Clinical Significance of Cyclophosphamide-induced Cardiotoxicity

Key words: cardiotoxicity, hemorrhagic myocarditis, chemotherapeutic agents, cyclophosphamide

Cardiotoxicity can be induced by a number of chemotherapeutic agents and particularly by anthracyclines, such as doxorubicin. Doxorubicin-induced cardiotoxicity is recognized to follow a chronic clinical course that depends on cumulative dose. On the other hand, cardiotoxicity due to cyclophosphamide (CY) was initially described as a complication of bone marrow transplantation by Santos et al (1) in 1972. In protocols of bone marrow transplantation and peripheral blood stem cell transplantation (PBSCT), high-dose chemotherapy, including CY, is largely employed. High doses of CY, however, rarely cause serious cardiotoxicity and cardiac death. In contrast to doxorubicin-induced cardiotoxicity, high-dose CY causes acute cardiac dysfunction that is independent of cumulative dose. Acute heart failure secondary to cardiotoxicity has been reported about 1 week after CY administration, and the incidence rate is about 20% and mortality about 8% after bone marrow transplantation (2, 3). Although the mortality is high, survivors may show no residual cardiac abnormality.

The pathogenesis of CY-induced cardiotoxicity is still poorly understood, however, it is thought to involve direct endothelial damage, leading in turn to leakage of plasma proteins and erythrocytes. The histological findings indicate acute pericarditis and hemorrhagic myocarditis with fibrin-platelet microthrombi in capillaries and fibrin strands in the interstitium on ultrastructural examination (4). Wall thickening due to interstitial edema and hemorrhage may reduce left ventricular (LV) diastolic compliance as LV diastolic dysfunction and present as restrictive cardiomyopathy. In patients undergoing high-dose CY therapy who show evidence of clinical and radiological cardiac failure, hemorrhagic myocarditis should be suspected and carefully considered.

While serious cardiotoxicity associated with high-dose CY is rare, it can occur easily under certain clinical conditions, such as excess doses of CY, previous anthracycline treatment, and presence of left ventricular (LV) dysfunction (ejection fraction less than 50%). It has been reported that a young patient with mediastinal seminoma and a history of radiation therapy caused cardiomyopathy after administration of high-dose CY (5). Radiation therapy to the chest wall may cause direct cardiac toxicity or augment the effects of chemotherapy. Some reports indicated that prior radiation therapy to the mediastinum or chest wall is an independent predictor of cardiotoxicity in patients with lymphoma and breast cancer undergoing high-dose chemotherapy (6, 7).

From the clinical perspective, cardiac monitoring including ECG and ultrasound cardiography (UCG) are important for the detection of early clinical signs of cardiotoxicity. ECG monitoring shows reversible reduction of QRS voltage and/or ST abnormalities. However, those findings are not specific for CY-induced cardiotoxicity. On the other hand, UCG shows a transient increase in LV diastolic/systolic diameter without a concomitant decrease in FS% and EF% and abnormalities of diastolic function (E/A mitral Doppler ratio). CY-induced myocarditis increases blood levels of cardiac enzymes (e.g. CK, CK-MB, and troponin-I), however, these parameters can not predict the early phase of cardiotoxicity (8). Recently, the noninvasive method of cardiac magnet resonance imaging (MRI) has proved useful for evaluating LV function and contrast enhancement of cardiac MRI may detect myocardial interstitial edema (9). Although there are no specific predictive parameters of cardiotoxicity, cardiac monitoring in high-risk patients undergoing high-dose CY therapy may help to prevent serious cardiotoxicity.

With regard to treatment in an animal model, it has been reported that cyclosporin-A, administered with cyclophosphamide, prevents cardiotoxicity (10), suggesting that CY-induced cardiotoxicity is associated with mitochondrial membrane permeability to Ca\(^{2+}\) and that cyclosporin-A may restore mitochondrial permeability and prevent apoptosis of cardiomyocytes (11). However, clinically there are, as yet, no reports of specific and useful therapies for CY-induced cardiotoxicity. Therefore, to prevent cardiotoxicity in high-risk patients, physicians should consider reducing the dose and using cardiac monitoring to detect the early phase of cardiotoxicity.

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References
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