5-Fluorouracil-induced coronary vasospasm: case report and discussion

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5-Fluorouracil is one of the most widely used chemotherapeutic agents. It has been included in the treatment of a number of solid tumours, including upper gastrointestinal, colorectal and breast cancer, for many years. It is the backbone of several chemotherapy regimens, particularly in the treatment of gastrointestinal tract adenocarcinomas. Unfortunately, cardiotoxicities may be expected to occur regularly. As 5-fluorouracil is widely used, cardiotoxicity due to 5-fluorouracil is a relatively common problem. The case of a 64-year old man with invasive intestinal adenocarcinoma, who developed chest pain during his first mFOLFOX cycle, is presented. We see in this case and in the literature that recurrence of cardiac toxicity is high, even with premedication. There is some evidence that replacing the fluoropyrimidine by raltitrexed is safe and efficacious for patients with 5-fluorouracil (cardiac) toxicity in the setting of colorectal cancer.

(Belg J Med Oncol 2015;9(5):194-98)

Introduction

5-Fluorouracil (5-FU) is one of the most widely used chemotherapeutic agents. It has been included in the treatment of a number of solid tumours, including colorectal, breast, gastric, pancreatic, prostate, and bladder cancer for many years. It is the backbone of several chemotherapy regimens, particularly in the treatment of gastrointestinal tract adenocarcinomas. 5-FU is a fluoropyrimidine agent and belongs to the family of drugs called the antimetabolites. It is a pro-drug that acts during the S-phase of the cell cycle. The active metabolite 5-fluorodeoxyuridylate (5-FdUMP) inhibits the thymidylate synthase, thus preventing DNA synthesis. This leads to imbalanced cell growth and later cell apoptosis.[1]

Frequent toxicities of 5-FU are leukopenia, diarrhoea, stomatitis, nausea, vomiting, and alopecia; toxicities differ with the drug's schedule of administration. Dose-limiting toxicities of bolus 5-FU are diarrhoea and myelosuppression. Hand-foot syndrome and stomatitis are more frequent with prolonged infusion. A wide range of 5-FU cardiotoxicities have been reported. Cardiac toxicity occurs less frequently but is typically more serious.[2] The incidences reported range from 1.27-18%, and occur with 5-FU administered either as a single agent or in combination with other chemotherapy agents.[3,4] Cardiotoxicity is observed with both bolus and continuous infusion administration and at various dose levels. Cardiogenic shock, supraventricular and ventricular arrhythmias, aberrant ventricular function and ischemic events have been reported.[5]

We report the case of a patient with sigmoid cancer, who experienced severe cardiac complications on

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Conflict of interest: The authors have nothing to disclose and indicate no potential conflict of interest.

Keywords: cardiotoxicity, coronary vasospasm, 5-fluorouracil, raltitrexed.

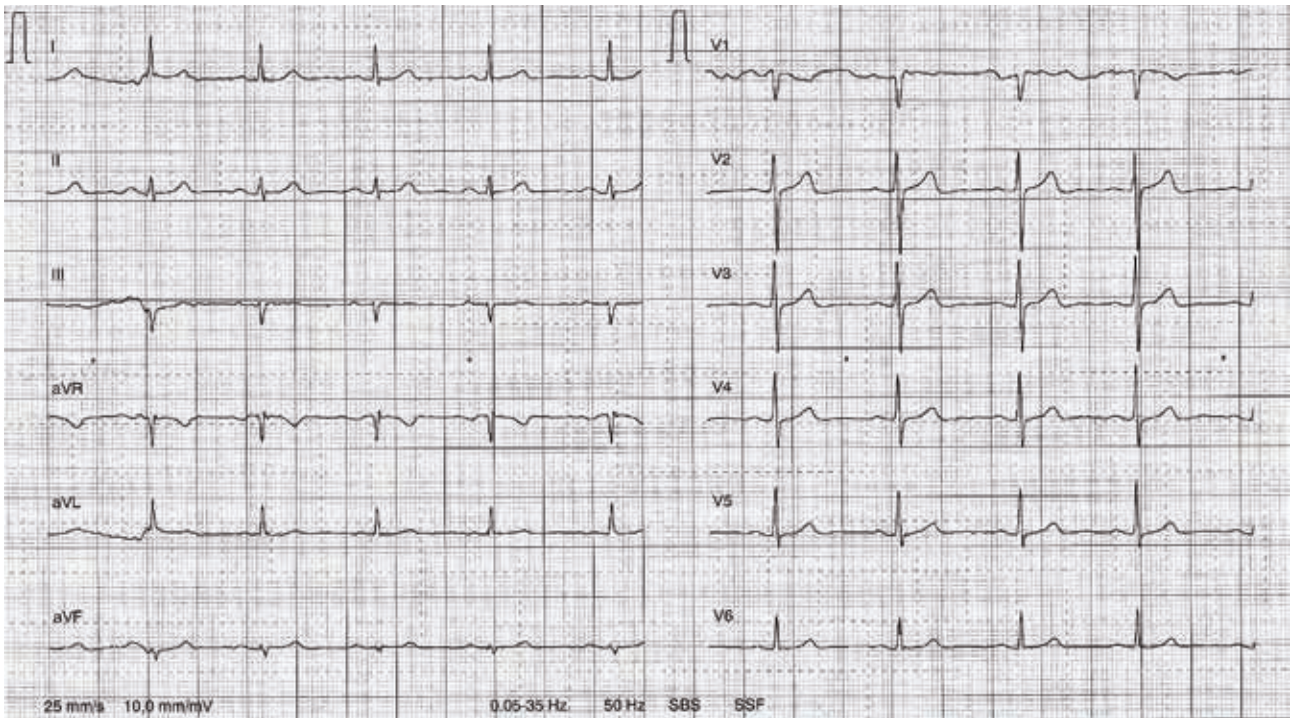

Figure 1. The pre-operative ECG, no signs of possible ischemia.

5-FU. The patient underwent a cardiac catheterisation twice. There were no critical atherosclerotic plaques observed. Further, we discuss the literature and the possibilities of a rechallenge.

Case report

A 64-year old man was diagnosed with a moderately differentiated invasive intestinal adenocarcinoma. He was referred for a colonoscopy after a period of change in bowel habits and a positive Faeces Occult Blood (FOB) test. The colonoscopy showed a tumoral process in the sigmoid. Further staging showed no metastatic disease. The multidisciplinary oncologic team proposed primary surgery, to be followed by adjuvant chemotherapy in case of lymph node invasion. A laparoscopic total mesorectal excision was performed. The pathology report confirmed the diagnosis of sigmoid cancer with one of fifteen nodes invaded (pT3N1M0). Microsatellite instability was high. Adjuvant chemotherapy was started using mFOLFOX regimen (leucovorin – 5-fluorouracil – oxaliplatin). An electrocardiogram (ECG) obtained before surgery was normal. The second day of the first mFOLFOX-cycle the patient was admitted to the emergency department with severe chest pain. A 12-lead ECG showed atrial fibrillation with rapid ventricular response and ST and T abnormalities in the inferior region, suggestive of possible ischemia. Bedside echocardiography was performed, showing a largely hypokinetic heart, especially at the inferolateral wall. 5-FU administration was stopped. Cardiac catheterisation showed only a slight stenosis (25%) in the mid-LAD. Because of the severity of the cardiac symptoms, chemotherapy was stopped and quarterly follow-up was started. Two years after the initial diagnosis a chest X-ray showed a solitary lung lesion. Further investigations showed no other lesions. The decision was made to resect the lung nodule. Pathology confirmed the diagnosis of a solitary lung metastasis.

After a long discussion it was decided to rechallenge 5-FU. The patient was pretreated with nitrates (molsidomine) and a calcium channel blocker (nifedipine). The patient was admitted to the intensive care unit for administration of the 5-FU infusion and monitoring of

Table 1. Cardiac toxicity.

Cardiac Toxicity of Fluorouracil
Angina
Myocardial Infarction
Arrhythmia
Congestive Heart Failure
Cardiogenic shock
Sudden death

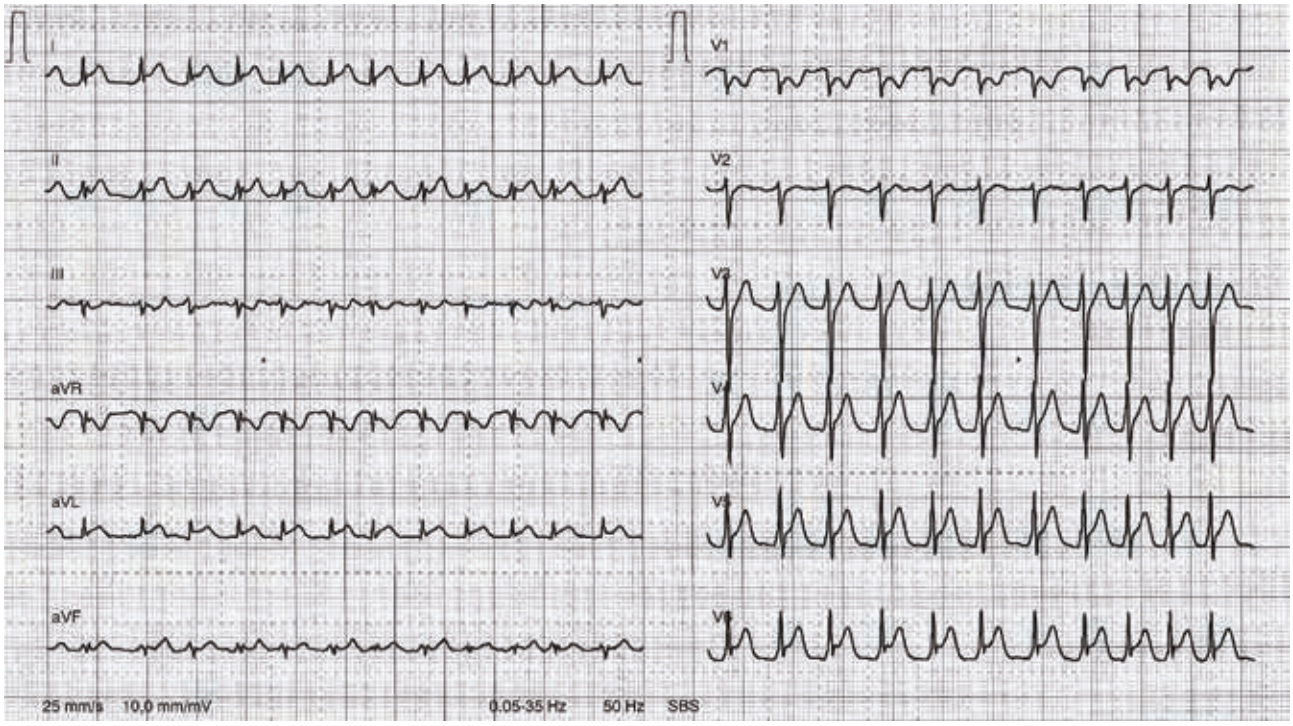

Figure 2. The ECG after chemo, showing atrial fibrillation with rapid ventricular response and ST and T abnormalities, suggestive of possible ischemia.

ECG and vital signs. However, he again experienced chest pain; the ECG revealed diffuse ST-T abnormalities. It was decided to permanently discontinue mFOLFOX and start raltitrexed (tomudex) - oxaliplatin every three weeks. Six administrations were performed without problems. The patient is currently in follow-up.

Discussion

We present the case of a patient who experienced severe cardiac ischemia after administration of 5-fluorouracil. The cardiotoxic effects of the antimetabolite fluorouracil (FU) were first recognised by Dent and McColl96 in 1975.[6] 5-FU has been shown to induce a plethora of cardiac abnormalities. Precordial chest pain, both angina and non-cardiac, have been reported in patients during continuous 5-FU infusion. Chest pain may occur with or without ECG changes mimicking acute myocardial infarction, but myocardial enzyme levels (creatine phosphokinase and lactate dehydrogenase) often remain normal. Cases of cardiac rhythm disturbances, e.g. atrial arrhythmias (including atrial fibrillation) and ventricular ectopy (including ventricular tachycardia and ventricular fibrillation), as well as ventricular dysfunction which persisted for days to weeks after cessation of FU-treatment have been reported. Some patients initially required inotropic and vasodilator support. Cardiogenic shock and even sudden death has been documented.[7] More recently, effort-induced myocardial ischemia in combination with 5-FU treatment has been described.[8] The exact mechanism of 5-fluorouracil cardiac toxicity remains unresolved. Although the pathogenesis of cardiotoxicity is unknown, proposed mechanisms include effects on the vasculature, such as coronary artery thrombosis, arteritis, or coronary vasospasm and direct myocardial toxicity, such as accumulation of metabolites that interfere with cellular metabolism and apoptosis leading to inflammatory lesions, which could mimic myocarditis. Risk assessment for the individual patient is difficult, but a history of coronary artery disease, previous mediastinal radiotherapy and concomitant cisplatin therapy are reported to be risk factors. Toxicity appears to be dose and infusion-rate dependent.[9,10] Capecitabine, an oral 5-FU prodrug, can cause the same cardiac events as 5-FU.

A major issue with 5-FU cardiotoxicity is the high rate of recurrence even after rechallenge. As a consequence, rechallenging patients with 5-FU who previously had 5-FU-related cardiac toxicity remains controversial. Rates of recurrent cardiac toxicity after rechallenge are reported to vary from 20-100%. If rechallenged, this population of patients need careful observation during

Key messages for clinical practice

1. Cardiac toxicity induced by fluoropyrimidines is a relatively common clinical problem.
2. The rate of recurrence of cardiac toxicity is very high even with premedication.
3. There is limited evidence to suggest that replacing the fluoropyrimidine by raltitrexed is safe and efficacious.

drug infusion and may benefit from treatment with calcium channel blockers or nitrates.[11] The problem of re-challenge is important since 5-FU is the backbone for almost all chemotherapeutic regimens for colorectal cancer both in the adjuvant and metastatic setting.

The survival benefit of a combination therapy of fluoropyrimidines and oxaliplatin in the adjuvant setting in patients with resected stage III colorectal cancer has been shown in several randomised trials and is considered standard treatment (level I evidence) in the ESMO guidelines.[12-14]

There are no randomised trials evaluating the benefit of resection of solitary long nodules in metastatic colorectal cancer. However, retrospective reports showed encouraging results with an aggressive surgical approach in carefully selected patients. In a series of 378 patients that were undergoing surgery for pulmonary metastases from colorectal cancer, they found a recurrence free survival of 49% at three years for those with a single lesion. The disease free interval between the primary and the occurrence of the lung lesion was more than one year.[15]

Although there is no high-quality evidence from clinical trials, both ESMO and NCCN guidelines suggest a six month perioperative course of chemotherapy in patients undergoing resection of either isolated liver or lung metastases from colorectal cancer. Folfox is the regimen of choice.[16,17]

In a recent retrospective analysis, the Australasian gastrointestinal trials group demonstrated that of 42 patients with prior cardiac toxicity from 5-FU or capecitabine none experienced a cardiac event after the administration of raltitrexed. Seven patients (17%) had bolus 5-FU regimens, 26 patients (62%) had infusion 5-FU regimens, and nine patients (21%) had capecitabine alone or in combination. Angina was the most common cardiac toxicity from 5-FU or capecitabine and it usually occurred in the first or second cycle. Four patients continued with the same 5-FU or capecitabine regimen after their first cardiac event with the addition of nitrates and calcium antagonists but still had further cardiac events.[18] Raltitrexed is a folate analogue with potent inhibitory activity against thymidylate synthase. Randomised trials comparing raltitrexed to intravenous (IV) 5-FU have indicated non-inferiority in patients with metastatic colorectal cancer.[19,20] With a dosing schedule of a fifteen minute IV infusion, once every three weeks, raltitrexed is potentially more convenient than IV 5-FU with equivalent activity. However, the drug has not achieved widespread use, partly due to a lack of superiority to 5-FU and excess treatment-related mortality in a large adjuvant study.[21]

Raltitrexed inhibits thymidylate synthase directly without requiring a modulating agent. Raltitrexed is predominantly excreted by the kidneys with some hepatic clearance. In patients with impaired renal function, doses should be modified if the creatinine clearance is <65 ml/min and completely withheld if the creatinine clearance is <25 ml/min.[14-16] The toxicity profile of raltitrexed is that expected of an anti-metabolite with diarrhoea, nausea, and vomiting being the most frequently reported adverse events. When compared with bolus 5-FU plus leucovorin (Mayo schedule), there was less mucositis but more thrombocytopenia and elevated liver transaminases.[22,23]

Conclusion

Cardiotoxicities may be expected to occur frequently with the use of 5-FU. As 5-FU is widely used, cardiac toxicity due to 5-FU is a relatively common problem. Pre-treatment with nitrates or calcium channel blockers may eventually help to reduce the incidence of recurrence. However, recurrence is common even with premedication; close monitoring is mandatory. There is some evidence that raltitrexed, a folate analogue, is a safe alternative for patients with 5-FU (cardiac) toxicity in the setting of colorectal cancer.

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