Acute Coronary Syndrome During Oral Capecitabine Monotherapy

To the Editor:

Cardiotoxicity induced by 5-fluorouracil (5-FU), a pyrimidine analog used endovenously, is well known.\(^1\) Capecitabine is a new oral fluoropyrimidine that undergoes enzyme conversion to 5-FU mainly in the tumor and results in a lower concentration in the healthy tissues and lower systemic toxicity.\(^2\) We report a patient who presented an acute coronary syndrome (ACS) that was attributed to oral monotherapy with capecitabine given as treatment for a rectal adenocarcinoma.

The patient, a 61-year-old man who had no toxic habits or coronary risk factors, presented to the hospital with rectorrhagia. Fiber colonoscopy showed an ulcerated lesion on the anal margin. Histological study showed a rectal adenocarcinoma and an extension study resulted in a classification of T3 N1 M0. Treatment was started with capecitabine at 1500 mg per day each 12 h. On the third day the patient reported oppressive chest pain on effort lasting 15 minutes. A few hours later he had 2 new episodes at rest accompanied by profuse sweating and he was taken to the Emergency Department. An electrocardiogram, enzyme curves, and an echocardiogram were all normal. An exercise stress test showed inferolateral ST segment elevation associated with angina, at a heart rate of 157 beats per minute, and an exercise MET level of 9. The electrical changes and the pain remitted on stopping the test and giving the patient sublingual nitrates. Capecitabine was withdrawn. Given the possibility of a coronary artery spasm, treatment was started with amlodipine at 5 mg per day and
acetylsalicylic acid 100 mg per day. A coronary angiogram, done in order to rule out the possibility of organic coronary vessel disease, showed normal coronary arteries. No coronary spasm or intracoronary thrombus was seen. A further exercise stress test carried out 1 month later with no medication was normal, at a heart rate of 141 beats per minute and an exercise MET level of 9. The patient was scheduled for surgery after radiotherapy.

The course of the patient reported here shows that oral capecitabine monotherapy may cause an ACS. The patient was not a smoker nor did he have any coronary risk factors. The coronary angiogram ruled out arteriosclerotic coronary lesions. Although no vasospasm was found on coronary angiography, the patient was treated empirically with amlodipine. The efficacy of the symptomatic treatment of these patients with arterial vasodilators, such as nitrates, calcium antagonists, or angiotensin converting enzyme inhibitors, is variable and the symptoms do not cease until the fluoropyrimidine drug is withdrawn.\textsuperscript{3,4} The mechanism of myocardial ischemia is likely to be multifactorial. Capecitabine, or its metabolites, could directly damage the endothelial cells due to a cytotoxic effect on cell metabolism. Experimental animal models treated with 5-FU showed a reduction in high energy phosphates and an accumulation of citrates in the myocardium associated with electrocardiographic changes.\textsuperscript{5} Use of the Naranjo scale\textsuperscript{6} to identify adverse drug reactions indicated a possible association between ACS and treatment with capecitabine.

In conclusion, the patient reported here should warn us of the risk that oral monotherapy with capecitabine may cause an ACS. In the event that this occurs, the patient should be monitored, capecitabine withdrawn immediately, and the pain relieved. Caution should be exercised when prescribing capecitabine in patients with a history of ischemic heart disease, arrhythmia or Prinzmetal’s angina.

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REFERENCES