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In Reply

In their Letter to the Editor, Lestuzzi et al. [1] propose that the incidence of fluoropyrimidine cardiotoxicity may be several-fold higher than we observed in our recent study [2]. There is indeed a large variation in the incidence of fluoropyrimidine cardiotoxicity reported in the literature, ranging from 0% to over 30% [3]. However, prior reports have commonly defined cardiotoxicity to include asymptomatic electrocardiographic changes and other nonspecific findings that would be unlikely to prompt a change in clinical management at our institution. The study by Koca et al., which reported an incidence of cardiotoxicity of 34%, included prolongation of the PR interval greater than 200 milliseconds, prolongation of the corrected QT interval greater than 440 milliseconds, tachycardia, and hypotension [4]. None of the patients in this study experienced a myocardial infarction. Despite the rigorous cardiovascular evaluation performed in Koca et al.'s prospective study, the incidence of severe cardiotoxicity was only slightly higher than in our retrospective analysis (5.8% vs. 4.5%). A similar incidence of myocardial ischemia was reported by Lestuzzi et al. in their prior publication (5.9%) [5].

Our study reflected a single-institution experience in a real-world population. As such, cardiovascular screening was not performed routinely in patients who were asymptomatic from a cardiovascular perspective before or during chemotherapy. We considered cardiotoxicity as an event that was actionable, resulting in a discussion with the oncologist about whether or not to discontinue fluoropyrimidine therapy. If fluoropyrimidines were continued, it was recommended that all future doses of 5-fluorouracil be administered as an inpatient to monitor for recurrent cardiotoxicity or that dose reduction be considered for patients on capecitabine. In their Letter, Lestuzzi et al. fail to mention the potential for strict ECG surveillance to overdiagnose cardiovascular events, which can lead to interruption or discontinuation of first-line cancer therapy. Exclusion of fluoropyrimidine therapy can be especially detrimental in patients with gastrointestinal malignancies, as it is a necessary component of potentially curative neoadjuvant or adjuvant treatment for colorectal (folinic acid, fluorouracil, and oxaliplatin) and pancreatic cancers (folinic acid, fluorourcil, irinotecan, and oxaliplatin), and for the preferred curative regimen for gastric cancer (folinic acid, fluorouracil, oxaliplatin, and docetaxel). Interruption or discontinuation of fluoropyrimidine therapy may result in substantial loss of benefit in these aggressive malignancies. Although vasodilators are commonly used in patients with documented angina or coronary vasospasm, there are no data to support their use for asymptomatic ECG changes during fluoropyrimidine treatment. In the absence of therapeutic approaches that are supported by evidence, diagnosing subclinical cardiac phenotypes remains of questionable benefit to the patient and may in fact be harmful if appropriate chemotherapy is withheld as a result.

Although the overall event rate was low at our institution, patients with cardiotoxicity did have a higher prevalence of pre-existing coronary artery disease (CAD). It is certainly possible that physicians obtained testing to evaluate for cardiotoxicity more frequently in patients with underlying CAD, although we found no difference in ECG testing in patients with and without CAD at our institution. Other studies have also suggested high rates of fluoropyrimidine cardiotoxicity in patients with ischemic heart disease [6, 7]. In a prospective study of 483 patients treated with 5-fluorouracil, individuals with pre-existing cardiac disease were found to have an increased risk of cardiotoxicity (relative risk = 6.8; p = .002) [8]. However, fluoropyrimidine cardiotoxicity also occurs in many patients without CAD, and we agree with Lestuzzi et al. that the role of pre-existing CAD is not well-defined. Our study, as well as previously published data by Lestuzzi and others, highlights the imperative to incorporate more comprehensive cardiovascular phenotyping into large prospective cancer trials [8]. Our observations also underscore the importance of the collaborative cardio-oncology team in diagnosing and treating fluoropyrimidine cardiotoxicity, which remains a challenge in the absence of randomized controlled trial data to guide management decisions.

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Disclosures

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