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VIEWPOINT

Preventing Anthracycline-Associated Heart Failure: What Is the Role of Dexrazoxane?

JACC: CardioOncology Controversies in Cardio-Oncology

Haoyi Zheng, MD, PhD,[a] Huichun Zhan, MD[b,c]

"The superior physician treats the disease before it manifests; the average physician treats the disease on the verge of developing; the inferior physician treats the fully manifested diseases." This quotation is from one of the earliest books on traditional Chinese medicine, written more than 1,400 years ago by the legendary physician and philosopher Sun Simiao. The statement echoes the essence of preventive medicine. More than a millennium later, it still holds true, testifying to its enduring wisdom and legacy.

The primary prevention of anthracycline-induced cardiotoxicity (AIC) aims to mitigate the cardiac injury during treatment. Ideally, the most effective approach would involve minimizing exposure to anthracyclines or avoiding their use entirely. Nevertheless, despite substantial advancements in cancer therapy, anthracyclines, which have been in clinical use for more than one-half a century, are still the mainstay for treating numerous cancers, including breast cancer, sarcoma, leukemia, and lymphoma. Consequently, AIC continues to hold importance in cardio-oncologic practice. Various cardioprotective strategies, including neurohormonal antagonists and statins, have been explored to mitigate AIC. Previously published small to medium-sized randomized trials have reported mixed results. Meta-analyses have showed an absolute 2% to 4% attenuation of left ventricular ejection fraction (LVEF) declines in groups with neurohormonal blockade compared with placebo, but these analyses are marked by heterogeneity (I^2 >90%, where >50% indicates severe heterogeneity), severely limiting the interpretability of pooled estimates.[1] Recent randomized studies further investigated their effects on LVEF decline measured by cardiac magnetic resonance, which is considered the gold standard for LVEF measurements (**Table 1**).

PRADA (Prevention of Cardiac Dysfunction During Adjuvant Breast Cancer Therapy) demonstrated that candesartan but not metoprolol had an early protective effect on LVEF decline, but this effect was not apparent at 2-year follow-up.[2] The mean LVEF decline was only 2.6% in the placebo group. With a cumulative doxorubicin-equivalent dose of 192 mg/m^2, among 120 patients with breast cancer, 1 patient developed heart failure (HF) concurrent with atrial fibrillation. The PREVENT (Preventing Anthracycline Cardiovascular Toxicity With Statins) trial comparing atorvastatin 40 mg/d with a placebo revealed no difference in mean LVEF decline after anthracycline-based chemotherapy.[3] Most patients had breast cancer, with a median cumulative dose of 240 mg/m^2 doxorubicin equivalent, and had up to 2-year follow-up. The mean LVEF decline in the placebo group was 3.3%, and 1 HF event was reported among 279 patients.

The small to moderate cumulative doses of anthracycline in these 2 studies are likely a main factor accounting for the subtle declines in LVEF observed in the placebo group, which potentially renders the difference in LVEF decline a limited

From [a]Saint Francis Hospital, The Heart Center, Roslyn, New York, USA; [b]Department of Medicine, Stony Brook School of Medicine, Stony Brook, New York, USA; and the [c]Medical Service, Northport VA Medical Center, Northport, New York, USA.

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TABLE 1 Incidence of Heart Failure and Efficacy of Cardioprotection in Patients Receiving Anthracycline Therapy in Randomized Placebo-Controlled Trials

Trial (Year of Publication)	Cardioprotective Agent	Study Population	Anthracycline Agent	N	Age, y	Anthracycline Cumulative Dose, mg/m² (range)[a]	Study Period, mo	Absolute LVEF Decline in Placebo Group, %	Heart Failure
PRADA Extended (2021)[2]	Candesartan/ metoprolol	Breast cancer	Epirubicin	120	51 ± 9	192 (192-320)	23	2.6	1 (<1%)
PREVENT (2022)[3]	Statin	Breast cancer (85.3%), lymphoma (14.7%)	Doxorubicin	279	49 ± 12	240 (60-480)	24	3.3	1 (<1%)
STOP-CA (2023)[5]	Stain	Lymphoma	Doxorubicin, daunorubicin	300	50 ± 17	300 (50-312)	12	5.4	13 (4%) (4 with statin, 9 with placebo)
Study 088001 (1997)[8]	DZR	Breast cancer	Doxorubicin	349	56 (25-84)[b]	NA[c]	17	NA	15 (8%) (0 with DZR, 15 with placebo)
Study 088006 (1997)[8]	DZR	Breast cancer	Doxorubicin	185	57 (23-79)[b]	NA[c]	13	NA	9 (5%) (2 with DZR, 7 with placebo)

The table represents a partial list of studies of cardioprotection, with a focus on those presented in this viewpoint. [a]Doxorubicin equivalent dose. [b]Age was reported as median (range). [c]The median cumulative dose of doxorubicin was not provided. However, among the 24 patients who developed heart failure, only 1 patient had heart failure at a cumulative dose of 150 mg/m², 4 at 300 mg/m², and 19 at doses exceeding 400 mg/m².[9]

DZR = dexrazoxane; LVEF = left ventricular ejection fraction; NA = not available; PRADA = Prevention of Cardiac Dysfunction During Adjuvant Breast Cancer Therapy; PREVENT = Preventing Anthracycline Cardiovascular Toxicity With Statins; STOP-CA = Statins to Prevent the Cardiotoxicity of Anthracyclines.

primary outcome for these trials. Notably, the incidence of HF events is scarce in these studies. It is well known that AIC is dose dependent, with risk escalating at a cumulative dose exceeding 250 mg/m².[4] This relationship is well reflected in the findings of the recently published STOP-CA (Statins to Prevent the Cardiotoxicity of Anthracyclines) trial.

The STOP-CA trial, investigating the efficacy of atorvastatin 40 mg/d in patients with lymphoma and a median cumulative dose of 300 mg/m² doxorubicin equivalent, demonstrated a significant reduction in the primary endpoint of a 10% decrease to an LVEF <55% at 1 year in patients randomized to atorvastatin compared with placebo (9% vs 22%; $P = 0.002$).[5] The mean LVEF decline of 5.4% in the placebo group was larger than in the PRADA and PREVENT trials. However, the overall difference in LVEF decline between the placebo and atorvastatin groups was only 1.3% ($P = 0.029$). In contrast, a much larger mean LVEF decline of 7.1% in the placebo group, with a cumulative dose of ≥250 mg/m², was observed. Of particular note, among 300 patients, 13 adjudicated HF events (4% in total, 9 in the placebo group and 4 in the atorvastatin group) were reported over a 24-month follow-up. The study was not powered to show the benefit of atorvastatin in reducing HF events.

To date, no studies involving either neurohormonal therapies or statins have demonstrated a benefit in reducing the incidence of HF.[4] The clinical implication of a mild LVEF decline and the risks for progression to HF are poorly understood, but HF has a profound clinical impact, with a 5-year mortality rate exceeding 50%, a rate worse than for many types of malignancy.[6] The increased incidence rate of HF (4%) in the STOP-CA trial is concerning, which brings another cardioprotective medication, dexrazoxane, back into focus.

Dexrazoxane is the only U.S. Food and Drug Administration-approved drug for the prevention of AIC. This approval in 1997 was based on 2 randomized trials (088001 and 088006) involving 534 women with advanced breast cancer (Table 1).[7] In these studies, women were randomized to receive doxorubicin, with or without dexrazoxane. Cardiac events were defined as a decline in LVEF from baseline of ≥10% and below the institution's lower limit of normal, a decline in LVEF of ≥20% from baseline, or the new onset of HF. In study 088001, dexrazoxane was associated with a significant reduction in cardiac events at 15%, compared with 31% in the placebo group (HR: 2.63; 95% CI: 1.61-4.27). Study 088006 mirrored these findings, with 14% of dexrazoxane recipients experiencing cardiac events, compared with 31% in the placebo group (HR: 2.0; 95% CI: 1.01-3.96). The substantial effect led to open-label dexrazoxane use in patients on placebo who had received a cumulative doxorubicin dose of 300 mg/m². Again these patients experienced a remarkable reduction in cardiac events, even with the delayed initiation of dexrazoxane (HR: 3.5; 95% CI: 2.2-5.7).[8] In total, 24 patients (8%) developed HF: 22 in placebo groups and only 2 patients in dexrazoxane groups. The median cumulative dose of doxorubicin was not detailed in these studies. However, among those who developed HF, only 1 patient had HF at a cumulative dose of 150 mg/m², 4 at 300 mg/m², and the remaining 19 at doses exceeding 400 mg/m².[9]

Subsequent trials and the most recent Cochrane analysis have consistently corroborated dexrazoxane's efficacy in reducing the HF risk (2.5- to 4.5-fold compared with placebo) without compromising the anticancer efficacy of chemotherapy or increasing secondary malignancy risks in adults.[10]

Moreover, certain malignancies still necessitate large cumulative doses of anthracycline because of its substantial antitumor efficacy. Cardiotoxicity increases markedly when the cumulative dose of doxorubicin exceeds 400 mg/m^2, with 26% of patients developing HF at doses reaching 550 mg/m^2. In a pediatric trial (P9754) involving 242 patients with osteosarcoma, all patients received doxorubicin together with dexrazoxane. The cumulative dose of doxorubicin was between 450 and 600 mg/m^2. Only 5 patients developed grade 1 or 2 cardiotoxicities (LVEF decline to ≤50%), and 4 of them were transient. Remarkably, there were no HF events, and concurrent use of dexrazoxane allowed cumulative doxorubicin doses up to 600 mg/m^2.[11] This underscored dexrazoxane's efficacy in mitigating AIC, enabling the administration of higher cumulative doses of anthracycline while mitigating HF risk.

At present, the 2022 European Society of Cardiology (ESC) cardio-oncology guidelines do not recommend the routine use of dexrazoxane in patients undergoing anthracycline treatment. Dexrazoxane is listed as a Class 2a recommendation (Level of Evidence: B) for the primary prevention of AIC in adult patients at high and very high risk.[4] These risk parameters, as outlined in the guidelines, include LVEF <50%, age ≥80 years, prior anthracycline exposure, and an intended cumulative dose of doxorubicin or its equivalent ≥250 mg/m^2, among others, as categorized in the guidelines.[4] In the STOP-CA trial,[5] 73% patients received cumulative doses ≥250 mg/m^2, and 55% of patients received ≥300 mg/m^2. None of them received dexrazoxane. Although the trial did not specify cumulative doses for the 13 patients who developed HF, given the well-established correlation between cumulative dose and HF, we speculate that the majority likely received doses exceeding 300 mg/m^2. In such cases, the early introduction of dexrazoxane might have mitigated many of these HF events, given its proven efficacy in clinical studies. The STOP-CA trial preceded the current ESC guideline recommendations, but the significant benefits of dexrazoxane have been validated over 2 decades. In cardio-oncology, defining a primary vs secondary prevention strategy is complex. The current ESC cardio-oncology guideline recommendations regarding the specific indications for dexrazoxane use for primary prevention may require further validation. Nevertheless, the concomitant administration of doxorubicin and dexrazoxane (with dexrazoxane administered at least 30 minutes prior to each anthracycline cycle) could be valuable for patients at high or very high risk, who might otherwise be precluded from treatment because of baseline left ventricular dysfunction and other cardiovascular conditions. Furthermore, initiating dexrazoxane when the intended cumulative dose of doxorubicin exceeds 250 mg/m^2, even for patients at otherwise low or moderate risk, could prevent AIC and allow patients to receive higher cumulative anthracycline doses for curative purposes. Therefore, it is our view that in clinical practice, dexrazoxane should not be overlooked, particularly for high-risk patients including those receiving atorvastatin. The use of dexrazoxane could further decrease the incidence of AIC, as uniformly demonstrated in clinical studies.

Dexrazoxane has been significantly underused since its approval, despite compelling evidence of its efficacy in mitigating anthracycline-induced HF, which reflects a broader disconnect between clinical trial evidence and real-world clinical practice. Oncologists' reluctance to use dexrazoxane may stem from several concerns. The impact of dexrazoxane on antitumor efficacy was initially observed in 1 early study in which it was used concurrently with doxorubicin.[7] However, this concern was not confirmed in the same study with longer follow-up[8] or in subsequent studies and meta-analyses.[10] Concerns regarding secondary malignancies, such as acute myeloid leukemia and brain tumors, have been reported only in pediatric patients, with a slight trend favoring the control group.[10] Furthermore, there is a consideration that dexrazoxane may exacerbate myelosuppression caused by chemotherapeutic agents, as evidenced by a lower nadir in white blood cell count in the dexrazoxane group, although no significant differences were observed in the incidence rates of thrombocytopenia, neutropenia, and anemia.[10] Overall, the totality of available evidence robustly supports the use of dexrazoxane in adult patients at high risk for developing AIC. To bridge this gap, a focused educational initiative is pivotal to augment awareness of dexrazoxane's role in mitigating AIC and to translate trial findings into tangible clinical benefits. A coordinated effort should be made by cardio-oncology programs to have direct case-by-case discussions between cardiologists and oncologists to assess cardiotoxicity risks in patients undergoing anthracycline-based chemotherapy. An update to existing guidelines to reinforce the substantial cardioprotective evidence supporting dexrazoxane and to lessen the concern regarding its impact on chemotherapy efficacy and secondary malignancy

risks could significantly aid such initiatives. Furthermore, in our view, a larger trial is needed to further explore the cardioprotective effect of dexrazoxane, both alone and possibly in combination with statins in patients receiving high cumulative doses of anthracycline, with the outcomes of LVEF decline and HF incidence. Defining the patient subset who would derive the greatest benefit is also an important priority for both cardiologists and oncologists.

In summary, with a low to moderate cumulative dose of anthracycline (<250 mg/m^2), the LVEF decline tends to be modest, and the occurrence of HF events remains relatively rare. Although neurohormonal therapies and statins hold equivalent ESC guideline recommendations as dexrazoxane,[4] the existing body of evidence for dexrazoxane is notably more compelling and consistent. In clinical practice, a reasonable approach would involve continuing statins or neurohormonal antagonists for those already receiving these drugs for the management of atherosclerotic cardiovascular disease[5] and considering to start statins for those at high risk. Dexrazoxane should be considered for patients at high risk, and it is our view that there is benefit, particularly for those intending to receive cumulative doses of doxorubicin ≥250 mg/m^2. Implementing such approaches in daily oncologic practice could significantly decrease the incidence of AIC and holds a promise for making anthracycline-induced HF a rarity in clinical practice.

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ADDRESS FOR CORRESPONDENCE: Dr Haoyi Zheng, Saint Francis Hospital, The Heart Center, 100 Port Washington Boulevard, Roslyn, New York 11576, USA. E-mail: haoyi.zheng@chsli.org. @HaoyiZhengMD, @HuichunZ.

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