Prediction and Prevention of Chemotherapy-Induced Cardiomyopathy
Can It Be Done?

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Although anthracyclines are highly effective at treating certain cancers, their use is limited by the potential for cardiotoxicity. Studies report a wide range of the incidence of cardiotoxicity, related to differences in definitions, chemotherapy regimens, and patient populations. The occurrence of clinical heart failure seems to be in the range of 1% to 5%, and asymptomatic decrease in left ventricular function is in the range of 5% to 20%.1,2 Toxicity can occur early (within 1 year) or late (particularly among children, where late cardiac abnormalities are detectable in two thirds of surviving patients).3 The occurrence of cardiomyopathy is related to cumulative dose of anthracycline (especially doxorubicin doses >550 mg/m²), dosing schedule, age, gender, mediastinal irradiation, and combination with other agents, including trastuzumab.4 Other chemotherapy, including imatinib mesylate,5 can also cause cardiotoxicity, suggesting a broader potential for adverse cardiac effects from novel chemotherapy and, especially, from inhibitors of nonreceptor tyrosine kinases. Anthracycline-induced cardiomyopathy seems to have a similar impact on survival as other forms of heart failure.6 Thus, identification of individuals at risk, prevention, early diagnosis, and effective treatment are all important goals. Most of these needs have been addressed by uncontrolled or small studies, and guidelines have relatively sparse information on which to base recommendations for care, other than careful monitoring of left ventricular function and interrupting or discontinuing anthracyclines once significant decrease in ejection fraction is detected, which is often too late.7

Cardinale et al2 have addressed 2 of the challenges: How does one identify who is likely to develop (or is developing) cardiotoxicity before left ventricular function decreases, and once an at-risk patient has been identified, how can one prevent deterioration in left ventricular function? Although not all studies have been consistent,8,9 the largest has shown that elevation of troponin just after high-dose chemotherapy and 1 month later are predictive of who will develop cardiac events (mainly heart failure and asymptomatic left ventricular dysfunction) during the next year. Nearly 10% of patients had persistent elevation of troponin I a month after treatment, and more than 80% of these patients developed a more than 15% decrease in left ventricular ejection fraction. There has been only 1 study including several hundreds of patients, and although the results were quite convincing, confirmatory studies are needed.

Even more important for its implications for patient care was the finding by the same group of investigators that enalapril seems to prevent deterioration of left ventricular function among chemotherapy-treated patients with elevated troponin values. In this issue of Circulation, Cardinale et al10 report a randomized trial of patients after high-dose chemotherapy. One hundred fourteen adult patients who had elevated troponin I soon after high-dose chemotherapy (one quarter of the treated population) were randomized to enalapril (target of 20 mg/day) or open-label control, with treatment initiation delayed until 1 month after chemotherapy and continued for 1 year. The results were spectacular: Forty-three percent of the control and none of the enalapril group had a more than 10% drop in left ventricular ejection fraction, and clinical cardiac events were likewise nearly eliminated with enalapril, from 30 events in the control population to 1 event with enalapril. This was primary attributable to reductions in heart failure and arrhythmias.

These results are impressive and should be taken seriously. There are limitations, however. The trial was a single-center, open-label trial, and some bias (especially in the subjective clinical end points) is likely. Experience in heart failure trials has taught us to be skeptical of very large and unexpected treatment effects, particularly in small trials.11 Is it plausible that treatment of subclinical cardiac toxicity with an angiotensin-converting enzyme (ACE) inhibitor would completely eliminate deterioration of ejection fraction and clinical events? ACE inhibitors have been shown to be remarkably effective across a broad range of cardiovascular conditions,12 and they generally result in an approximately 20% relative risk reduction in clinical events. Moreover, another similarly sized randomized trial studying an anthracycline-treated pediatric population with cardiac abnormalities at the time of enrollment showed only modest benefits of enalapril in improving cardiac function.13

The treatment effect seen in this small trial is most likely an overestimate. Nevertheless, the concept that ACE inhibitors may prevent heart failure in at-risk populations is not a novel one,14 and the risk of treatment seems to be low. Thus, it would be reasonable to use ACE inhibitors for prevention of
chemotherapy-induced cardiotoxicity on the basis of this study. Because cardiomyopathy may appear late, would treatment with ACE inhibitors for longer than 1 year prevent later development of heart failure? This is an important unanswered question.

How could enalapril improve outcomes in this population? Chemotherapy-induced cardiotoxicity is not well understood, but it is believed, at least with anthracyclines, to be caused partly by generation of free radicals, mitochondrial dysfunction, iron- and calcium-handling abnormalities, and resulting apoptosis. ACE inhibitors have a wide variety of effects that could be beneficial, including the limiting of oxidative stress, largely mediated through inhibition of the effects of angiotensin II. This raises the question of whether more specific and potent inhibition of the angiotensin II type 1 receptor with angiotensin receptor blockers might also be effective, as suggested by animal models.15

There are other treatments that have been shown to prevent anthracycline cardiotoxicity, including dexrazoxane, a derivative of EDTA that chelates iron.8,16 Because of the possibility that it may decrease antitumor activity, the use of dexrazoxane has been limited to use with higher-dose anthracyclines for selected malignancies. A number of other agents including erythropoietin,17 thrombopoietin,18 and iloprost19 have shown promise in animal models, although it is not clear how well these models predict human response. β-Blockers have not been properly studied for prevention and treatment of chemotherapy-induced cardiomyopathy, but their proven benefits in heart failure and anecdotal reports suggest they may also be effective.20

Cardinale et al20 have presented an important paradigm: They have developed a tool to identify early disease coupled with a treatment to prevent its consequences. Although additional work is needed to confirm these benefits, this set of studies provides important new information for management of patients treated with high-dose chemotherapy.

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