Capecitabine in Breast Cancer: The Issue of Cardiotoxicity During Fluoropyrimidine Treatment

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Abstract: Capecitabine is an orally available fluoropyrimidine carbamate that selectively delivers fluorouracil (5-FU) to tissues expressing high levels of thymidine phosphorylase (TP) such as tumors. The drug has demonstrated efficacy in metastatic breast cancer, colorectal, and pancreatic cancer. Although these are considered safe drugs, a growing body of literature reports adverse cardiac effects. Clinical trials indicate that capecitabine has a cardiac toxicity similar to that of infused fluoropyrimidines such as 5-FU. Here, we review cardiotoxicity in the use of fluoropyrimidines, with particular attention toward capecitabine. We also describe a severe, reversible cardiac event that occurred in a 39-year-old woman, with no cardiac risk factors, treated with capecitabine for advanced breast cancer. This review and our experience confirm that fluoropyrimidine cardiotoxicity is an infrequent but documented side effect. Oncology patients under treatment should be closely observed and monitored for cardiac symptoms with particular attention in case of signs or symptoms of cardiovascular complications. The implementation of cardio-oncology interdisciplinary teams should, in the future, reduce the impact of cancer treatment–associated cardiotoxicity syndromes.

Key Words: breast cancer, capecitabine, cardiogenic shock, cardiotoxicity, fluoropyrimidine

Capecitabine is an oral fluoropyrimidine analog approved by the Food and Drug Administration as adjuvant treatment for stage III colon cancer, for metastatic disease and for the treatment of metastatic breast cancer in patients whose pathology did not improve during treatment with other therapeutic agents (1). Capecitabine is a prodrug, and it is selectively activated by tumor cells to its cytotoxic moiety, 5-fluorouracil (5-FU), by thymidine phosphorylase (TP), which is generally expressed at high levels in tumors. Subsequently, 5-FU is metabolized to two active metabolites, 5-fluoro-2-deoxyuridine monophosphate (FdUMP) and 5-fluorouridine triphosphate (FUTP), by both tumor cells and normal cells. FdUMP inhibits DNA synthesis and cell division by reducing normal thymidine production, while FUTP inhibits RNA and protein synthesis by competing with uridine triphosphate for incorporation into the nascent RNA strand (1). The most commonly reported grade 3–4 adverse events of capecitabine are hand–foot syndrome (17%), diarrhea (17%), and nausea (15%). Grade 3–4 neutropenia is very uncommon (<3%), hyperbilirubinemia is reported in 15% of the cases, and all the above toxicities are reversible (2).

CARDIAC TOXICITY OF FLUOROPYRIMIDINES

Cardiotoxic side effects of anticancer drugs can be potentially life-threatening (3), and with the increasing aging of the population, the incidence of cardiotoxicity is growing (4). Cardiotoxicity is a rare, but potentially serious, toxicity of fluoropyrimidine (5); the incidence of oral fluoropyrimidine-induced cardiotoxicity is similar to that reported for 5-FU (6). As capecitabine is a 5-FU prodrug, its cardiotoxicity would likely be due to the effects of 5-FU. A retrospective analysis of 1189 patients noted a 3% overall incidence and a 0.8% incidence of grade 3 or 4 cardiotoxicity in patients receiving capecitabine monotherapy, with a similar

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incidence noted in comparison with the arm receiving bolus 5-FU (2). The majority of the events occurred within cycle one, and angina was the predominant event. Other signs and symptoms included dysrhythmias, dyspnea, ST-T-wave changes on ECG, myocardial infarction, and pulmonary edema. These complications were reversible in the majority of cases after the cessation of the administration of the drug and with symptomatic treatment. However, in rare cases, sudden death has been reported (7), and our recent experience indicated that severe cardiotoxicity can occur even in relatively young, low-risk patients.

SEVERE CARDIOTOXICITY IN A 39-YEAR-OLD PATIENT WITH BREAST CANCER

In our clinic, we encountered severe cardiotoxicity in a case of a 39-year-old nonsmoker, nonobese woman that was diagnosed in July 2004 with right inflammatory breast cancer associated with a single palpable homolateral axillary lymph node. The tumor was estrogen receptor (ER) positive (90%) and progesterone receptor (PgR) positive (65%). The patient was treated with four cycles of adriamycin (60 mg/mq) and cyclophosphamide (600 mg/mq) followed by four cycles of docetaxel (75 mg/mq) concomitant with an LH-RH analog, obtaining partial remission. She then underwent a radical mastectomy and axillary dissection in January 2005. The histologic evaluation revealed an isolated ductal neoplastic cell in the nipple area with neoplastic infiltration of axillary soft tissue, ER positive 70%, PgR negative, Herceptest score 1+, and an absence of neoplastic cells in the 13 axillary lymph nodes retrieved by the axillary dissection. She was treated with radiotherapy on the right thoracic chest wall, right axilla, and supraclavicular region. Tamoxifen 20 mg once daily was added to the LH-RH analog.

Two years later, a serological, osseous, and nodal mediastinal relapse was diagnosed. In March 2007, she began letrozole 2.5 mg once daily associated with LH-RH analog with initial partial remission. Exemestane 25 mg once daily was started in November 2007 because of serological, lymph node, and cutaneous progression, without beneficial effect. Capecitabine 1000 mg/mq twice daily was then started. Three days following initiation of capecitabine, she developed tachycardia, with normal blood pressure and no other symptoms. An electrocardiogram showed sinus tachycardia without ST-T changes. Over the next 2 days, she developed abdominal pain in the right upper quadrant and a general discomfort. On the seventh day of therapy (after a cumulative dose of 12,000 mg/mq of capecitabine), the asthenia worsened and she was admitted to an emergency room. On arrival to the emergency room, blood pressure was adequate (110/80 mm/Hg) and an electrocardiogram showed only sinus tachycardia. However, the hemodynamic condition of the patient rapidly worsened with loss of conscience, hypotension (AP 85/65 mm/Hg) associated with tachycardia (140 bpm) and a T-wave inversion in antero-lateral leads. She was transferred to a coronary unit with a diagnosis of cardiogenic shock. The 2D echocardiography showed a severe cardiac failure, with an ejection fraction (EF) of 28%, a biventricular and left atrial dilatation, and a superior vena cava distension. Blood examinations revealed only an elevated troponin I value of 0.18 ng/mL (normal level: 0–0.06), the maximum troponin I value, reached eight hours later, was 0.34 ng/mL. A dopamine infusion (5 µg/Kg/min), steroid (methylprednisolone, 40 mg, endovenous), and enoxaparin (2000 UI subcutaneous twice daily) were started. After 72 h, the dopamine infusion was stopped, and an oral therapy with the beta blocker bisoprolol was started (1.25 mg os). After 7 days, blood pressure improved to 120/70 mmHg and the EF improved to 62%. The patient was then discharged in good clinical condition.

Subsequent cardiologic assessments (including echocardiography) were consistently normal, and the ejection fraction was constantly within the normal range. After a few months of treatment with bisoprolol, dosage of the drug was halved for a tendency for sinus bradycardia. Because of neoplastic progression (skin, bone, and liver) the patient subsequently received additional chemotherapy (gemcitabine, carboplatin, vinorelbine, paclitaxel, pemetrexed) and hormonal therapy (anastrozole, fulvestrant). The patient died in March 2010 because of terminal liver failure.

CAUTION WITH FLUOROPYRIMIDINES: GROWING ATTENTION TO CARDIAC TOXICITIES

These observations indicate that capecitabine can induce cardiogenic shock even in low-risk patients without apparent or previous cardiologic risk factors. The only risk factor in our patient was the previous treatment with anthracyclines and taxanes, both reported to have cardiac toxicity, although the EF at
the end of the treatment with antracycline and taxanes was normal. The symptoms did not occur after the first dose of capecitabine, but after five doses and persisted for 72 h following ingestion of the last dose of capecitabine. One possible explanation for the prolonged toxicity is the fact that exposure to capecitabine cannot be interrupted after oral ingestion of the drug, leading to a prolonged generation of the cardiotoxic agent (8). A recent report describes ischemia with an ejection fraction reduction in a 38-year-old woman treated with capecitabine, after undergoing an exercise stress echocardiogram, although the patient had a history of hyperlipidemia and a family history of premature coronary artery disease (CAD) (9). Thymidine phosphorylase, one of the enzymes involved in the conversion of capecitabine to 5-FU, can also be expressed in higher concentrations in atherosclerotic plaques as well as in tumor tissues, potentially contributing to the higher prevalence of cardiotoxicity in patients with CAD. The role of pre-existing clinical risk factors has been already recognized and well described in the literature. Labianca et al. evaluated 1083 patients treated with 5-FU, the global incidence of cardiopathy was 1.6%, with a significantly greater risk (4.5% versus 1.1%) for patients with a positive history of previous cardiopathy (10). A prospective study that evaluated 644 patients treated with capecitabine or 5-FU, but with a negative medical history for coronary artery disease, symptomatic cardiac disease, diabetes mellitus, or peripheral vascular disease, found an incidence of drug-related cardiotoxicity of 4% (11). Coronary artery vasospasm is the most commonly evoked hypothesis, but other explanations have been proposed, i.e., direct toxicity to the myocardium, thrombogenic effects, autoimmune phenomena, and reduction of antioxidant defense capacities in myocardial tissue (3,4). Vasospasm is a reasonable mechanism, as it would explain the reports of efficacy of vasodilating drugs given prophylactically to patients who had experienced a previous episode, even if the efficacy of these drugs is variable (12–15). Nonetheless, our case indicates that patients without risk factors can develop cardiotoxicity, the pathogenesis of which is not fully understood.

The echocardiography of our patient demonstrated severe reduced ejection fraction and a global akinesia that did not correspond to a segmental distribution of the major coronary arteries. The observations suggested either a transient and global vasospasm of the microvasculature or a direct drug or drug metabolite-mediated toxic action on the myocytes. Interestingly, a recent case report of a relatively young patient with colorectal cancer with no cardiovascular history treated with 5-FU showed a severe cardiovascular event after 20 h of infusion (16). This patient had ST alterations, elevated troponin I (4.07), a global left ventricle systolic dysfunction and an ejection fraction of 30%, suggesting multiple mechanisms of toxicity were ongoing. Symptomatic bradycardia and sinus arrest have also been reported for a patient after 6 days of capecitabine (17). Experimental evidence supports a potential direct toxic effect of 5-FU on the coronary endothelial intima (18,19). Cwikiel et al. observed injuries of the vascular endothelium in the central ear arteries of rabbits that could result in arterial thrombosis (19). In another study, human and bovine endothelial cells incubated with increasing concentrations of 5-FU and methotrexate (MTX) indicated that 5-FU, but not MTX, increased significantly the release of prostacyclin, indicating leakage secondary to endothelial cell injury (18). Other data based on pathological findings suggested a toxic myocarditis as a possible pathogenic mechanism underlying 5-FU cardiotoxicity (20). A reduction in antioxidant defense capacities is another hypothesis. Durak et al. demonstrated that the administration of 5-FU to guinea pigs reduced the activity of the enzymes superoxide dismutase and glutathione peroxidase with a concomitant increase in the activity of catalases and concentration of malondialdehyde (21). An increased concentration of this enzyme is observed in myocardial ischemia and is prevented by calcium inhibitors (22). The risk of recurrence of cardiotoxicity when patients are rechallenged with 5-FU and capecitabine is high; thus, at disease progression, we decided to treat our patient in the first instance with gemcitabine.

**CONCLUSIONS**

The cardiotoxicity because of treatment with capecitabine is an event described only when it becomes clinically evident, but considering the diverse pathogenetic mechanisms that may be involved, we would argue that there is a higher subclinical frequency. It would be therefore useful to study earlier laboratory markers, such as troponin I and T, and instrumental markers of damage. In clinical daily practice, we would recommend careful cardiologic monitoring, in particular on the first days of treatment, for all patients, including individuals apparently not at risk.
The development of cardio-oncology disease management teams is becoming an impelling issue (4,23).

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