Letter by Kounis and Soufras Regarding Article, “Myocardial Protection During Cardiotoxic Chemotherapy”

To the Editor:

In the very interesting review published in Circulation1 dealing with cardiac complications of chemotherapy with a focus on myocardial complications, the authors did not refer to the cardiac hypersensitivity that is associated with chemotherapy. Acute cardiovascular events associated with hypersensitivity to chemotherapeutic drugs pose a real threat for the myocardium. Rare and very rare, but also common and very common acute myocardial ischemic events are usually attributable to myocardial hypersensitivity. Taxanes including paclitaxel and docetaxel; platin including cisplatin, carboplatin, and oxaliplatin; and monoclonal antibodies including rituximab, infliximab, and trastuzumab have induced acute and immediate hypersensitivity reactions in 10% to 30%, 5% to 27%, 2% to 10% patients, respectively, necessitating rapid desensitization.2 Antimetabolites such as 5-fluorouracil and its prodrug capecitabine can also induce hypersensitivity reactions, whereas anti–rituximab-specific immunoglobulin E antibodies and TH2 cells, suggesting type I hypersensitivity, have been detected in rituximab-induced infusion cardiovascular reactions.3 It is surprising that cardiovascular toxicity to chemotherapeutic agents is usually confused with cardiovascular hypersensitivity. Cardiovascular hypersensitivity affecting the coronary arteries can lead to significant morbidity and mortality when the first-line chemotherapy cannot be used. Hypersensitivity denotes immunoglobulin E–induced inflammation, and Kounis hypersensitivity-associated coronary syndrome has already been reported with the use of carboplatin.4

Hypersensitivity is an acute, not dose-dependent process that may arise at any time during treatment, whereas cardiotoxicity refers to chronic events and denotes dose-dependent action with progressing effects resulting in cardiac fibrosis, which has never been proven in acute cardiac side effects of anticancer agents.

Although the National Cancer Institute has defined cardiotoxicity generally as “toxicity that affects the heart,” the Cardiac Review and Evaluation Committee supervising trastuzumab clinical trials5 has defined cardiotoxicity as follows:

1. Cardiomyopathy with reduction in left ventricular ejection fraction either globally or more severely in the septum.
2. Symptoms or signs of heart failure such as audible third heart sound associated with gallop rhythm and tachycardia.
3. Reduction in left ventricular ejection fraction in the range of ≤5% to ≤55%, with accompanying signs or symptoms of heart failure, or reduction in left ventricular ejection fraction in the range of ≤10% to ≤55%, without accompanying signs or symptoms. This Committee has concluded that an ideal definition of cardiotoxicity is still lacking, and the current definition does not include subclinical cardiovascular damage that may occur early in response to some chemotherapeutic agents.

Therefore, until further studies characterizing, predicting, and confirming the incidence, the course, and the cause of any cardiac event associated with anticancer therapy, it will be worthwhile, especially for atopic and susceptible individuals, to take careful histories of adverse drug reactions and hypersensitivities together with ordering intradermal skin tests for every planned chemotherapy and deciding on making alternative therapy or desensitization strategies where this is possible.

Disclosures

None.

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