Acute coronary syndrome induced by oral capecitabine

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A 41-year-old woman who was undergoing oral chemotherapy with capecitabine for metastatic breast cancer presented with recurrent episodes of chest pain associated with electrocardiographic signs of diffuse ST segment elevation. After spontaneous pain relief, the electrocardiogram showed ischemic evolution in the anterior precordial leads. Coronary and ventricular angiography, performed 24 h later, showed normal coronary arteries and normal left ventricular function. After therapy with capecitabine was discontinued, the patient did not experience further episodes of chest pain. After a nine-month follow-up, she remains alive, with a good performance status and without clinical evidence of persistent ischemia.

Key Words: *Acute coronary syndrome; Capecitabine; Oral chemotherapy; ST segment elevation*

Several drugs and conditions can induce acute coronary syndrome (ACS) in patients without underlying cardiovascular disease (1,2). Among these, the cardiotoxic effects of 5-fluorouracil (5-FU), a pyrimidine analogue commonly administered intravenously for the treatment of several different types of solid tumours, have been previously described, with a reported incidence ranging from 1% to 68% (3,4). The cardiotoxic effects of capecitabine (Xeloda, Roche Pharmaceuticals, USA), an oral formulation of 5-FU, are less familiar to clinicians, particularly to cardiologists. We report the case of a 41-year-old patient with metastatic breast cancer in whom ACS occurred during oral therapy with capecitabine.

CASE PRESENTATION

A 41-year-old woman was admitted to the emergency room due to chest discomfort that started during ambulatory oncological control. She reported several transient episodes of chest pain during the previous 24 h. She had no history of cardiac disease, coagulation disorders or drug abuse, and no cardiovascular risk factors. She had previously undergone a left mastectomy and received left chest radiotherapy. Later, she developed bone and liver metastases. After the failure of three consecutive chemotherapeutic lines, she began a new regimen with intravenous vinorelbine (38 mg once weekly). More recently, treatment with oral capecitabine (1500 mg twice daily) was initiated. Two days after beginning capecitabine, she developed chest pain. The electrocardiogram (ECG), which was recorded during chest pain, showed ST segment elevation in the anterior (V2 to V6, and D1) and inferior leads (Figure 1). After spontaneous symptom relief,

Un syndrome coronarien aigu induit par de la capécitabine orale

Une femme de 41 ans sous chimiothérapie orale à la capécitabine en traitement d'un cancer du sein métastatique a consulté en raison d'épisodes récurrents de douleurs thoraciques associées à des signes électrocardiographiques de surélévation diffuse du segment ST. Après un soulagement spontané de la douleur, l'électrocardiogramme a révélé une évolution ischémique dans les dérivations précordiales antérieures. Une coronarographie et une angiographie ventriculaire exécutées 24 heures plus tard ont permis de visualiser des artères coronaires et une fonction ventriculaire gauche normales. Après l'abandon du traitement à la capécitabine, la patiente a cessé de souffrir de douleurs thoraciques. Au bout d'un suivi de neuf mois, elle était toujours vivante et présentait un bon indice fonctionnel, sans manifestations cliniques d'ischémie persistante.

within 10 min, the ST segment normalized, and the T wave inverted in the anterior precordial leads (Figure 2). Intravenous therapy with nitrates and unfractionated heparin was immediately given, and capecitabine was discontinued. Echocardiography, performed 15 min after symptom relief, showed normal ventricular volumes, segmentary wall kinetics and a left ventricular ejection fraction of 63%, an abnormal peak E wave/peak A wave velocities ratio (0.68) and the absence of pericardial effusion. Since then, she has experienced no further episodes of angina. Daily ECGs showed progressive recovery of ventricular repolarization abnormalities. Serum cardiac markers, including troponin I, remained within the normal range. Coronary and ventricular angiography, performed 24 h later, revealed a normal epicardial coronary artery tree and normal left ventricular function. She was discharged without active coronary therapy. To control the oncological disease, only intravenous vinorelbine was continued. After nine months, she showed a good performance status, and she experienced no further episodes of chest pain. The ECG confirmed a normal repolarization pattern.

DISCUSSION

5-FU is a synthetic pyrimidine that is effective in the treatment of numerous malignant lesions. Several studies have shown that continuous infusion is associated with greater antitumour activity and lower toxicity than bolus administration (5). However, continuous infusion is costly and requires an infusion catheter and pump. The use of an oral formulation of 5-FU allows a patient protracted exposure without the disadvantages and costs of the intravenous infusion regimen.

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Figure 1) Initial presenting electrocardiogram showing diffuse ST segment elevation

Capecitabine is an oral fluoropyrimidine that offers improved efficacy, tolerability and convenience for patients. Although it is simply considered an oral version of 5-FU, designed to mimic 5-FU continuous infusion, capecitabine has the important advantage of being able to concentrate in the targeted tumour, resulting in favourable efficacy and toxicity profiles (5). Moreover, capecitabine is more convenient for patients, most of whom prefer oral to intravenous treatment, especially in a palliative setting (6). Finally, by allowing home-based therapy, capecitabine represents a significant advance in the treatment of oncological patients. All of these properties widely justify capecitabine's increasing use in cancer patients.

Cardiotoxicity is a recognized side effect of 5-FU. It can manifest as angina pectoris, myocardial infarction, cardiogenic shock, arrhythmias or sudden death (4). Several predisposing factors have been identified. Patients with ischemic heart disease or prior chest irradiation, or who are being administered concurrent anthracyclines are at higher risk (4,7-9). Its administration schedule may also influence the risk of cardiotoxicity; incidences of cardiotoxicity have proven to be lower after bolus administration than after continuous infusion (10). The mean reported time interval between 5-FU administration and

Figure 2) ST segment normalization and T wave inversion in the anterior precordial leads

the onset of cardiac symptoms is three days (range two to five days). Symptoms are usually relieved within 48 h after drug discontinuation, but they usually recur when infusion is restarted. The most frequent ECG abnormalities (acute ST segment changes and T wave inversion) are mostly resolved from within a few hours to up to three days after withdrawal (10).

The mechanism underlying 5-FU cardiotoxicity is not fully understood, but coronary vasospasm and thrombus formation are the most widely accepted hypotheses (4,11-13).

The present case report, confirming several previous communications (14-19), shows that capecitabine can induce ACS. Although the true incidence of this complication has not yet been defined, chest pain during capecitabine therapy has been reported in 6% of patients (20). Because capecitabine is metabolized to 5-FU *in vivo*, we assume that it can induce cardiotoxic effects by the same mechanism(s). Acute transient coronary thrombosis cannot completely be excluded by angiography. Coronary vasospasm is another reasonable mechanism that is possibly involved. However, the efficacy of vasodilating drugs, given prophylactically to patients with previous episodes of chest pain during 5-FU treatment, has been reported with inconsistent results (16). Capecitabine-induced coronary

vasospasm and other forms of coronary spasm (Prinzmetal's angina) cannot formally be ruled out in our patient because angiography was performed when the patient was no longer symptomatic. Frickhofen et al (16) have reported no evidence of vasospasm in a patient still symptomatic during angiography. This finding argues against vasospasm of the large coronary arteries, although a transient spasm of the small coronary vessels (not detectable by angiography) cannot be excluded. Interestingly, in our patient, the observed ECG evolution (straight ST segment in leads V2 and V3 passing into a negative T wave at an angle of 60° to 90°, and a symmetrically inverted T wave) exactly resembled the characteristic pattern indicating a critical stenosis high in the left anterior descending coronary artery (21).

Although our patient had no classic coronary risk factors, she underwent chest radiotherapy after mastectomy, and was previously treated with anthracyclines. According to previous findings, she was at higher risk for fluoropyrimidine-related cardiotoxicity (4,7-9).

In our patient, symptoms did not occur after the first dose of capecitabine, but only after three or four tablets were given. The rapid resolution of angina and of ST segment elevation, without an increase in the serum markers of myocardial necrosis,

confirmed that this event is transient and reversible after treatment is discontinued (14-19). Moreover, in our patient, the nine-month, symptom-free follow-up points out a long-term positive cardiac outcome for this form of cardioxicity. Notably, the follow-up duration was rarely described in previous reports, and never clearly defined (14-19).

CONCLUSIONS

Capecitabine-related cardiotoxicity is a rare but nevertheless potentially serious event (19,22). However, because of its promising antitumour efficacy, its use should not be discouraged. Both oncologists and cardiologists should be aware of its potential cardiac hazard, especially in patients with recognized risk factors, as well as the need to promptly discontinue treatment in patients developing ACS. Moreover, in view of the increasing use of capecitabine, patients should be warned about the possibility of chest pain, particularly during the first few days. Most importantly, patients developing ACS should not be re-treated with capecitabine.

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