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Prospective Evaluation of Doxorubicin Cardiotoxicity in Patients with Advanced Soft-tissue Sarcoma Treated in the ANNOUNCE Phase III Randomized Trial

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ABSTRACT

Purpose: Few prospective studies have assessed anthracycline-associated cardiotoxicity in patients with sarcoma. We evaluated cardiotoxicity in patients with soft-tissue sarcomas administered doxorubicin in the phase III ANNOUNCE trial (NCT02451943).

Patients and Methods: Patients were anthracycline-naïve adults with locally advanced or metastatic disease and left ventricular ejection fraction (LVEF) ≥50%. Patients could receive eight cycles of doxorubicin at 75 mg/m^2. The cardioprotectant, dexrazoxane, was allowed at investigator discretion. Symptomatic cardiac adverse events (AEs) were recorded using Medical Dictionary for Regulatory Activities and graded using Common Terminology Criteria for Adverse Events 4.0. LVEF deterioration was measured by echocardiogram or multigated acquisition scan, defined as a decrease to <50%, or decrease from baseline value >10%.

Results: A total of 504 patients received ≥1 cycles of doxorubicin [median cumulative dose, 450.3 mg/m^2 (range, 72.3–634.0)]. Median follow-up of cardiac AEs was 28 weeks. Dexrazoxane was coadministered more frequently to patients receiving higher cumulative doxorubicin doses (38.6% receiving <450 mg/m^2, 88.5% receiving 450–<600 mg/m^2, and 90% receiving ≥600 mg/m^2) and did not affect treatment efficacy. LVEF deterioration was seen in 62 of 153 (40.5%) patients who received a cumulative dose <450 mg/m^2, 82 of 159 patients (51.6%) who received 450–<600 mg/m^2, and 50 of 89 patients (56.2%) who received ≥600 mg/m^2. Grade ≥3 cardiac dysfunction occurred in 2% of patients at <450 mg/m^2, 3% at 450–<600 mg/m^2, and 1.1% at ≥600 mg/m^2. Incidence of treatment-related cardiac AEs was low across all dose ranges.

Conclusions: Although follow-up was short, these results suggest doxorubicin can be administered at high cumulative doses (>450 mg/m^2), with a low rate of cardiotoxicities, in the context of dexrazoxane coadministration.

Introduction

Despite the development of novel systemic anticancer therapies, anthracyclines remain a long-standing and common treatment for many patients, including those with sarcomas, breast cancer, lymphomas, and many childhood cancers (1). An association between anthracycline exposure and cardiotoxicity has been recognized since the 1970s (2). Although the precise mechanisms are not fully understood, they may involve direct pathways for reactive oxygen species generation and topoisomerase-IIβ, as well as other indirect pathways (3, 4). Forty years ago, the original case series of doxorubicin-associated cardiotoxicity reported an overall congestive cardiac failure incidence of 2.2% (88 cases from 4,018 patient records), based on clinical signs and symptoms of congestive heart failure (2). Cardiac risk increased as the cumulative dose of doxorubicin increased. New cardiac imaging technologies later revealed the incidence of anthracycline-associated cardiotoxicity was higher, with clinical heart failure incidences of up to 26% for cumulative doxorubicin doses of 550 mg/m^2 based on combined clinical characteristics and changes in cardiac systolic function without use of the cardioprotectant, dexrazoxane (5). Consequently, the recommended lifetime maximum cumulative dose of doxorubicin was 400 to 450 mg/m^2 (6). These recommendations may no longer be relevant to patients living in an era with different cardiovascular risks, considering the changes in rates of smoking and obesity, as well as more advanced medical and interventional cardiovascular support.

Predictors of anthracycline-associated cardiotoxicity include cumulative dose, preexisting cardiovascular risk factors, and age at commencing treatment, with elderly and very young patients being at higher risk (2, 7). Cardiotoxicity is usually detected clinically or as a decrease in the left ventricular ejection fraction (LVEF), measured by echocardiography, MRI, or multigated acquisition (MUGA) scans (6), and is commonly defined as an LVEF decline of ≥5%–<55% with heart failure symptoms or an asymptomatic decrease of LVEF ≥10%–<55% (8). Diastolic dysfunction has also emerged as a possible late effect from childhood cancer therapy, although its clinical significance is uncertain (9).

Few therapies have been proven to prevent anthracycline-associated cardiotoxicity, and only one cardioprotective agent, dexrazoxane, is FDA approved in this setting (10). Yet, dexrazoxane is inconsistently

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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Translational Relevance

Anthracycline chemotherapy is associated with cardiotoxicity, especially at higher cumulative doses. Few prospective studies have assessed the cardiac safety of anthracyclines in patients with advanced sarcomas, for whom higher doses are recommended than for other malignancies. This analysis evaluated cardiac safety data obtained from 504 patients with soft-tissue sarcomas administered doxorubicin in an international phase III trial. The trial allowed for 600 mg/m^2 of doxorubicin to be delivered. The cardioprotective agent, dexrazoxane, was coadministered more frequently to patients receiving higher cumulative doxorubicin doses. Left ventricular ejection fraction deterioration was seen in approximately 50% of patients, whereas incidences of grade ≥3 cardiac dysfunction were low. The recommended lifetime maximum cumulative dose of doxorubicin is set at 400 to 450 mg/m^2; however, these results suggest cumulative doses more than 450 mg/m^2 are possible for patients with metastatic soft-tissue sarcomas, with a low rate of cardiotoxicities in the context of dexrazoxane coadministration.

used in clinical practice to manage anthracycline-associated cardiotoxicity, and its use has previously been restricted in pediatric patients because of a concern for reduced anticancer activity (11) and suspected higher incidence of infections and secondary malignancies (12, 13). Subsequent studies and meta-analyses suggested this not to be the case (10, 13), and the European Medicines Agency removed their restriction on dexrazoxane use in 2017 (14). The cardioprotective effect of dexrazoxane is thought to be due to its ability to chelate iron and reduce the number of metal ions complexed with anthracyclines, consequently decreasing the formation of superoxide radicals (6, 15). However, dexrazoxane is also a topoisomerase II inhibitor (16) and it may have other important mechanisms of action, because other iron chelators do not provide cardioprotection (6). Many studies have also shown potential benefit of beta-blockers and ACE inhibitors for patients receiving anthracycline-containing chemotherapy regimens (17), but prophylactic use of these agents is minimal in clinical practice.

Soft-tissue sarcomas are a group of heterogeneous cancers of mesenchymal origin. Since the 1970s, anthracyclines have formed a mainstay of management of advanced sarcomas, usually with a doxorubicin dose of 75 mg/m^2 per cycle to a maximum of six cycles (450 mg/m^2). There are few prospective, contemporary data of the cardiac safety of anthracyclines in sarcomas. The aim of this analysis was to evaluate the cardiac safety data obtained in patients with soft-tissue sarcomas administered doxorubicin in an international, multicenter phase III trial.

Patients and Methods

Study design

This was a retrospective analysis of cardiotoxicity safety data from the double-blind, randomized, phase III ANNOUNCE trial of doxorubicin plus olaratumab (mAb to platelet-derived growth factor receptor α; Eli Lilly and Company) in patients with advanced soft-tissue sarcomas (NCT02451943; ref. 18). The trial was approved by the institutional review board at each study site and was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki. Written informed consent was provided by all patients. Patients had to be anthracycline-naïve adults and have unresectable locally advanced or metastatic soft-tissue sarcoma, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1, and an LVEF of ≥50%. Patients could not have a prolonged QT_CB (>450 msec for males and >470 msec for females) as calculated by Bazett formula ($QT_C = QT/\sqrt{RR}$, where the RR interval = 60/heart rate). Patients were randomized to receive 21-day cycles of olaratumab or placebo (days 1 and 8, 20 mg/kg i.v. in cycle 1 and 15 mg/kg in subsequent cycles) in combination with doxorubicin for up to eight cycles, followed by olaratumab or placebo monotherapy (cycle 9 onward). Doxorubicin (75 mg/m^2) was administered intravenously on day 1 of each cycle. The maximum allowed cumulative doxorubicin dose was 600 mg/m^2 (eight cycles). Dexrazoxane was allowed at the discretion of the investigator prior to any administration of doxorubicin and was recommended for all patients receiving five or more cycles. Further details of the study and the primary efficacy and safety results are described elsewhere (18).

The objective of this exploratory analysis was to assess the cardiotoxicity associated with doxorubicin in this contemporary, prospective cohort of patients with soft-tissue sarcoma. Cardiac monitoring consisted of LVEF determination by echocardiogram or MUGA scan at baseline, prior to cycles 5, 7, and 9, and then every 3 months until treatment discontinuation or as clinically indicated. Following completion of treatment, cardiac monitoring with echocardiography or MUGA continued every 3 months for the first year, every 6 months for the second year, and annually thereafter. Electrocardiograms (ECG) were performed at baseline, day 1 of cycles 1 to 9, then every 3 months for the first year, every 6 months for the second year, and annually thereafter. All treatment-emergent adverse events (AEs) of cardiac dysfunction occurring up to 30 days (±7 days) after the last doxorubicin dose (e.g., reported symptomatic changes) were identified using the Medical Dictionary for Regulatory Activities (MedDRA) Cardiac Failure Standardised MedDRA Query and were recorded by investigators in electronic case report forms. After the 30-day follow-up visit, only new and ongoing serious AEs deemed related to study treatment were collected. Cardiac dysfunction was graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. All analyses related to change in LVEF were completed using echocardiogram/MUGA results, independent of AEs reported by the investigator.

Statistical analysis

Cardiotoxicity was analyzed in all patients who received any quantity of study treatment. Given the rarity of cardiac AEs and no differences in primary outcome between the olaratumab and placebo arms (18), results from both treatment arms were pooled [$N = 258$ (50.7%) receiving olaratumab and $N = 251$ (49.3%) receiving placebo]. Analyses were descriptive in nature. Deterioration in LVEF was defined as a decrease to <50%, or an absolute decrease in LVEF from baseline >10%, based on the echocardiogram and MUGA data. LVEF and AEs are presented for patients receiving cumulative doxorubicin doses of <450, 450–<600, and ≥600 mg/m^2.

Results

Detailed demographics of the study population ($N = 509$) are available elsewhere (18). Briefly, most patients were consistent with the anticipated profile of patients with soft-tissue sarcomas, with a slight female predominance ($n = 296$, 58.2%) and median age of 57 years (range, 29–82). Less than one-third of patients ($n = 149$; 29.3%) were 65 years of age or older. Disease status at randomization

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Table 1. Baseline cardiac characteristics.

Characteristic	Value ($N = 509$)
Cardiac medical history, *n* (%)	12 (2.4)
Abnormal rhythm events	6 (1.2)
Ischemic events	5 (1.0)
Cardiac failure	1 (0.2)
Aortic valve stenosis	1 (0.2)
Cardiac conditions present at enrollment, *n* (%)	33 (6.5)
Abnormal rhythm	22 (4.3)
Valvular abnormalities	7 (1.4)
Coronary artery disease	3 (0.6)
Bundle branch block	2 (0.4)
Other[a]	4 (0.8)
LVEF, median %	65%[b]

[a]Includes congestive cardiac failure, ischemic cardiomyopathy, myocardial ischemia, and Prinzmetal angina ($n = 1$ for each).
[b]Baseline ejection fraction ≥50% required for trial entry.

was metastatic for 422 patients (82.9%) and locally advanced for 87 (17.1%). More than half of the patients had an ECOG performance status of 0 ($n = 303$, 59.5%) with the remainder having a performance status of 1 ($n = 206$, 40.5%).

Twelve patients (2.4%) had a cardiac medical history, which included abnormal rhythm events ($n = 6$, 1.2%) and ischemic events ($n = 5$, 1%; **Table 1**). In addition, 33 patients (6.5%) had ongoing cardiac conditions at enrollment, including abnormal rhythm ($n = 22$, 4.3%), valvular abnormalities ($n = 7$, 1.4%), and coronary artery disease ($n = 3$, 0.6%). The median LVEF at baseline was 65%.

Of the 506 patients who received at least one study treatment in the ANNOUNCE study, 504 (99.6%) received ≥1 cycles of doxorubicin, 347 (68.6%) received ≥4 cycles, 287 (56.7%) received ≥6 cycles, and 219 (43.3%) received eight cycles (**Table 2**). On the basis of the reported duration noted in cycle 1 of treatment ($n = 497$), 90.5% of patients received their doxorubicin dose in less than 60 minutes. The median number of cycles of doxorubicin per patient was six, with a median cumulative dose of 450.3 mg/m^2 (range, 72.3–634). Given the maximum cumulative dose received was 634 mg/m^2, we expect that dose rounding explains why 90 patients were subsequently noted to have received cumulative doxorubicin doses ≥600 mg/m^2. Two-thirds of the patient cohort ($n = 324$, 64.0%) received at least one dose of dexrazoxane. The median number of cycles of dexrazoxane per patient was four, with a median cumulative dose of 2,945.3 mg/m^2 (range, 451.7–6,870.8). Of the 251 patients who received a cumulative dose of doxorubicin <450 mg/m^2, 97 (38.6%) were coadministered with dexrazoxane. Patients receiving higher cumulative doses of doxorubicin were more frequently coadministered dexrazoxane: 146 of the 165 patients (88.5%) who received a cumulative doxorubicin dose of 450–<600 mg/m^2, and 81 of the 90 patients (90%) who received a cumulative dose ≥600 mg/m^2. Dexrazoxane was most frequently initiated at cycle 1 (in 106 patients) or at cycle 5 (154 patients).

Table 2. Doxorubicin and dexrazoxane exposure summary.

	Total ($N = 506$[a])	
	Doxorubicin	Dexrazoxane
Treatment cycles received, *n* (%):		
≥1 cycle	504 (99.6)	324 (64.0)
≥2 cycles	478 (94.5)	290 (57.3)
≥4 cycles	347 (68.6)	206 (40.7)
≥6 cycles	287 (56.7)	70 (13.8)
8 cycles	219 (43.3)	33 (6.5)
Cumulative dose (mg/m^2), median (range)	450.3 (72.3–634.0)	2,945.3 (451.7–6,870.8)
Median cycles per patient, *n*	6	4
Dexrazoxane initiation, *n*		
Cycle 1	—	106
Cycles 2, 3, or 4	—	49
Cycle 5	—	154
Cycles 6 or 7	—	15

[a]Results are presented for the pooled population of all patients who received at least one dose of trial treatment.

Median follow-up for cardiac AEs was 6.4 months (range, 1–36.6) and median follow-up of LVEF by echocardiogram/MUGA was 11.4 months (range, 0.03–36.5). LVEF decreases (<50% or an absolute decrease in LVEF from baseline >10%) occurred in 40.5% of the patients who received a cumulative doxorubicin dose <450 mg/m^2, in 51.6% who received 450–<600 mg/m^2, and in 56.2% who received ≥600 mg/m^2 (**Table 3**). Most cases of reduced LVEF comprised patients with an absolute decrease from baseline >10%. LVEF decreases in patients receiving higher cumulative doses (≥450 mg/m^2) were not clearly impacted by dexrazoxane use ($P = 0.682$). In addition, no difference was seen when considering only patients who initiated dexrazoxane at cycle 1 ($P = 0.844$ for patients receiving <450 mg/m^2; $P = 0.199$ for ≥450 mg/m^2).

Cardiac dysfunction of grade ≥3 per CTCAE definition was reported in 2% of patients receiving a doxorubicin cumulative dose of <450 mg/m^2, in 3% of those receiving 450–<600 mg/m^2, and in 1.1% of those receiving ≥600 mg/m^2 (**Table 4**). The rates of the treatment-emergent AEs, cardiac failure and diastolic dysfunction, were low across all doxorubicin cumulative dose groups. Few ECG changes were observed (15/506, 3.0%) and their frequency did not appear to increase with higher cumulative doses. QTc prolongation was the most common ECG change (12/506, 2.4%), with 1 patient having grade 3 prolongation (0.2%) and no grade 4 or 5 events were reported (Supplementary Table S1). Rates of cardiotoxicities were similar between the doxorubicin + olaratumab and doxorubicin + placebo arms.

As an exploratory analysis, treatment efficacy (doxorubicin + olaratumab and doxorubicin + placebo groups combined) was evaluated in relation to dexrazoxane use and the timing of dexrazoxane initiation. Efficacy was not different for patients who received dexrazoxane starting with cycle 1 ($n = 106$) versus all other patients regardless of dexrazoxane coadministration ($n = 400$), with median overall survival (OS) of 18.8 months [95% confidence interval (CI), 14.7–22.7 months] versus 20.8 months (95% CI, 18.1–23.4 months; $P = 0.325$) and median progression-free survival (PFS) of 5.5 months (95% CI, 4.1–6.9 months) versus 5.8 months (95% CI, 5.3–6.9 months; $P = 0.337$), respectively. Efficacy was greater in patients who received any dexrazoxane ($n = 324$) compared with those who did not receive any dexrazoxane [$n = 182$; median OS, 24.4 months (95% CI, 21.2–27.3) vs. 12.4 months (95% CI, 10.2–14.5) and median PFS, 8.3 months (95% CI, 7–8.5) vs. 1.5 months (95% CI, 1.4–1.6); $P < 0.001$ for both]. Given that more than half of patients who received any dexrazoxane had it initiated at cycle 5 or later, this greater efficacy is more likely to be related to duration of doxorubicin therapy than an effect of dexrazoxane itself.

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Table 3. Changes in LVEF from baseline.

Doxorubicin cumulative dose	Variable	Total	Dexrazoxane		
			Yes	No	*P*
Any	*N*	401	290	111	—
	LVEF[a], *n* (%):				
	<50%	48 (12%)	35 (12.1%)	13 (11.7%)	—
	>10% decrease from baseline	191 (47.6%)	149 (51.4%)	42 (37.8%)	—
	<50% and/or >10% decrease from baseline	194 (48.4%)	151 (52.1%)	43 (38.7%)	—
<450 mg/m^2	*N*	153	68	85	
	LVEF[a], *n* (%):				
	<50%	16 (10.5)	11 (16.2)	5 (5.9)	0.060
	>10% decrease from baseline	59 (38.6)	32 (47.1)	27 (31.8)	0.094
	<50% and/or >10% decrease from baseline	62 (40.5)	34 (50.0)	28 (32.9)	0.046
450–<600 mg/m^2	*N*	159	142	17	—
	LVEF[a], *n* (%):				
	<50%	18 (11.3)	14 (9.9)	4 (23.5)	0.009[b]
	>10% decrease from baseline	82 (51.6)	74 (52.1)	8 (47.1)	0.673[b]
	<50% and/or >10% decrease from baseline	82 (51.6)	74 (52.1)	8 (47.1)	0.682[b]
≥600 mg/m^2	*N*	89	80	9	—
	LVEF[a], *n* (%):				
	<50%	14 (15.7)	10 (12.5)	4 (44.4)	—
	>10% decrease from baseline	50 (56.2)	43 (53.8)	7 (77.8)	—
	<50% and/or >10% decrease from baseline	50 (56.2)	43 (53.8)	7 (77.8)	—

Note: Results shown for the population with echocardiogram or MUGA scan data at baseline and at least one other timepoint ($N = 401$).
[a]On the basis of worst postbaseline abnormal LVEF result.
[b]*P* values calculated for all patients who received a doxorubicin cumulative dose ≥450 mg/m^2.

Two patients were reported to have died from heart failure deemed related to study treatment. Neither had a preexisting cardiac history. One was a 70-year-old female with baseline ejection fraction of 65% who received seven cycles of doxorubicin (cumulative dose = 450 mg/m^2) + olaratumab with dose reduction of doxorubicin in cycles 3 to 7 due to febrile neutropenia in cycle 2. She did not receive dexrazoxane. No follow-up echocardiography or MUGA was recorded and acute cardiac failure was reported 157 days after randomization with death 86 days later. The other patient was a 46-year-old female with baseline ejection fraction of 60% who received eight cycles of doxorubicin (cumulative dose = 588 mg/m^2) + placebo, with no dose reductions and with dexrazoxane with cycles 5 to 7. Lowest reported ejection fraction was 50% at a long-term follow-up visit approximately 1 year after randomization. Congestive heart failure was reported 580 days after randomization with death 2 days later.

Discussion

In this analysis of the ANNOUNCE phase III trial, we have shown that 57% of all patients received six cycles of doxorubicin (at a dose of 75 mg/m^2) and 43% received eight cycles. The cardioprotective agent, dexrazoxane, was used at the discretion of the investigator in 64% of patients. Although approximately 50% of patients developed a decrease in LVEF, clinical cardiotoxicity was only observed in approximately 1% of patients.

Our study is limited by the relatively short follow-up for cardiac events (median, 28 weeks). However, a common manifestation of anthracycline-associated cardiotoxicity is early-onset chronic progressive cardiomyopathy that tends to present during, or within 1 year following therapy (2, 19). Furthermore, late-onset asymptomatic cardiotoxicity, cardiomyopathy, and arrhythmias have been described years and decades after chemotherapy (2, 19). Because of the poor prognosis of advanced soft-tissue sarcomas, early-onset

Table 4. Adverse events.

	Cumulative doxorubicin dose					
	<450 mg/m^2 (*n* = 251)		450–<600 mg/m^2 (*n* = 165)		≥600 mg/m^2 (*n* = 90)	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Cardiac dysfunction[a]	10 (4.0)	5 (2.0)	13 (7.9)	5 (3.0)	3 (3.3)	1 (1.1)
LVEF decrease/LV dysfunction	9 (3.6)	4 (1.6)	11 (6.7)	4 (2.4)	2 (2.2)	1 (1.1)
Cardiac failure	1 (0.4)	1 (0.4)	1 (0.6)	1[b] (0.6)	0	0
Diastolic dysfunction	0	0	1 (0.6)	0	1 (1.1)	0

Note: Data are presented as *n* (%).
Abbreviation: LV, left ventricle.
[a]Cardiac dysfunction was defined by preselected terms from Standardized MedDRA Query "cardiac failure," omitting nonspecific terms "edema" and "peripheral edema," and was graded using the NCI CTCAE version 4.0.
[b]Grade 5 event (resulting in death).

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cardiotoxicity remains the major challenge in clinical practice. Another limitation was that the original trial was not designed to collect detailed cardiac safety data, for example, diastolic dysfunction was not specifically measured by echocardiography, meaning asymptomatic cases could have been underreported. The importance of diastolic dysfunction has been highlighted in a recent longitudinal cohort study of 362 patients with breast cancer treated with anthracyclines (20). Those treated with doxorubicin or doxorubicin followed by trastuzumab demonstrated a persistent worsening in diastolic function, although no cardioprotectant was coadministered. These changes were not observed in patients treated with trastuzumab alone. Abnormal and worsening diastolic function was associated with a small risk of subsequent systolic dysfunction. A further limitation to our study was that the timing and reasons for initiating dexrazoxane were left to the discretion of individual investigators, and consequently dexrazoxane was initiated at different cumulative doxorubicin doses per patient or not initiated at all.

Despite its limitations, this study does provide a contemporary benchmark of the cardiac safety profile of doxorubicin in advanced soft-tissue sarcomas. These prospectively obtained data, while not the primary endpoint to the trial, are important given the large number of patients in a rare group of cancers (for which higher doses of an anthracycline are recommended than for other malignancies) and the current lack of published prospective clinical data. The systemic treatment options available to treat advanced sarcomas are limited and the outcome remains poor. For the foreseeable future, it is likely that anthracycline-based schedules will remain the standard first-line therapy for advanced disease. Consequently, our study is important as it highlights the safety and feasibility of administering doxorubicin at a dose of 75 mg/m^2 to eight cycles (cumulative dose, 600 mg/m^2) with dexrazoxane cardioprotection. Schwartz and colleagues have also shown the feasibility and safety of increasing the cumulative dose of doxorubicin with dexrazoxane in localized osteosarcoma (23). In their study of 242 patients with osteosarcoma aged <31 years, dexrazoxane did not interfere with the efficacy of preoperative anthracycline-based chemotherapy. Taken together, these data support further evaluation of dexrazoxane in sarcomas.

The rate of cardiotoxicities was lower than in studies where patients received higher cumulative doses of doxorubicin (2, 5). Although presumably due to the use of dexrazoxane, this may also partly be explained by other factors, such as improvements in blood pressure management and lower rates of smoking since these earlier data. There have been more recent retrospective reports of administering high cumulative doses of doxorubicin with dexrazoxane. A retrospective study of 32 patients reported a median cumulative doxorubicin dose of 450 mg/m^2 before adding dexrazoxane, and a cumulative dose of 750 mg/m^2 after the administration of the last doxorubicin dose (21). In that study, two of 27 patients (7%) without preexisting major cardiac history developed anthracycline-associated cardiotoxicity, and the median OS from commencing anthracycline was 46 months. Similar to the current study, cardiac AEs due to high cumulative doses of anthracyclines were rare. A current prospective, noninferiority clinical trial is evaluating the role of dexrazoxane plus doxorubicin in patients with advanced sarcomas (NCT02584309).

In an exploratory analysis, we found dexrazoxane use and timing were unlikely to impact treatment efficacy in terms of median OS and PFS. This is important and supports evidence that dexrazoxane does not impede clinical activity of anthracyclines (10, 13), considering a prior contrary report of lower doxorubicin efficacy in patients receiving dexrazoxane early in therapy (11). Preclinical data have indicated that dexrazoxane combined with anthracyclines may lead to a synergistic cytotoxic response in acute myeloid leukemia cell lines (22). In our study, greater efficacy was observed in patients treated with dexrazoxane, but we suspect that this is due to the longer duration of anthracycline therapy, with which investigators would add dexrazoxane at higher doses. However, synergy with dexrazoxane cannot be ruled out, and these hypothesis-generating data warrant further evaluation of dexrazoxane–doxorubicin schedules in sarcomas. The use and timing of dexrazoxane coadministration are highly variable in clinical practice because no specific guidelines are available. Physician choice to coadminister dexrazoxane may depend on whether the patient has a preexisting cardiac history, prior administration of anthracyclines, or is reaching the anthracycline cumulative dose limit (21).

Anthracycline-containing chemotherapy is one of the most effective therapeutic options for patients with unresectable or metastatic sarcomas, but treatment is often discontinued because of the risk of cumulative cardiotoxicity. This analysis in a large soft-tissue sarcoma cohort found that patients with doxorubicin cumulative doses more than 450 mg/m^2, most of whom also received the cardioprotectant, dexrazoxane, had a low rate of cardiotoxicity.

Authors' Disclosures

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Authors' Contributions

R.L. Jones: Conceptualization, resources, investigation, writing–original draft, writing–review and editing. **A.J. Wagner:** Investigation, writing–review and editing. **A. Kawai:** Investigation, writing–review and editing. **K. Tamura:** Investigation, writing–review and editing. **A. Shahir:** Conceptualization, data curation, writing–review and editing. **B.A. Van Tine:** Investigation, writing–review and editing. **J. Martín Broto:** Investigation, writing–review and editing.

P.M. Peterson: Data curation, formal analysis, methodology, writing–review and editing. **J. Wright:** Conceptualization, data curation, formal analysis, supervision, investigation, writing–original draft, project administration, writing–review and editing. **W.D. Tap:** Investigation, writing–review and editing.

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