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Case Report

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CARDIOTOXICITY INDUCED BY CAPECITABINE: A CASE REPORT AND REVIEW OF THE LITERATURE

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ABSTRACT

Capecitabine is a chemotherapy drug that is widely used in several types of cancer. The majority of its side effects are moderately severe except for cardiac toxicities which are of low incidence but should be managed with knowledge as they are potentially fatal. In this article, we report a case of cardiac toxicity and review the literature to identify common risk factors, frequent clinical manifestations and approaches to manage these toxicities.

KEYWORDS: Capecitabine, Cardiotoxicity, Algorithm.

INTRODUCTION

Capecitabine is an oral prodrug of 5-fluorouracil (5FU) which belongs to the family of anti-metabolites, subgroups of flyuoropyrimidine analogs. It is a cytotoxic drug that is generally well tolerated and the adverse effects often reported are Hand-foot syndrome (17%), diarrhea (17%), Nausea and vomiting (15%). Despite its good tolerance, the incidence of cardiac toxicity induced by 5FU and its pro-drugs is increasing and can reach 20% depending on the study.

Major cardiac events such as myocardial infarction, cardiogenic shock and sudden death are rare and occur in 0% to 2% of patients depending on the study.[1]

We report a case of STEMI in a patient with metastatic breast cancer treated with Capecitabine.

OBSERVATION

This is a 67-year-old patient with a history of hyperuricemia, hypercholesterolemia and diabetes type 2 ; who presented in 2013 an infiltrating ductal carcinoma of the left breast (RE 90% RP 50% Her2 score1+) with immediate bone metastasis. She received in 1st line of treatment 7 cycles of AC60 (Doxorubicin + Cyclophosphamide) until April 2014 then a maintenance by hormone therapy type Letrozole 2,5mg per day.

In April 2018, a CT scan showed a progression of bone lesions and she was put on a 2nd line of taxane-based treatment (7 cycles of paclitaxel) with stability of lesions and then maintenance with Anastrozole 1mg daily until October 2019 when a surveillance scan concluded that the disease had progressed at the lymph node level (supraclavicular adenopathy).

A biopsy of the adenopathy for immunohistochemical analysis was decided in a multidisciplinary consultation meeting and showed: supraclavicular location of a moderately differentiated ADK. IHC: ER 100% RP 60% HER2 score1+.

The patient was treated with CAPECITABINE in 3rd line after a cardiac workup: normal ECG and ejection function at 53%. After the 2nd cycle, she presented significant chest pain and was admitted to the emergency room for management. An ECG performed showed a myocardial infarction with ST-segment elevation (Fig. 1); Troponin H1 was 50000. Cardiac ultrasound revealed a decreased LVEF of 45%.

After good progress on the cardiac level, the case was discussed at the medical oncology staff and the resumption of chemotherapy was conditioned by a favorable cardiological opinion given the patient's history. Thus, the cardiological opinion was unfavorable for the resumption of capecitabine but also vinorelbine. The collegial decision was to put the patient on hormone therapy with regular cardiological follow-up because cardiovascular adverse effects have been reported in the literature. She was treated with Exemestane for three months with an unfavourable clinical, biological and radiological evolution.

DISCUSSION AND REVIEW OF THE LITERATURE

The incidence of cardiac toxicities is variable according to the data in the literature. The incidence of cardiac abnormalities after fluoropyrimidine-based chemotherapy varies from 1.2% to 18%, with a mortality rate between 2.2% and 13%.[2] However, in several trials, the incidence of this cardiac toxicity is 1.2% to 4.3% during treatment. This low incidence is confirmed by a large meta-analysis of patients followed for colorectal and breast cancers treated with fluoropyrimidine-based chemotherapy, revealing an incidence of 3%.[3]

The mechanism of fluoropyimidine-induced cardiotoxicity is not well understood. During 5FU infusion, the hypothesis of coronary spasms was raised in view of the regression of symptoms when the infusion was stopped and confirmed by the visualization of spasms during coronary angiography but also in peripheral arteries such as the brachial artery.[4,5] These spasms would be linked to the release of vasoconstrictor substances such as endothelin-1, which is at the origin of endothelial dysfunction.[6] However, this hypothesis, which can explain the occurrence of chest pain during perfusion, does not explain other cardiac manifestations, particularly those occurring at distance from the perfusion.[7]

The risk factors for cardiotoxicity have been evaluated in several studies and the results remain contradictory. For example, a prospective study carried out in 35 hospitals showed that a pre-existing cardiovascular pathology significantly increased the risk of cardiac toxicity compared to the absence of cardiovascular pathology.[8] These results are also reported in retrospective studies specific to Capecitabine.[9,10] A history of ischemic heart disease was a risk factor in one study, but not confirmed in two other studies.[11]

For our patient, her history of hypercholesterolemia and diabetes could have been factors leading to the myocardial infarction.

As in our patient, chest pain is the most frequent clinical manifestation in the majority of cases, 80%.[1] Koca et al[10] reported 34.6% of symptomatic cardiac toxicity in 52 patients treated with Capecitabine alone or in combination with other chemotherapies, and chest pain and palpitations were the most frequent clinical manifestations. Severe clinical manifestations have been reported in some cases, including coronary dissections, ventricular tachycardia, cardiogenic shock, and cardiac arrest.[12-14]

Currently, there is no consensus on the management of cardiac toxicities. Therefore, current practices are heterogeneous and some algorithms (fig.2) are published[1,15,16] A multidisciplinary discussion is required between oncologists and cardiologists, especially in patients with cardiovascular risk factors.

In 2015, uridine triacetate was approved by the FDA as an antidote to 5FU (or Capecitabine) overdose but in case of severe toxicity affecting cardiac function or the central nervous system.[17] It is a naturally occurring pyrimidine nucleoside that represents one of the four basic constituents of RNA. After administration, it is converted into uridine triphosphate which competes with the toxic metabolite of 5FU for incorporation into normal body cells. It has been shown in a small cohort study that the survival rate of patients who received this antidote was superior to that of supportive care.[18] However, given the limitations of this study, further studies are needed to demonstrate the value of this therapy in fluoropyrimidine-induced cardiac toxicities.

In general, before initiating fluoropyrimidine-based treatment, a minimal cardiac work-up is required (ECG +/- cardiac ultrasound); in the event of a history of cardiovascular disease, consultation with a cardiologist seems important in order to set up rigorous monitoring. If cardiac symptoms occur during treatment, the first step is to stop the treatment, perform an electrocardiogram and measure troponin. In case of persistent chest pain and/or ECG changes, whether or not associated with troponin elevation, a cardiological opinion is necessary to set up specialized management.

In case of anginal pain, which is the most frequent symptom, anti-angina treatment (calcic inhibitor or nitrates) can be initiated, although the level of evidence remains low and the results discordant.[19,20] Larger randomized studies seem necessary to evaluate these practices.

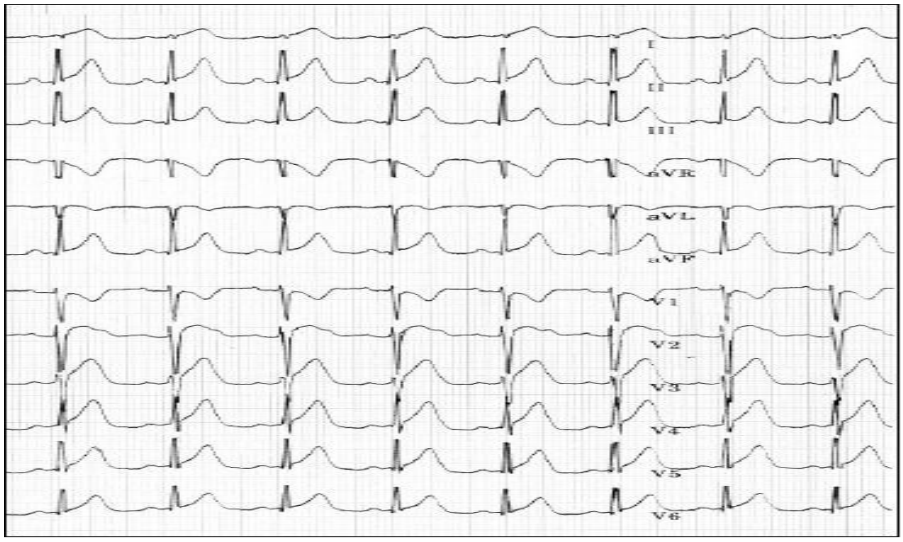

Figure 1: ST-segment elevation in D1 and from V2 to V6.

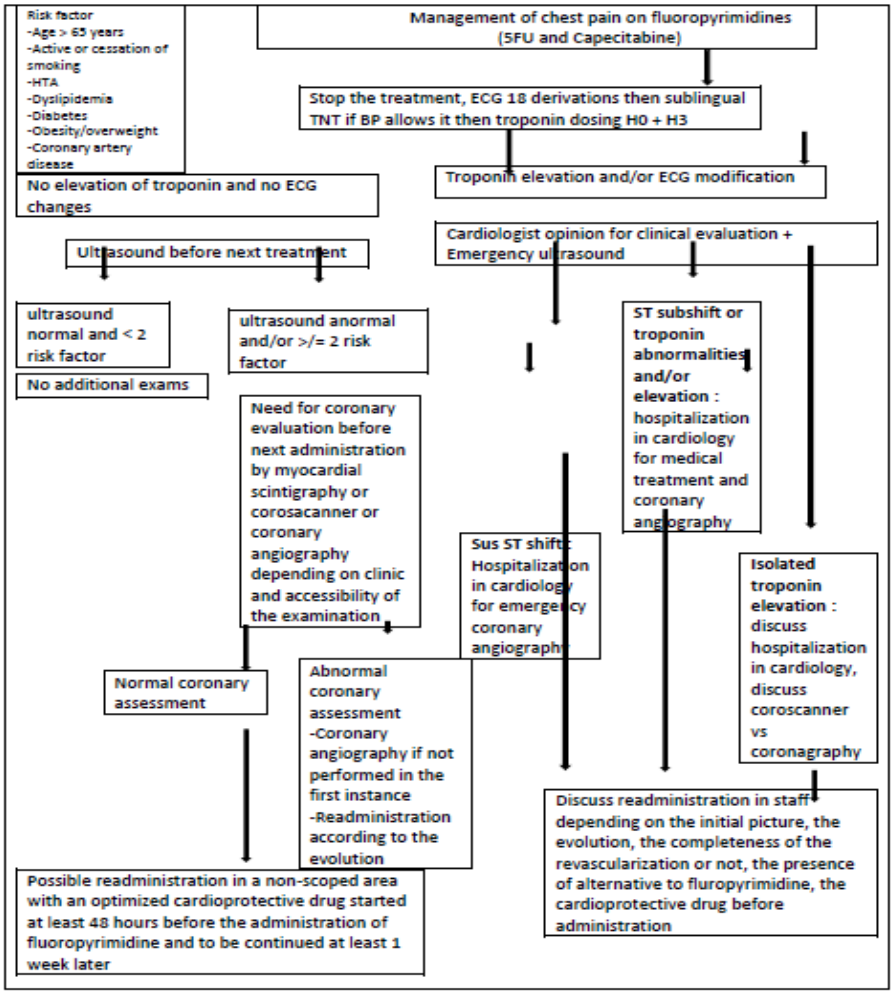

Figure 2: An algorithm for the management of chest pain on fluoropyrimidine.

CONCLUSION

Despite its relatively low incidence, cardiotoxicity of capecitabine and more generally of fluoropyrimidines constitutes a serious adverse event with a potential fatal outcome. The clinical manifestations remain varied and chest pain is the most frequent symptom.

A comprehensive pre-treatment workup should be performed before starting treatment, and cardiologists should be involved in treatment decisions in patients with conventional risk factors such as hypertension, dyslipidemia, diabetes, and history of heart disease.

Consensus management should be established with the development of practical algorithms. In case of improvement of toxicity, the reintroduction or change of treatment should be discussed in a multidisciplinary consultation meeting including cardiologists.

BIBLIOGRAPHIES

1. Bouhier-Leporrier K, Ederhy S, Alexandre J. Cardiotoxicity induced by 5-fluorouracil and capecitabine. Hepato-Gastro and Digestive Oncology, 2019; 26: 882-888.
2. Lamberti M, Porto S, Zappavigna S, et al. A mechanistic study on the cardiotoxicity of 5-fluorouracil in vitro and clinical and occupational perspectives. *Toxicol Lett*, 2014; 227(3): 151–156.
3. Van Cutsem E, Hoff PM, Blum JL, Abt M, Osterwalder B. Incidence of cardiotoxicity with the oral fluoropyrimidine capecitabine is typical of that reported with 5-fluorouracil. *Ann Oncol*, 2002; 13(3): 484–485.
4. Luwaert RJ, Descamps O, Majois F, Chaudron JM, Beauduin M. Coronaryartery spasm induced by 5-fluorouracil. Eur Heart J, 1991; 12: 468-70.
5. Südhoff T, Enderle M-D, Pahlke M, Petz C, Teschendorf C, Graeven U, Schmiegel W. 5-Fluorouracil induces arterial vasocontractions. Ann Oncol, 2004; 15: 661-4.
6. Cwikiel M, Zhang B, Eskilsson J, Wieslander JB, Albertsson M. The influence of 5-fluorouracil on the endothelium in small arteries. An electron microscopic study in rabbits. Scanning Microsc, 1995; 9: 561-76.
7. Stewart T, Pavlakis N, Ward M. Cardiotoxicity with 5-fluorouracil and capecitabine : more than just vasospastic angina. Intern Med J, 2010; 40: 303-307.
8. Meyer CC, Calis KA, Burke LB, Walawander CA, Grasela TH. Symptomatic cardiotoxicity associated with 5-fluorouracil. *Pharmacotherapy*, 1997; 17(4): 729–736.
9. Jensen SA, Sørensen JB. Risk factors and prevention of cardiotoxicity induced by 5-fluorouracil or capecitabine. *Cancer Chemother Pharmacol*, 2006; 58(4): 487–493.
10. Koca D, Salman T, Unek IT, et al. Clinical and electrocardiography changes in patients treated with capecitabine. *Chemotherapy*, 2011; 57(5): 381–387.
11. Polk A, Shahmarvand N, Vistisen K, et al. Incidence and risk factors for capecitabine-induced symptomatic cardiotoxicity: A retrospective study of 452 consecutive patients with metastatic breast cancer. BMJ Open, 2016; 6: e012798.
12. Rateesh S, Shekar K, Naidoo R, Mittal D, Bhaskar B. Use of extracorporeal membrane oxygenation for mechanical circulatory support in a patient with 5-fluorouracil induced acute heart failure. Circ Heart Fail, 2015; 8(2): 381–3.
13. Hollriegel R, Fischer J, Schuler G. Early extracorporeal membrane oxygenation support for 5-fluorouracil-induced acute heart failure with cardiogenic shock. Heart Views, 2014; 15(1): 26–8.
14. David JS, Gueugniaud PY, Hepp A, Gaussorgues P, Petit P. Severe heart failure secondary to 5-fluorouracil and low-doses of folinic acid: usefulness of an intra-aortic balloon pump. Crit Care Med, 2000; 28(10): 3558–60.
15. Clasen SC, Ky B, O'Quinn R, Giantonio B, Teitelbaum U, Carver JR. Fluoropyrimidine-induced cardiac toxicity: Challenging the current paradigm. J Gastrointest Oncol, 2017; 8: 970-979.
16. Sara JD, Kaur J, Khodadadi R, et al. 5-fluorouracil and cardiotoxicity: A review. Ther Adv Med Oncol, 2018; 10: 1758835918780140.
17. Ison G, Beaver JA, McGuinn WD Jr, Palmby TR, Dinin J, Charlab R, et al. FDA approval: uridine triacetate for the treatment of patients following fluorouracil or Capecitabine overdose or exhibiting early-onset severe toxicities following Administration of these Drugs. Clin Cancer Res, 2016; 22(18): 4545–9.
18. Ma WW, Saif MW, El-Rayes BF, Fakih MG, Cartwright TH, Posey JA, et al. Emergency use of uridine triacetate for the prevention and treatment of lifethreatening 5-fluorouracil and capecitabine toxicity. Cancer, 2017; 123(2): 345–56.
19. Eskilsson J, Albertsson M. Failure of preventing 5-fluorouracil cardiotoxicity by prophylactic treatment with verapamil. Acta Oncol Stockh Swed, 1990; 29: 1001-3.
20. Ambrosy AP, Kunz PL, Fisher GA, Witteles RM. Capecitabine induced chest pain relieved by diltiazem. Am J Cardiol, 2012; 110: 1623-6.