tumor cells to 5-FU by the enzyme thymidine phosphorylase. Nowadays, it is being widely used into the management of colorectal, breast and head and neck cancers because of its oral route and its comparable efficacy with 5-FU. 5-FU induced cardiotoxicity (angina and myocardial infarction) has been reported the literature, but capecitabine induced cardiotoxicity is less reported event. We report a patient with diagnosis of locally advanced adenocarcinoma of rectum who developed symptomatic bradycardia and acute ischemia while receiving oral capecitabine 825mg/m^2 twice daily with preoperative radiation.

Keywords: Capecitabine, side effects, cardiotoxicity, coronary vasospasm.

INTRODUCTION

Capecitabine is an orally administered prodrug of 5-fluorouracil (5-FU). Nowadays, it is replacing 5-FU in the management of various malignancies including colorectal, breast and head and neck because of its three fold advantages; first; easy oral administration, second; comparable efficacy over intravenous 5-FU (Ramani *et al*., 2010). An additional advantage, which makes capecitabine an attractive compound, is its assumed targeting of tumor cells (Schuller *et al*., 2000). The capecitabine is converted to 5-FU into the tumor cells by three step enzymatic process fig. 1.

Targeting of tumor cells by capecitabine may result in a favorable balance of treatment efficacy and toxicity. Cardiotoxicity due to 5-FU is rare but serious side effect, reported in 1%-18% of cases (Van Cutsem *et al*., 2002; Dalzell and Samuel, 2009). The most common symptoms are angina like chest pain and less common symptoms are cardiac arrythmias, congestive heart failure, cardio-myopathy, cardiac arrest and cardiac death.

The exact mechanism of 5-FU induced cardiotoxicity is not known, but it is related to coronary spasm during initial course of therapy, usually reversible on drug withdrawal and with a small proportion of patients (18%) with previous cardiac history (Paiva *et al*., 2009). With frequent use of capecitabine, few cases of associated cardiac events have been reported (Frickhofen *et al*., 2002).

We report a patient with established diagnosis of locally advanced adenocarcinoma of rectum who developed symptomatic bradycardia and acute ischemia while receiving oral capecitabine 825 mg/m^2 twice daily with preoperative radiation.

CASE REPORT

A 56-year old non-smoker male with diagnosis of locally advanced rectal carcinoma was referred to our radiation oncology department for preoperative chemoradiation. His past medical history was non significant. His baseline electrocardiography (ECG) was of normal pattern. He was taking tramadol 50 mg twice daily for pelvic pain and lactulose syrup 30 ml daily for constipation. His family history was significant for colorectal and breast cancer in several family members.

On digital rectal examination (DRE), an annular growth in rectum, about 8 cm from anal verge was noticed. Remaining physical examination was unremarkable. Hematology and chemistry analysis reports were within normal limits. Baseline carcinoembryonic antigen (CEA) level was 5 ng/ml (reference range <2.5 ng/ml in non-smokers). Computed tomography (CT) scan showed annular growth of rectal wall, size 3 x 3 cm which about 8 cm from anal verge and invading up to muscularis. No perirectal lymphadenopathy was seen. Radiological stage was made T3N0M0.

He was started on preoperative chemoradiation with oral capecitabine 825 mg/m2 twice daily during radiation days. Planned radiotherapy dose was 5040 centi Gray (cGy) in 28 fractions (5 fractions/week). Prior to therapy, baseline ECG and cardiac enzymes were done and were found within normal limits (fig. 2).

During second week at day 15 of oral capecitabine, the patient developed severe chest pain and dyspnoea for 5

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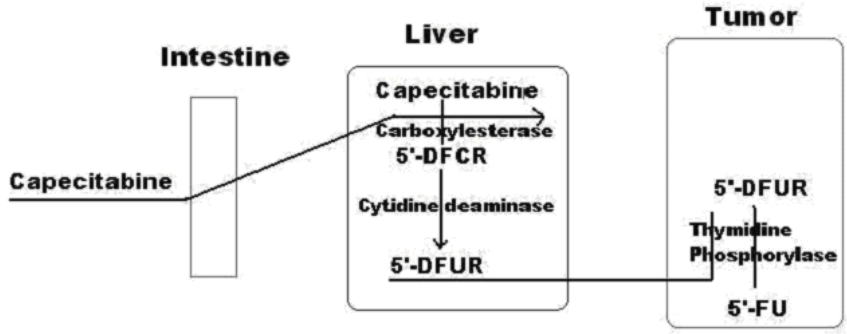

Fig. 1: Schematic diagram of activation of capecitabine in the human body.

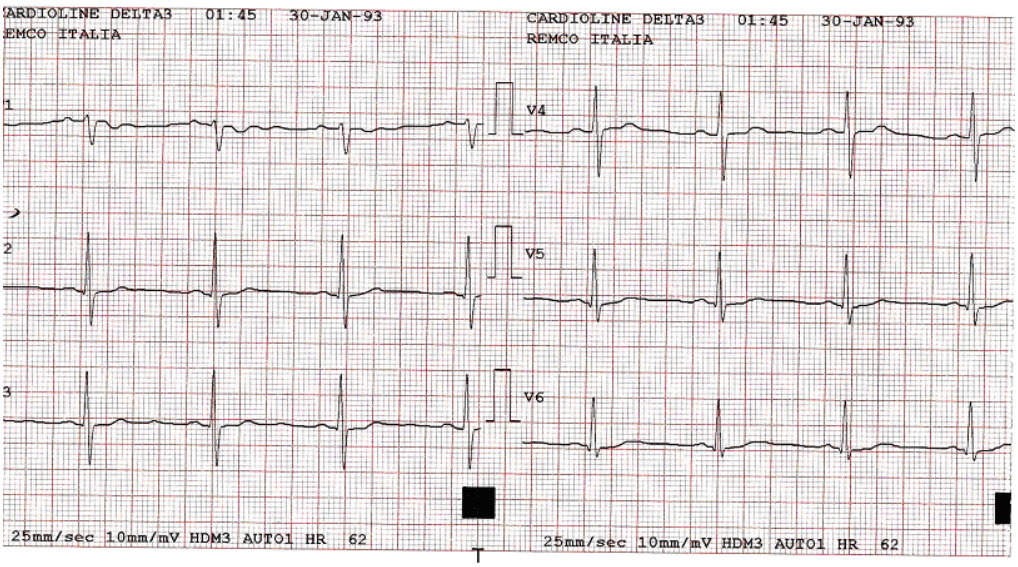

Fig. 2: Patients' baseline electrocardiography (ECG) before taking the drug.

hours after 3 hours of taking the drug, suggestive of cardiac ischemia and was brought in cardiac emergency. ECG showed bradycardia, ST-segment depression and left ventricular dysfunction with repolarization abnormalities (fig. 3). Serial analysis of creatine kinase (including the CK-MB subforms), troponin T and lactate dehydrogenase was negative. Chest pain was initially unresponsive to treatment with nitroglycerine (0.4 mg sublingual.), metoprolol {5 mg intravenous (IV)}, morphine (10 mg IV) and aspirin (500 mg IV). Only after initiating continuous infusion of nitroglycerine (4 mg/h) pain subsided. ECG returned to normal within 24 hours and patient was discharged on oral calcium channel blockers and nitrates, and was followed up in outpatient care. Angiography showed mild coronary spasm. Subsequent echocardiography revealed an ejection fraction of 55%; mild left ventricular diastolic dysfunction otherwise normal readings. Follow up treadmill exercise using the Bruce Protocol for 5 minutes, the heart rate quickly rose from 66 to 170 (93% predicted heart rate) and he developed dyspnoea which resolved immediately after the exercise was stopped.

After recovery from cardiac events, it was decided to stop capecitabine and oxaliplatin as radiosenistizer was given with radiation. After the completion of chemoradiation patient was referred to surgery team for low anterior resection.

DISCUSSION

As the use of capecitabine becomes more widespread, rare but perilous side effect of cardiotoxicity is now being reported. In a retrospective analysis performed on studies of patients undergoing chemotherapy for metastatic breast and colon cancer, the incidence of cardiotoxicity with capecitabine was found to be comparable to that of 5-FU (Kosmas C *et al*, 2008). To date 53 patients who experienced cardiotoxicity during capecitabine treatment are reported in world literature. The most frequent manifestations of capecitabine cardiotoxicity included: angina in 38/53 (71.7%), arrhythmia in 6/53 (11.3%), myocardial infarction in 6/53 (11.3%) and cardiac death in 6/53 (11.3%) patients (table 1). The combination chemotherapy regimens may increase the risk of cardiotoxicity than monotherapy (Farina *et al*., 2009).

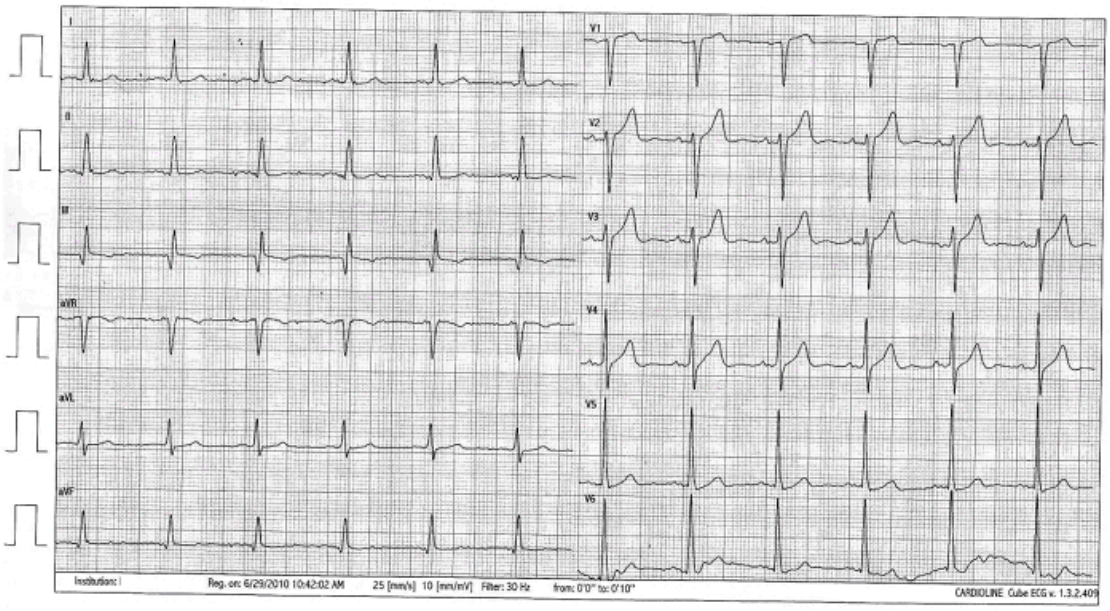

Fig. 3: Electrocardiography (ECG) showed bradycardia, ST-segment depression and left ventricular dysfunction with repolarization abnormalities.

Table1: similar published case report on capecitabine induced cardiotoxicity.

Case report	Age and sex of patient with type of malignancy	Capecitabine dosage	Type of cardiotoxicity	Management
Ang *et al.*, 2010	75 yrs, male, Adenocarcinoma rectosigmoid IIIB	1500 mg/m^2 twice daily monotherapy	Repeated syncope	Permanent pacemaker No further chemotherapy
Senturk *et al.*, 2009	34 yrs, male, adenocarcinoma rectum III	2000 mg/m^2 daily + oxaliplatin	Acute myocardial infarction	Nitrates, calcium channel blockers Oxaliplatin alone was continued
Goldsmith *et al.*, 2008	38 yrs, female, Recurrent breast cancer	3500 mg daily monotherapy	Left ventricular dysfunction	Aspirin and beta-blocker Capecitabine was stopped
Arbea *et al.*, 2007	71 yrs, male, adenocarcinoma of rectum T3N0M0	825mg/m^2 + oxaliplatin + radiation	Chest pain, angina	Nitrates, calcium channel blockers Oxaliplatin continued with radiation
Frickhofen *et al.*, 2002	60 yrs, male, adenocarcinoma of rectum T3N1M1 (liver)	1250mg/m^2 twice daily	Chest pain, angina	Nitrates, calcium channel blockers Capecitabine was stopped

The exact pathogenesis of capecitabine induced cardiotoxicity is not known, but hypothesized mechanisms are:

1. The metabolites of 5-FU, in particular fluoroacetate (FAC), is known to be directly myocardiotoxic and interferes with citrate cycle (Lemaire *et al*., 1992).
2. Direct cytotoxic endothelial injury and subsequent thrombus formation has been observed in animal models (Cwikiel *et al*., 1995).
3. Coronary vasospasm secondary to subendothelial dysfunction and reduced bioavailability of nitric oxide (Kugiyama *et al*., 1996).
4. Higher of thymidine phosphorylase activity in atherosclerotic plaques, which results in more metabolites of 5-FU (Boyle *et al*., 2000).
5. Drug pharmacokinetics and pharmacodynamics: The deficiency of dihydropyridine dehydrogenase (DPD), the first enzymatic step in 5FU catabolism may increase the cardiotoxicity (Ciccolini *et al*., 2006). Excessive levels of Cytidine deaminase (CDA) resulting in overmetabolism of capecitabine into 5FU could explain the development cardiotoxicity even in patients who are not DPD-deficient (Mercier *et al*., 2009).

6. Geographic differences may result in variation in tolerance to capecitabine, with the higher toxicity occurring in American patients as compared to East Asian patients (Haller, 2008).

For oncologists, it is very important to address the issue of identifying patients who may be at risk of developing capecitabine induced toxicity. The history of heart disease, elderly age, renal dysfunction and mediastinal irradiation (which induces coronary artery intraluminal hyperplasia and collagen deposition) have been found important risk factors for developing capecitabine induced (Ng *et al*., 2005; Jensen and Sorensen, 2006).

It is also very important to monitor these patients who are on capecitabine. One study (Holubec *et al*., 2007) evaluated the role of measuring brain natriuretic peptide (BNP) and troponin I (TnI) in patients receiving 5-FU chemotherapy for colorectal cancer. In that study, 57% of patients were found to have laboratory evidence of ischemia and heart failure. As capecitabine has similar mechanism, all patients for whom oral capecitabine is planned should undergo baseline electrocardiography and in those with prior cardiac history, echocardiography. Further DPD, BNP and TnI levels shall be monitored as surrogate markers of cardiotoxicity if facilities are available.

The treatment of choice for capecitabine induced cardiotoxicity is the drug withdrawal after managing the cardiac events. However some studies have used rechallenging and giving prophylaxis to patients who have experienced cardiotoxicity from capecitabine (Saif *et al*, 2009).

CONCLUSION

Capecitabine induced cardiotoxicity may occur more frequently similar to 5-FU induced cardiotoxicity. Though this is transient and reversible side effect, but can be perilous to the patient. Currently there are no set guidelines for screening, monitoring and treatment of this side effect; the cardiologists shall be encouraged to be part of multidisciplinary team when patients are planned for capecitabine and other flouropyrimidines.

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