Cardiotoxicity of 5-flourouracil: two case reports

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Abstract

Cardiotoxicity is a rare but serious side effect of 5-flourouracil (5-FU). The cardiotoxicity incidence of 5-FU is increasing with its frequent use in chemotherapy protocols. To explain the mechanism of this cardiotoxicity, many theories have been suggested by different authors. Most commonly, coronary artery vasospasm and flouroacetate, a toxic metabolite of 5-FU, are considered responsible for the toxicity. Ischemic symptoms and signs related to 5-FU are observed during the late phase of the administration of the drug. The close and careful monitorization of all the patients, especially the ones with pre-existent coronary artery disease, during 5-FU infusion is mandatory. Because there is not a single and effective modality of treatment or prophylaxis for 5-FU cardiotoxicity, the patients should be selected carefully for 5-FU administration and 5-FU infusion should be stopped as soon as a symptom is encountered. © 2001 Elsevier Science Ireland Ltd. All rights reserved.

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1. Introduction

5-Flourouracil (5-FU) is a synthetic, flourinated pyrimidine antagonist which is a cytostatic agent. 5-FU is used widely in the chemotherapy protocols of various solid tumors. Although cardiotoxicity is a rarely seen side effect of 5-FU, cases of 5-FU cardiotoxicity increased because of its increased use in chemotherapy in the last few years. The main symptom of cardiotoxicity is angina pectoris at rest together with ischemic electrocardiographic changes [1]. Here two different cases in which ischemic symptoms and signs appeared after 48 h of 5-FU administration are presented.

2. Case report 1

A 49-year-old female patient presented to our clinic in May, 1999 with fullness in the right ear and right-sided facial hypoestesia. In her physical examination, serous otitis media of the right ear, a nasopharyngeal mass narrowing the right choana and 6th cranial nerve (N. Abducens) palsy were detected. The pathology of the nasopharyngeal punch biopsy from the lesion was reported as nasopharynx undifferentiated carcinoma. The clinical stage of the patient was T4N0M0. The patient did not have a pre-existent coronary heart disease. The electrocardiography (ECG) prior to the treatment was normal. In the routine work-up of the patient, there was no evidence of distant metastase, secondarily active malignancy or any other disease. After the diagnosis, the patient was taken under the sandwich protocol of chemotherapy (CT) and radiotherapy (RT). On the first day of chemotherapy, cisplatin 100 mg/m² infusion; on days 2, 3 and 4 750 mg/m²/day 5-FU continuous infusion were planned. During the first 2 days of treatment, no significant side effect except nausea and vomiting was seen. After 48 h of continuous infusion of 5-FU, the typical angina pectoris appeared. The 5-FU administration was stopped immediately and 10 mg nifedipine was applied to the patient to relieve the symptom. The blood pressure of the patient was 190/100 mmHg. The angina pectoris of the patient lasted 20 min. The ECG after the angina disappeared was also in normal pattern. 5-FU infusion restarted. Approximately 1 h later, the patient had the same angina...
pectoris episode with chest pain. This time the blood pressure was 150/90 mmHg and the ECG taken during the angina pectoris showed typical changes of ischemia. In the derivations of D1–2–3, aVF and V4-6 the T amplitude increased. Five milligrams of Isordil was applied to the patient. The angina pectoris and pain disappeared after 20 min. Similarly, ischemic changes in the ECG also disappeared. After the patient got stabilized vital functions, 5-FU infusion restarted. Again the typical angina appeared after 1 h. This time in the derivations of D1–2–3, aVF, V4-6 ST elevations in ECG were observed. Although the pain disappeared after 20 min, changes in ECG did not disappear. (Figs. 1–3) It was decided that this condition was due to myocardial ischemia associated with 5-FU infusion and the patient was taken into the coronary intensive care unit for further evaluation and treatment. Chemotherapy program was stopped. In the coronary intensive care unit, nitrate infusion and morphine started to relieve pain. Still the ECG changes were observed during angina periods. The patient underwent coronary angiography. However, a synchronized vasospasm with 5-FU was not observed. When vasospasm was induced with ergonovin maleat, angina pectoris appeared. Vasospasm disappeared with nitrate infusion. However, the patient had a severe angina pectoris attack after angiography. This was considered as a late effect of 5-FU (Figs. 4–7). Considering the past medical literature and previous cases, a synchronized angina pectoris with 5-FU infusion during angiography was not expected. All cardiac symptoms of the patient were considered a result of 5-FU infusion and as a treatment of the primary disease of the patient, radiotherapy alone was decided.

3. Case report 2

A 55-year-old male patient with T4N0M1 laryngeal cancer presented with recurrence at the base of the tongue in March, 2000. He had total laryngectomy and right radical neck dissection in November, 1997. The pathological diagnosis was squamous cell carcinoma. After surgical excision of the tumor, he had totally 60 Gray (Gy) external radiotherapy; 50 Gy to the supraclavicular region, 46 Gy to the bilateral cervical region and 14 Gy to the medulla spinalis of the same region. For his pulmonary metastases, he had thoracotomy and metastasectomy in December, 1998. As the patient presented with recurrent tumor, a biopsy sample from the suspected area was taken. The pathology was reported as squamous cell carcinoma. The patient was decided to be put on a chemotherapy protocol for the tumor at the base of the tongue. The patient had hypertension under control with medications in his past medical history. The chemotherapy protocol was the sandwich protocol of chemotherapy (CT) and radiotherapy (RT). On the first day of chemotherapy cisplatin 100 mg/m² infusion; on days 2, 3 and 4 5-FU 750 mg/m²/day infusion were planned. On the 48th h of 5-FU infusion, angina pectoris began. The ECG taken during this period showed ischemic changes. The patient was in atrial fibrillation. In the V5–V6 derivations of the ECG, negative T waves were observed (Fig. 8). These changes were con-
sidered as cardiotoxicity of 5-FU. And the infusion of the drug was stopped immediately and the angina disappeared.

4. Discussion

The ischemic cardiac toxicity of 5-FU has been reviewed. The pathophysiology of this rare condition still remains unclear. The cardiovascular side-effects of 5-FU was first documented by Gaveau in 1969 [2] and Carpenter in 1972 [3]. The relative risk of a cardiovascular problem after 5-FU administration is 1.7% [4] and this cardiotoxicity presents clinically with myocardial ischemia symptoms [5]. After a prospective study which inspected 367 patients who had 5-FU administration, the cardiotoxicity associated with 5-FU was reported as 7.6% and mortality as 2.2%. The clinical manifestations of this cardiotoxicity may be atrial and ventricular arrhythmia, congestive heart failure, myocardial ischemia and sudden deaths [6]. The treatment of the patients who have cardiovascular side effects during 5-FU infusion is still unclear. The symptoms have usually a recurrent character and the efficacy of prophylactic or symptomatic treatment can not be predicted [5,7,8]. The interval between 5-FU infusion, and angina pectoris and ECG changes is 24–48 h. The risk of cardiotoxicity is increased if there is a pre-existent coronary heart disease. In the cases presented here and in many other cases in literature, there is not a pre-existent coronary heart disease. For this reason coronary vasospasm is considered and accepted as a possible mechanism [9].

Nasopharyngeal carcinoma is a malignant condition originating from nasopharyngeal epithelial cells. Radiotherapy is the standard treatment modality of nasopharynx carcinoma. Although several results have been reported about the role of chemotherapy, it is concluded that combination of radiotherapy and chemotherapy increases survival of the patients. In our clinic, the standard treatment of nasopharynx carcinoma is RT plus CT protocol. Treatment protocol consists of four chemotherapy periods which includes a 5-day chemotherapy every 3 weeks and radiotherapy between the two chemotherapy periods. The radiotherapy dose is 70 Gray for nasopharynx and 50 Gray for neck region. In the first day of the chemotherapy periods, cisplatin 100 mg/m²/day infusion is administered and in the remaining 4 days 5-FU 750
mg/m²/day infusions are administered. In this chemotherapy protocol, the pattern of cardiotoxicity, its recurrent character and disappearance after the infusion of 5-FU is stopped, shows that the responsible agent for cardiotoxicity is 5-FU [2–5].

The underlying mechanism of cardiotoxicity induced by 5-FU is still not fully understood. Coronary artery spasm has been suspected and has been shown in some laboratory studies. Endothelin, which is a potent vasoconstrictor, is thought to be mediator in this process. In the cancer patients under 5-FU treatment, the serum levels of endothelin was determined in high concentrations. And in the patients who had cardiac effects of 5-FU, endothelin concentrations were even higher [6]. The time interval between the infusion of the drug and the appearance of toxic effects of the drug is approximately 24 hours. If we consider the half-life of 5-FU, we should exclude it as an agent responsible for cardiotoxicity. The plasma half-life of 5-FU and its toxic metabolites is quite short [10]. However, we do not have enough information about the accumulation of these metabolites in the myocardium. It is known that the amount of ATP and the other high energy compounds decreases for a long time [11]. Apart from this, fluorocacetate (a toxic metabolite produced during 5-FU metabolism) is suspected as a responsible agent for 5-FU cardiotoxicity [12,13]. The cardiotoxicity incidence of bolus infusion of 5-FU is less than the continuous 5-FU infusion. After bolus administration of the agent, 5-FU is rapidly metabolized and leave the circulation. As the half-life of 5-FU is \( \sim 15 \) min, the probability of the presence of a direct effect of 5-FU in the occurrence of cardiac symptoms is not a possible mechanism [6].

5. Conclusion

According to our clinical observations and the medical literature, the physicians must be aware of the possible cardiotoxic side effects of 5-FU. Especially in patients with an active coronary heart disease, the decision of 5-FU administration should be carefully taken. The monitoring of high-risk patients during 5-FU infusions is mandatory. As we can not predict which group of patients are more prone to 5-FU cardiotoxicity, we should make careful and appropriate patient selection for 5-FU administration. There is not a single and effective prophylaxis and treatment modality and the ratio of fatal and recurrent cardiotoxicity is high. For all of these reasons, as soon as the symptoms appear, 5-FU infusion should be stopped immediately. The treatment should be continued with another chemotherapy agent or with radiotherapy alone.

References