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VIEWPOINT

Dexrazoxane to Prevent Cardiotoxicity in Adults Treated with Anthracyclines

JACC: CardioOncology Controversies in Cardio-Oncology

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Heart failure (HF) resulting from anthracycline chemotherapy was first recognized in the 1970s, shortly after this class of highly effective cancer therapies was discovered. Through 50 years of research, HF risk has been reduced by: 1) the understanding that HF risk is related to the cumulative anthracycline dose leading to efforts to decrease cumulative doses; 2) the development of alternative nonanthracycline regimens for many cancer types; and 3) the improved recognition of risk factors for the development of anthracycline cardiotoxicity. The latter 2 advances have allowed oncologists to avoid anthracyclines in some patients at the highest risk for HF, such as older patients with multiple cardiac risk factors and patients with established heart disease. However, the routine use of cardioprotective agents is notably missing from these aforementioned strategies to reduce anthracycline cardiotoxicity. In 1995, dexrazoxane was the first agent to gain U.S. Food and Drug Administration approval for anthracycline cardiotoxicity prevention.[1] Despite evidence for reduced HF events in addition to subclinical cardiotoxicity, dexrazoxane is infrequently used in clinical practice. In this viewpoint, we explore the evidence gaps that may underpin the low usage of dexrazoxane in adults and suggest future research directions to address these gaps. The use of dexrazoxane in pediatric cancer treatment is not extensively discussed here.[2]

Dexrazoxane inhibits DNA topoisomerase IIb-anthracycline-mediated double-stranded DNA breaks and reduces oxygen-free radical formation in cardiomyocytes. Most randomized studies in adults were conducted in patients with metastatic breast cancer who historically received high cumulative doses of anthracyclines (eg, the median cumulative doxorubicin equivalent dose was 669 mg/m^2 [range 247-936 mg/m^2] in one such study).[3] In this population, dexrazoxane reduced the risk of HF (risk ratio: 0.22; 95% CI: 0.11-0.43) with no significant difference in oncologic outcomes and no signal for an increase in other adverse events.[2] The Food and Drug Administration indication for dexrazoxane reflects this evidence base, and dexrazoxane is specifically approved for patients with metastatic breast cancer who have already received more than 300 mg/m^2 doxorubicin and who would benefit from ongoing doxorubicin therapy.[1] The management of metastatic breast cancer has changed dramatically since these trials were conducted in the 1990s, and the use of high cumulative doses of anthracyclines is much less common. In addition, liposomal doxorubicin is another available strategy to reduce cardiotoxicity.[4] There are no direct comparisons between dexrazoxane with nonliposomal anthracycline and liposomal anthracycline, such that it is uncertain if one strategy is superior to another. A trial comparing dexrazoxane with

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daunorubicin to a liposomal daunorubicin formulation in pediatric acute myeloid leukemia (NCT04293562) is ongoing; however, there are no comparative trials in adults.

Although some adults with metastatic breast cancer or sarcoma[5] may receive cumulative anthracycline doses that exceed doxorubicin 300 mg/m^2 (or equivalent), warranting cardioprotection with dexrazoxane or the use of a liposomal formulation, another adult population who could benefit from cardioprotective strategies are those who are at high risk for HF because of: 1) established cardiac disease; 2) prior anthracycline exposure for a different malignancy; or 3) combined modality therapy with an anthracycline and chest radiation (if the current cancer responds better to an anthracycline-based regimen than a non-anthracycline-based regimen). Patients with pre-existing cardiomyopathy, even those with a low-normal or mildly reduced left ventricular ejection fraction (LVEF), have an increased risk of HF with anthracyclines.[6] The 2016 American Society of Clinical Oncology clinical practice guidelines for Prevention and Monitoring of Cardiac Dysfunction in Survivors of Adult Cancers and the 2022 European Society of Cardiology guidelines on cardio-oncology recommend consideration of a cardioprotective strategy such as dexrazoxane, liposomal formulations, or continuous infusion in patients at higher risk for anthracycline cardiotoxicity.[7,8]

However, despite the compelling hypothesis that the cardioprotective effects of dexrazoxane can likely be extrapolated from older studies, the following gaps in evidence likely limit current use (**Table 1**):

1. Lack of cardiac safety data in patients with reduced LVEF or established HF. In a case series of 5 patients with a low LVEF before cancer diagnosis, treatment with dexrazoxane with doxorubicin allowed patients to receive planned doses of doxorubicin without a change in LVEF, cardiac biomarkers, or clinical HF events.[9] However, outside of case reports, there are limited published safety data for this approach of administering dexrazoxane with anthracyclines in patients with low LVEF or a history of HF. Given these gaps in evidence, it is unsurprising that dexrazoxane is used very rarely in patients with aggressive lymphomas and pre-existing HF treated with anthracyclines.[10] Additional studies are needed to assess the rates of worsening HF and other cardiac events with this strategy.
2. Lack of data on cancer-specific outcomes with dexrazoxane in combination with modern oncologic treatment regimens, especially in adults with leukemia and lymphoma. Meta-analyses of randomized trials of dexrazoxane in adults with cancer (mostly metastatic breast cancer) suggest that cancer-specific outcomes such as complete response rate, partial response rate, and progression-free survival are similar with and without dexrazoxane; however, there are no randomized trials in adults with lymphoma or leukemia.[2] Although randomized trials of dexrazoxane in adults with sarcoma are limited, large observational studies suggest that dexrazoxane does not impair the efficacy of doxorubicin and allows for higher cumulative doses to be given.[5] Pediatric trials of dexrazoxane also identified no difference in outcomes of the primary cancer, although there is a possibility that the risk of second malignant neoplasms increases because of dexrazoxane (a finding seen in some studies but not others).[2] Although second malignant neoplasms have not been assessed in dexrazoxane trials in adults, concern about this possible long-term adverse outcome may limit its use in adults.
3. Dexrazoxane may cause myelosuppression, although the data in adults are reassuring, with no differences observed in most measures of myelosuppression and no increase in infection events.[2] However, the lack of safety data specific to adults with lymphoma and leukemia may also cause uncertainty regarding the safety of dexrazoxane in these patients.

ABBREVIATIONS AND ACRONYMS

HF = heart failure

LVEF = left ventricular ejection fraction

In conclusion, dexrazoxane reduces clinical HF risk in adults with advanced breast cancer who are treated with high cumulative doses of anthracyclines without an apparent effect on cancer-specific outcomes or overall survival. However, these high doses are now rare because of a growing number of non-anthracycline-based regimens for use in breast medical oncology. In the setting of limited data relevant to modern-day cancer treatment, enthusiasm for dexrazoxane use is likely tempered by the lack of evidence in: 1) patients with low LVEF or a history of HF; 2) modern-day treatment regimens for adults with lymphoma and leukemia in which the cumulative dose of anthracycline typically does not exceed 300 mg/m^2; and 3) unresolved concerns regarding second malignant neoplasms. Additional multicenter observational and randomized trials to establish the safety and efficacy of dexrazoxane in adult populations other than those with advanced breast cancer could help address these evidence gaps. This area of need is well aligned with National Cancer Institute and National

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TABLE 1 Evidence Gaps in the Use of Dexrazoxane and Potential Solutions

Evidence Gap	Potential Strategies to Address Knowledge Gap
Cardiac safety: What is the incidence of worsening HF or significant LVEF declines with anthracyclines + dexrazoxane in patients with established HF, low LVEF, or prior anthracycline exposure?	Multicenter prospective study of cardiac events and longitudinal echocardiographic data in patients with established HF, low LVEF, or prior anthracycline exposure treated with anthracyclines with cardioprotection. Consideration of pragmatic trial designs and leveraging existing cancer clinical trial networks
Cancer outcomes: What are the cancer outcomes of patients with cancer (other than metastatic breast cancer) treated with anthracycline-containing regimens with dexrazoxane?	Randomized controlled trials of dexrazoxane vs placebo in addition to standard of care chemotherapy for adults with cancers other than metastatic breast cancer Multicenter retrospective or prospective studies of cancer-related outcomes with dexrazoxane
Noncardiac safety: Is there any increase in neutropenia, liver toxicity, infections, acute renal failure, or other noncardiac adverse events with dexrazoxane in addition to current multiagent chemotherapy regimens in adults with cancers other than metastatic breast cancer?	Multicenter retrospective or prospective studies of noncardiac, noncancer adverse events including abnormal laboratory findings with dexrazoxane in addition to standard of care chemotherapy for adults with cancers other than metastatic breast cancer
Comparative efficacy of dexrazoxane, liposomal doxorubicin, and continuous infusion doxorubicin. It is unknown whether 1 of these 3 mutually exclusive cardioprotective strategies is more effective than the others in preventing cardiotoxicity.	Randomized trial comparing these 3 treatment regimens

HF = heart failure; LVEF = left ventricular ejection fraction.

Heart, Lung, and Blood Institute priorities, which promote collaborative approaches to mitigate cardiovascular dysfunction while optimizing cancer outcomes.

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