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CORRESPONDENCE

Research Correspondence

Efficiency of Atorvastatin in the Protection of Anthracycline-Induced Cardiomyopathy

To the Editor: Antineoplastic agents of the anthracycline (ANT) group are commonly and effectively used in various forms of malignancies. Anthracyclines might lead to irreversible cardiomyopathy (CMP), despite their beneficial effects. A number of mechanisms, such as elevation in free superoxide anion radicals, apoptosis, and mitochondrial dysfunction have been implicated in ANT-induced CMP. However, oxidative stress has been widely considered as the major pathogenetic mechanism (1). Statins have been shown to possess antioxidative, pleiotropic effects (2) besides their anti-inflammatory and lipid-lowering effects, which led us to conduct the present study to test the potential role of statin in ANT-induced CMP prophylaxis.

In the present study, a total of 40 patients (17 men) with a mean age of 53 ± 15 years who were undergoing ANT chemotherapy were enrolled. The patients were randomized into statin group or control group (n = 20 in each group). The patients who had a history of chemotherapy or radiotherapy, with symptoms of heart failure or left ventricular (LV) dysfunction at baseline echocardiography, who had a history of CAD, or with moderate-to-severe valve disease were excluded. None of the patients were under medication that could affect cardiac functions. The statin group received administration of 40 mg/day atorvastatin before chemotherapy, regardless of their baseline lipid values, and the therapy continued for 6 months. All patients received chemotherapy 1/month with either adriamycin or idarubicin for a period of 6 months. The primary endpoint was the establishment of impairment in LV systolic functions defined as an ejection fraction (EF) of <50%. All patients were evaluated by echocardiography before and 6 months after chemotherapy by 2 independent, blinded cardiologists. Continuous variables were described as mean ± SD and analyzed with *t* test and Mann-Whitney *U* test when appropriate. Fisher exact test was used for categoric variables. Two-sample *t* test was used to compare mean changes after chemotherapy between 2 groups.

The statin and control groups were similar in age (53.7 ± 14.2 years and 52.6 ± 17.6 years, respectively), sex (male 40% and 45%, respectively), diagnosis (non-Hodgkin's lymphoma 60% and 55%; multiple myeloma 10% and 20%; leukemia 30% and 25%, respectively), and in treatment with other chemotherapeutic agents (vincristine 90% and 95%; cyclophosphamide 80% and 85%; methotrexate 25% and 25%; and prednisolone 60% and 55% or dexamethasone 10% and 15%, respectively). The doses of adriamycin (261.4 ± 61.1 mg vs. 251.1 ± 77.2 mg) or idarubicin (262.5 ± 55.6 mg vs. 330.0 ± 14.1 mg) were similar in statin and control groups. No differences were observed between the groups in terms of baseline glucose, lipid, high-sensitivity-C-reactive protein levels, or renal and liver function tests.

In the statin group, a significant decrease was observed with respect to lipid parameters, as expected. No elevation was observed in serum high-sensitivity C-reactive protein levels after chemotherapy in the statin group, whereas there was a significant increase in the control group (3.84 ± 0.89 mg/dl vs. 5.43 ± 1.78 mg/dl, p < 0.0001).

Table 1 Comparison of Echocardiographic Parameters in the Study Group Between Baseline and Follow-Up Values

	Statin Group (n = 20)	Control Group (n = 20)	p Value
LVEF (%)			
Baseline	61.3 ± 7.9	62.9 ± 7.0	
After 6 months	62.6 ± 9.3	55.0 ± 9.5	
Mean change	1.3 ± 3.8	−7.9 ± 8.0	<0.001
LVEDD (mm)			
Baseline	46.5 ± 7.2	47.2 ± 5.2	
After 6 months	46.3 ± 6.8	49.2 ± 6.2	
Mean change	−0.15 ± 4.0	2.0 ± 3.3	0.021
LVESD (mm)			
Baseline	30.9 ± 7.2	30.3 ± 5.4	
After 6 months	29.6 ± 6.1	32.3 ± 5.4	
Mean change	−1.35 ± 4.0	2.1 ± 1.8	<0.001

LVEF = left ventricular ejection fraction; LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter.

Compared with baseline value (Table 1), on control echocardiography, no difference was observed in the mean EF of the statin group (61.3 ± 7.9% vs. 62.6 ± 9.3%, p = 0.144). However, the decrease in the control group was significant (62.9 ± 7.0% vs. 55.0 ± 9.5%, p < 0.0001). Although 1 patient in the statin group was observed with an EF below 50%, 5 patients in the control group were observed with values below 50% (p = 0.18). In the statin group, no significant difference was observed between baseline and follow-up values in terms of systolic (30.9 ± 7.2 mm vs. 29.6 ± 6.1 mm, p = 0.148) and diastolic diameters (46.5 ± 7.2 mm vs. 46.3 ± 6.8 mm, p = 0.868). However, in the control group, significant increases were observed in the follow-up values of systolic (30.3 ± 5.4 mm vs. 32.3 ± 5.4 mm, p < 0.0001) and diastolic diameters (47.2 ± 5.2 mm and 49.2 ± 6.2 mm, p < 0.013). Mean reduction in left ventricular ejection fraction and mean increase in left ventricular end-diastolic diameter and left ventricular end-systolic diameter were significantly lower in the statin arm as compared with the control group (p < 0.0001; p = 0.021; p = 0.001, respectively).

The clinical use of doxorubicin and other quinone-hydroquinone antitumor ANTs is limited by dose-related cardiotoxicity. One-electron redox cycling of the quinone moiety has long been known to form reactive oxygen species in excess of the limited antioxidant defenses of cardiomyocytes, which render cardiomyocytes to oxidant stress and death (1). Strategies have been proposed to reduce ANT-induced cardiotoxicity, including continuous instead of bolus infusion, liposomal ANT administration, and addition of iron chelator dexrazoxane to chemotherapy

regime. Although data are inconclusive, various agents have been experimented with to provide protection against ANT-induced CMP both in animal models and humans (3,4).

Statins have been shown to decrease atherosclerosis-related morbidity and mortality. It is currently accepted that statins do exert protective cardiovascular effects not solely from their lipid-lowering capacity. In this regard, antioxidative properties are 1 of the main factors by which statins exert so-called pleiotropic effects. Because ANT-induced cardiotoxicity has been shown to be sufficiently triggered by cardiac oxidative stress and inflammation, in the present report it was hypothesized that statins, by their pleiotropic effects, might prevent ANT-induced cardiotoxicity. In a unique animal model, Riad et al. (5) have shown that pretreatment with fluvastatin attenuated ANT-induced CMP. They have demonstrated reduced oxidative stress, enhanced expression of antioxidative enzyme mitochondrial superoxide dismutase 2, and reduced cardiac inflammation shown by decreased tumor necrosis factor-alpha expression in fluvastatin-pretreated mice. They concluded that this outcome resulted from antioxidant and anti-inflammatory effects of fluvastatin.

In the present study, although the inter-group difference on our predefined primary endpoint of LV dysfunction did not reach statistical significance, we have shown that prophylactic use of atorvastatin could be effective in maintenance of LVEF in patients treated with ANT. We proposed that this effect could be related to pleiotropic effects of statins.

The major limitations of the present study are small sample size, lack of placebo group, and the limited measures of cardiac dysfunction that were studied. Also, due to the short follow-up period of the study, late CMP could not be assessed.

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Letters to the Editor

The Israel Screening Failure

Analyzing the Data to Understand the Results

The recent paper by Steinvil et al. (1) raised our concern and prompted the present considerations. The intriguing title conceals the idea that pre-participation screening including 12-lead electrocardiography is ineffective for modifying the occurrence of sudden cardiac deaths (SCDs) in young athletes, in contrast with previously reported Italian data (2).

The authors claim that the yearly incidence of SCDs has remained unchanged (i.e., 2.54 to 2.66 per 100,000 persons) in the periods 1985 to 1996 and 1997 to 2009, despite implementation of the screening program in Israel (1). Their conclusion was that efforts to prevent SCDs in young athletes by the electrocardiographic screening were worthless.

However, we believe that certain methodological limitations do greatly hamper the apparent strength of their conclusion. Primarily, both the number of cardiac events and the population of competitive athletes at risk were only roughly estimated.

First, the number of SCDs was derived only from 2 Israel newspapers, and not from a national prospective registry. Newspapers focus on fatalities occurring in elite/national-level professional athletes, whereas reports of SCDs in the much larger population of adolescents/adults engaged in nonprofessional/regional sports are usually overlooked. Moreover, an increase in the number of sports-related fatal events in more recent years in Western countries has been reported, a phenomenon that simply reflects enhanced public recognition due to increased media attention (3). This may also explain the relative lower prevalence of fatal events reported in the past decades and confirms the unreliability of estimating the time trend of SCDs in athletes based only on media reporting.

Second, the population of competitive athletes at risk is not known. Authors state that the number of registered competitive athletes was 45,000 in 2009. They claim that proportion of Israel population engaged in competitive sports remained unchanged over time, but the actual size doubled, based not on