Cardioprotection During Chemotherapy

Need for Faster Transfer of Knowledge From Cardiology to Oncology and Role for a Cardio-Oncologist*

Otto A. Smiseth, MD, PhD,†‡§|| Thor Edvardsen, MD, PhD,†‡¶ Helge Skulstad, MD, PhlD†‡§

Oslo, Norway

Advanced and intensive treatment of solid cancer and hematological malignancies is a success history in modern medicine. However, the flipside of treatment with ionization therapy, chemotherapeutic and antineoplastic drugs, is among others, risks for developing heart failure. Thus, treating a disease with high mortality with a therapeutic regimen that gives the patient another life-threatening disease is problematic.

There is a wide spectrum of anticancer drugs with a correspondingly wide spectrum of side effects. This includes a direct cardiotoxic effect with reversible or irreversible myocyte injury, which may result in temporary or permanent left ventricular (LV) systolic dysfunction. In addition, ischemia, arrhythmia, pericarditis, endomyocardial fibrosis, and hyper- and hypotension represent possible side effects and therefore also targets for treatment (1).

The incidence of cardiovascular side effects of modern cancer therapy is not well defined and varies among different agents. Anthracyclines, “the meanest boy in class,” induces irreversible myocardial damage, and the cardiotoxicity is dose-dependent and cumulative and can appear many years after exposition. Heart failure may appear in up to half of the patients receiving high doses (2) but may be as low as 3% for those receiving low doses (3). Newer agents like trastuzumab causes a reversible cardiomyopathy without myocyte loss (4). The risk of heart failure during treatment with trastuzumab as adjuvant therapy is approximately 5% but may be as high as 26% in combination with anthracyclines (5,6).

Presently, there is limited evidence regarding management of cardiovascular side effects during and after cancer therapy, and current practice is based largely on expert opinion (7). However, the best strategy for treatment and prevention of further deterioration of chemotherapy-induced cardiomyopathy is withdrawal or use of fewer cardiotoxic agents. This must always be balanced against the desire to cure the malignant disease. A few studies suggest that treatment with angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, or beta-blockers as single-drug therapy may protect against chemotherapy-induced cardiomyopathy (8,9). Interestingly, it has been proposed that carvedilol may exert its effect in part through a potent antioxidant effect, which could mean that it targets one of the mechanisms of anthracycline-induced cardiomyopathy (10).

In their paper in this issue of the Journal, Bosch et al. (11) report the first results from a new prevention strategy. The OVERCOME (preventing left Ventricular dysfunction with Enalapril and carvedilol in patients submitted to intensive ChemOtherapy for the treatment of Malignant hEmopathies) trial combined an ACE inhibitor (enalapril) with a beta-blocker (carvedilol) and was able to demonstrate that this regimen could prevent a reduction in LV ejection fraction in patients treated with intensive chemotherapy. They also report that the combined therapy was well tolerated and safe. The OVERCOME trial is the first cardiac failure prevention study in oncology to use both cardiac magnetic resonance (CMR) and echocardiography to assess LV function. The authors included 90 patients, 45 in the control group and 45 in the active treatment group. They were, however, only able to perform follow-up CMR studies of 59 patients, and differences between treated and control subjects were only marginally significant. The follow-up echocardiographic study included 79 patients and showed a significant benefit from treatment by enalapril and carvedilol. This result is in line with other relatively small studies that show positive effects on LV function by ACE inhibitor and beta-blocker therapy. The main effects in this trial originated from patients treated for leukemia, and the effect was neutral for patients treated for Hodgkin and non-Hodgkin lymphoma and multiple myeloma. Furthermore, the study did not compare combined therapy to therapy with beta-blocker or with ACE inhibition alone, and the study was not blinded. This study design leaves many questions that need answers. The paper does not detail the oncological treatment regimens, causes of deaths are not stated, and possible mechanisms of the positive effects on cardiac function can only be speculations.

As advised in current guidelines, treatment of chemotherapy-induced heart failure should follow the same principle as in treating other cardiomyopathies (12). The rationale is that treatment with beta-blockers and ACE-inhibitors reduces the adrenergic response and prevents
remodeling in a failing heart (13,14). One can always discuss whether this principle is valid independently of the reason for the heart failure, and further studies should be performed, focused on patients with chemotherapy-induced heart failure. The current main strategy is to stop ongoing chemotherapy and to avoid further use of anthracyclines along with traditional heart failure therapy. There are still some main questions that need further exploration. How much deterioration of the ventricle is acceptable before restart of chemotherapy? Which drug is the best for treating the heart failure, and is the combination as used in the study by Bosch et al. (11) even better? Is it possible to prevent heart failure during extensive therapy for malignant disease by using conventional heart failure therapy? And the more ethical question is: how much heart failure is acceptable as a prize for the cure of a malignant disease? The time has now come to answer these important questions in large multicenter trials. The means to detect ventricular function in the present OVERCOME trial was to some degree inadequate. Future trials should therefore include assessment of LV function by strain imaging, which represents a more sensitive method than ejection fraction with which to detect early cardiac function, which represents a more sensitive method than ejection fraction with which to detect early cardiac function (15), representing a more sensitive method than ejection fraction with which to detect early cardiac function (15). Furthermore, assessment of diastolic function may represent a means to identify patients who may be sensitive to chemotherapeutic cardiotoxicity because they have a filling problem, which may be aggravated if systolic function deteriorates. Because hypertension, even when mild, may represent a significant stress to myocardium with impaired function, it should be determined whether lowering of blood pressure to normal values may reduce the deleterious effects of chemotherapy on cardiac function.

It is striking that it has taken more than 15 years from the extensive documentation that the combination of ACE inhibition and beta-blocker can markedly reduce mortality in the general heart failure population to testing of this strategy during cancer therapy. This indicates the need for better and faster transfer of knowledge between cardiology and oncology, and the recently developed “specialty” cardiologist is a step in the right direction.

**REFERENCES**


**Key Words:** cardiac toxicity • carvedilol • chemotherapy • enalapril • left ventricular dysfunction.