Editorial / *Editöryal Yorum*

Anthracycline-induced cardiotoxicity

Antrasiklin ile ilişkili kardiyotoksisite

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Anthracyclines are the cornerstone in the treatment of numerous hematological and solid cancers, and they have been an unvarying agent in combinations for more than 50 years.[1,2] Great advances have been achieved after the entry of anthracycline-group chemotherapeutics into the cancer treatment, and the survival ratio has increased from 30% to 70%.[3] The most common side effect of anthracycline is cardiotoxicity, which may limit its use and increases mortality and morbidity rates.[4] The cardiotoxicity is cumulative, dose-dependent and irreversible. Improvements in protective mechanisms against the cardiotoxicity of anthracycline are important to avoid the discontinuation of these chemotherapeutics. Unfortunately, the only clinically accepted method to minimize the cardiotoxicity is dose modification and discontinuation of the anthracyclines.

Generally, the average cumulative doses of anthracyclines were not exceeded. Based primarily on the clinical events reported, the incidence of apparent cardiotoxicity is approximately 27% at cumulative conventional adriamycin doses up to 550 mg/m^2 and epirubicin doses up to 900 mg/m^2.[5,6] Thus, in many patients, clinically apparent cardiotoxicity may not occur. However, in patients with malignancies, radiotherapy to the chest and/or novel monoclonal antibodies including trastuzumab can be used as additional therapies. When we added the effects of radiation and trastuzumab, if applied, the risk of adverse events is even higher. Therefore, limiting the adverse effects of anthracyclines, although subclinical, is important in order to reduce the mortality rates as well as to make possible their use in the future as additional therapies, like radiotherapy and monoclonal antibodies.

Anthracyclines show their effects primarily on direct DNA damage and oxidative stress. They impair DNA and RNA synthesis, upon causing certain structural changes in DNA.[7] Additionally, anthracyclines further cause direct cell deaths by contributing to the formation of reactive oxygen radicals, and the side effects thereof on the slowly proliferating cells are shown primarily by this mechanism.[8]

In previous studies, numerous molecules were investigated to protect against anthracycline-induced cardiotoxicity. In a rat study conducted by Ibrahim et al.,[9] the authors showed that telmisartan and captopril showed biochemical cardioprotective efficacy against anthracycline cardiotoxicity. Oxidative stress indicators were examined further in the same study. In addition, a histopathological examination of the myocardium of rats was performed. Accordingly, telmisartan and captopril lowered cardiac fibrosis significantly when compared to the control group. It was concluded that both telmisartan and captopril showed similar protective efficacy against anthracycline-related cardiotoxicity. In another rat study, Iqbal et al.[10] demonstrated that telmisartan is an effective agent against anthracycline-related cardiotoxicity. Recently, two impor-

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tant studies were performed in our clinic. We enrolled 50 patients with various solid or hematological malignancies, who had been given anthracycline-group chemotherapeutics, and these were randomized into two different groups as carvedilol and placebo. At the end of the six-month period, an important protection was achieved in the systolic function of the carvedilol group with the administration of 12.5 mg carvedilol orally per day.[11] In our second study, 45 patients with breast cancer who were administered anthracycline were randomized into two groups. Nebivolol (5 mg/day) was administered to the nebivolol group. We concluded that both systolic and diastolic function was protected in the nebivolol group.[12] In such conducted studies, the investigators focused on BETA-blockage and RAAS inhibitors and successfully demonstrated their positive effects on anthracycline cardiotoxicity. The main mechanisms in this protective effect are the anti-fibrotic and antioxidative effects of these agents. On the other hand, use of agents such as digitoxin, ouabain, strophanthin dexrazoxane, and vitamin E has been examined in several experimental studies.[13-15] However, no significant improvement with these agents has been demonstrated yet.

In recent years, investigators focused on the protective effects of melatonin, which has a potent antioxidant action in the side effects of anthracyclines. In one study, Song et al.[16] examined the effect of melatonin on anticancer drug-induced cellular premature senescence. They demonstrated that the doxorubicin-induced increase in intracellular levels of reactive oxygen radicals was completely abolished upon melatonin co-treatment. They suggested that melatonin might be a therapeutic option to prevent the side effects of anthracyclines. In another study conducted by Lee et al.,[17] it was shown that melatonin had a protective effect against doxorubicin-induced testicular toxicity by means of both the inhibition of lipid peroxidation and increased antioxidant activity.

While increasing the evidences of the preventive effects of melatonin on anthracycline-related side effects, the role of melatonin in anthracycline-related cardiotoxicity was questioned. In the current issue of the Archives of the Turkish Society of Cardiology, Bilginoglu et al.[18] performed a study to test the hypothesis that pretreatment with melatonin protects cardiac tissue against adriamycin-induced oxidative cardiac damage in rats. The animals were randomly divided into four groups of seven rats each as: control group, adriamycin group, melatonin group, and adriamycin+melatonin group. They analyzed antioxidant enzyme activities, electrocardiographic changes, cardiac biomarkers, and lipid profile. However, additional echocardiographic evaluation would add valuable data to the study. Nevertheless, they successfully demonstrated that melatonin has positive effects on the protection of the heart against adriamycin-induced cardiotoxicity in rats. I think the present study will give a new perspective on the protection against anthracycline cardiotoxicity because anthracyclines remain an unvarying agent in combinations, and it appears that this will continue in the future. However, the protective mechanisms are still insufficient. The antioxidant actions make melatonin a suitable treatment for reducing the oxidative stress associated with chemotherapy, especially with anthracyclines. The study conducted by Bilginoglu et al. should be an inspiration for future randomized controlled studies in order to investigate new treatment options in the protection against anthracycline-induced cardiotoxicity.

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