The Oncologist®

Fluoropyrimidine-Associated Cardiotoxicity: Probably Not So Rare As It Seems

We read with interest Raber et al.'s report [1] of their retrospective case-control study of fluoropyrimidine-associated cardiotoxicity in patients with cancer. The study found a low rate of cardiotoxic events (4.5%). Cases had a significantly higher rate of coronary artery disease than did controls and higher rates, although not significantly so, of cardiovascular risk factors. According to other studies, however, the incidence of fluoropyrimidine-induced cardiotoxicity is higher. In the prospective study by Kosmas et al. [2], cited in the paper, the incidence of symptomatic cardiotoxicity was low (2.2%) for single infusion of 5-fluorouracil (59% of patients) but significantly higher for continuous infusion (6.7%) and oral capecitabine (5.5%); ECG abnormalities were observed in up to 12.5% during continuous infusion. Other studies that reported higher rates are not cited.

According to a recent review [3], the incidence in different studies ranges from 0% to 34%. This wide variability depends, in our opinion, on the study design (retrospective vs. prospective) and diagnostic criteria used. For example, a recent prospective study of 527 patients recorded a 30.6% incidence of cardiotoxic events [4]. The inclusion of sinus tachycardia or bradycardia and ectopic beats among the toxicities may have lead to overdiagnosis, but even after excluding arrhythmias and minor ECG abnormalities 27.7% of the patients had cardiotoxicity in the form of heart failure, myocardial infarction, or ischemic ST-T wave changes. In a prospective study of 52 patients receiving capecitabine, 9 patients (17%) had new-onset angina or dyspnea and 16 (30.8%) had new ECG changes [5]. In our prospective study [6] of 358 patients with cancer undergoing 5-fluorouracil continuous infusion, cardiotoxicity at rest was observed in 5.9% of cases, and stress-induced ischemia was found in 7% of the 228 patients well enough to do treadmill stress tests, for an overall 10.3% incidence of ischemia. We subsequently obtained similar findings in a prospective study of capecitabine in which 16.6% of patients had cardiotoxicity [7]. Of note, about half of the patients with documented cardiac ischemia in our two studies and Kosmas et al.'s study did not have typical angina.

Raber et al. do not specify if electrocardiography, biomarker testing, and cardiologic evaluation were done routinely in all patients or only in those with symptoms. If the only routine monitoring was clinical, asymptomatic ischemia or ischemia with atypical symptoms may have been missed. Interestingly, Jensen and colleagues found a 4.3% incidence of cardiotoxicity in a retrospective study based on symptoms [8] and 8.5% in a prospective study including ECG [9]. Furthermore, the reported association between cardiotoxic events and coronary artery disease at baseline might be affected by bias: cases with known coronary artery disease complaining of mild or atypical chest pain will probably receive more clinical attention than those without a history of cardiac disease, and the control group might include missed cases of cardiotoxicity.

In conclusion, the actual prevalence of fluoropyrimidine cardiotoxicity is likely at least twice as high as reported in this study, and the role of ischemic heart disease as a predisposing factor has not yet been demonstrated.

Chiara Lestuzzi, Lucia Tartuferi, Elda Viel
Cardiology Department, AAS5 Friuli Occidentale; and Cardiology and Cardio-Oncology Rehabilitation Unit, Centro di Riferimento Oncologico di Aviano, IRCCS, Aviano, Italy
Angela Buonadonna, Emanuela Vaccher, Massimiliano Berretta
Oncology Department, Centro di Riferimento Oncologico, National Cancer Institute, Aviano, IRCCS, Aviano, Italy

Disclosures

The authors indicated no financial relationships.

References

1. Raber I, Warack S, Kanduri J et al. Fluoropyrimidine-associated cardiotoxicity: A retrospective case-control study. ***The Oncologist*** 2019;25:e606–e609.

2. Kosmas C, Kallistratos MS, Kopterides P et al. Cardiotoxicity of fluoropyrimidines in different schedules od administration: A prospective study. J Cancer Res Clin Oncol 2008;134:75–82.

3. Sara JD, Kaur J, Khodadadi R et al. 5-fluorouracil and cardiotoxicity: A review. Ther Adv Med Oncol 2018 Jun 18;10:1758835918780140.

4. Peng J, Dong C, Wang C et al. Cardiotoxicity of 5-fluorouracil and capecitabine in Chinese patients: A prospective study. Cancer Commun (Lond) 2018;38:22.

5. Koca D, Salman T, Unek IT et al. Clinical and electrocardiography changes in patients treated with capecitabine. Chemotherapy 2011;57:381–387.

6. Lestuzzi C, Vaccher E, Talamini R et al. Effort myocardial ischemia during chemotherapy with 5-Fluorouracil: An underestimated risk. Ann Oncol 2014;25:1059–1064.

7. Lestuzzi C, Tartuferi L, Viel E et al. Incidence of capecitabine cardiac toxicity at rest and under effort: A prospective study. Eur Heart J 2016;37(suppl):782a.

8. Jensen SA, Sørensen JB. Risk factors and prevention of cardiotoxicity induced by 5-fluorouracil or capecitabine. Cancer Chemother Pharmacol 2006;58:487–493.

9. Jensen SA, Hasbak P, Mortensen J et al. Fluorouracil induces myocardial ischemia with increases of plasma brain natriuretic peptide and lactic acid but without dysfunction of left ventricle. J Clin Oncol 2010;28:5280–5286.

http://dx.doi.org/10.1634/theoncologist.2020-0053