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Dexrazoxane for cardioprotection in older adults with acute myeloid leukemia

Pankit Vachhani[a,*,1], Sarah Shin[b,1], Jeffrey Baron[c], James E. Thompson[a], Meir Wetzler[a], Elizabeth A. Griffiths[a], Evelena P. Ontiveros[a], Edward J. Spangenthal[a], Eunice S. Wang[a]

[a] Department of Medicine, Roswell Park Cancer Institute, Elm and Carlton Streets, Buffalo, NY, USA
[b] Department of Internal Medicine, Jacobs School of Medicine and Biomedical Sciences at the University at Buffalo, Buffalo, NY, USA
[c] Department of Pharmacy, Roswell Park Cancer Institute, Elm and Carlton Streets, Buffalo, NY, USA

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ABSTRACT

Anthracyclines constitute the backbone of intensive adult acute myeloid leukemia (AML) therapy. Cardiotoxicity is one of its most serious adverse effects, and its incidence increases with cumulative dose. Dexrazoxane is a cardioprotective agent used in conjunction with anthracycline therapy. There is limited data of its usage in adult AML patients. We report the outcomes of six older adults at high risk of anthracycline-induced cardiotoxicity who received dexrazoxane during induction/re-induction therapy. Five had preserved left-ventricular function while two proceeded onto stem-cell transplantation. Additional investigation of dexrazoxane in adult leukemia therapy is warranted, particularly in older patients at highest risk for cardiovascular mortality.

1. Introduction

Acute myeloid leukemia (AML) accounts for 80% of acute leukemia in adults with a median age at diagnosis of 65 years [1]. The standard upfront induction regimen for fit adult individuals remains "7 + 3", consisting of 7 days of continuous infusion cytarabine and 3 days of an anthracycline, either daunorubicin or idarubicin [2]. Variations of induction and re-induction regimens in the refractory/relapsed disease setting often include either idarubicin or mitoxantrone in conjunction with high dose cytarabine and sometimes purine analogues. Medical comorbidities, specifically cardiovascular morbidity, have been shown to negatively impact the clinical outcomes of AML induction therapy in older adults. Cardiotoxicity constitutes the most frequently feared adverse event associated with the use of anthracyclines (> 10%), and compromised cardiac function may compromise the use of potentially curative upfront and subsequent AML regimens in a patient's course. Prevention or mitigation of anthracycline-induced cardiotoxicity, particularly in older adults who constitute the majority of new AML diagnoses, is therefore an area of tremendous clinical relevance.

Cardiotoxicity of anthracyclines is dose-dependent and can occur at any time in the treatment course with acute, subacute, and late-onset presentations. Clinical symptoms include arrhythmias, myopericarditis, cardiomyopathy, and congestive heart failure with reduced left ventricular ejection fraction (LVEF) [3–5]. For example, the incidence of cardiotoxic events with use of doxorubicin was less than 5% at a cumulative dose of 400 mg/m^2, but increased in a dose-dependent manner to 16% at a cumulative dose of 500 mg/m^2, 26% at 550 mg/m^2, and 48% at 700 mg/m^2 [6,7]. For this reason, current recommendations limit the cumulative lifetime dose of doxorubicin to no more than 450 mg/m^2. Although the precise mechanisms of anthracycline-induced cardiac toxicities are not well elucidated, the most commonly proposed mechanism is drug-induced generation of iron-anthracycline complex mediated reactive oxygen species (ROS) which cause mitochondrial dysfunction leading to adenosine triphosphate depletion, lipid peroxidation, DNA damage, and subsequent myocardial injury [4,8].

Dexrazoxane (Cardioxane®; Zinecard®, Pfizer Inc., NY, NY) is a cyclic derivative of a strong metal-chelating agent which interferes with site-specific iron-based oxidative damage to cardiac mitochondria to exert its cardioprotective activity. By chelating free iron, dexrazoxane prevents the formation of iron-anthracycline complexes that lead to the formation of superoxide free radicals during redox reactions, thereby limiting cardiac injury [7]. Dexrazoxane was approved by the U.S. Food and Drug Administration (FDA) in 1995 for use as a cardioprotective agent in the treatment regimen of patients with metastatic or advanced breast cancer who have reached a cumulative anthracycline dose of 300 mg/m^2 and who are continuing to receive doxorubicin. Additionally, dexrazoxane was approved in 2007 by the FDA to decrease

* Corresponding author.
E-mail address: pankit.vachhani@roswellpark.org (P. Vachhani).
[1] These authors contributed equally to the manuscript.

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damage that may occur in the setting of inadvertent extravasation of anthracyclines into skin and subcutaneous tissue. Although not approved in the pediatric setting, dexrazoxane has also been extensively utilized in children with leukemia and lymphoma in order to mitigate the long-term cardiovascular effects of intensive chemotherapy regimens incorporating anthracyclines. Despite case reports of AML and myelodysplastic syndrome (MDS) developing in some children receiving dexrazoxane in conjunction with chemotherapy, the Children's Oncology Group recently reported that dexrazoxane did not appear to compromise long term survival of over 1000 pediatric patients treated with this agent on multiple clinical trials [9,10].

Evidence supporting the benefit of dexrazoxane as cardioprotective therapy in adults with acute leukemia are scant [11]. However, there is a significant need for cardioprotective therapy, particularly in older individuals with preexisting cardiovascular disorders and/or prior anthracycline exposure, who are otherwise considered good candidates for potentially remission-inducing intensive chemotherapy [12]. Here, we present the cases of six older adults with newly diagnosed or relapsed AML at high risk for cardiovascular morbidity who received dexrazoxane in conjunction with anthracycline containing induction/re-induction chemotherapy regimens.

2. Methods

Pharmacy database search at Roswell Park Cancer Institute was conducted to identify all adult patients (age ≥18 years) who had received any number of dexrazoxane doses during a 16 year time frame (January 2000 to October 2016). A total of eight patients who met the diagnosis of AML were identified. Two patients were then excluded (one patient had ongoing treatment while another patient had inadequate follow up due to death relatively soon after dexrazoxane from AML and its complications but unrelated to dexrazoxane). Deidentified data were collected on the remaining six patients by systematic electronic medical chart review. Patient characteristics like age, gender, race, and pertinent medical history such as the specifics of AML diagnosis and therapy course, cardiac and other medical histories, dose and reason for selection of dexrazoxane administration, echocardiogram and multigated acquisition scan findings, and post dexrazoxane outcomes were reviewed and recorded in Microsoft Word document and Excel sheet on a secure server. This retrospective study was approved by the institutional review board of the Roswell Park Cancer Institute, Buffalo, NY.

3. Results

The six identified patients (4 females, 2 males) were older adults with a median age of 61.5 years (range 55–71 years). The salient features of these patients are enlisted in Table 1. Two patients (cases 4, 5) had *de novo* AML while four patients had relapsed/refractory AML (case 1, 2, 3, and 6). Three patients (cases 1, 4, and 5) had good risk cytogenetics at AML diagnosis. Three patients (cases 3, 4, and 5) had known history of prior cardiac comorbidities (two patients had history of coronary artery disease and had undergone coronary artery stent placements with one of them also having had coronary artery bypass graft; one patient had history of viral cardiomyopathy). All three patients had a reduced LVEF of 40% prior to the dose of dexrazoxane. In all cases, the dexrazoxane was administered prior to the dose of anthracycline.

While four patients (cases 1, 3, 5, 6) experienced a drop in LVEF post-dexrazoxane, two of those patients (cases 1, 5) eventually recovered LVEF. The other two patients had a drop in LVEF that corresponded with development of sepsis (cases 3, 6). Additionally, the drop in LVEF for one patient (case 3) occurred later in the therapy course when dexrazoxane was not used. Besides LVEF reduction, conduction abnormality (right bundle branch block and Mobitz type II block) was noted in one patient (case 5). No patient died directly from cardiac complications.

Four of the six patients died from AML or its treatment related complications. The two patients alive (cases 4, 5) had *de novo* AML with good risk cytogenetics and both underwent allogeneic stem cell transplant for relapsed/refractory nature of their AML. Case 4 is day +350 and case 5 is day +605 post-transplant. Both are in remission and are actively followed in the clinic.

Three patients (cases 1, 4, 5) had eventual improvement in their LVEF post dexrazoxane. However, the time to improvement varied in these patients as shown in Table 2. Case 5 had two distinct episodes of reductions in LVEF. The association of the second of these two reductions to dexrazoxane cannot be established but appeared unlikely. All three patients underwent optimal heart failure management.

See Supplementary Data for details of each patient's clinical course.

4. Discussion

Here we describe six older adult patients (ages 55–71, median age 61.5 years) who received dexrazoxane to mitigate the cardiotoxicity of daunorubicin or mitoxantrone-based induction/re-induction chemotherapy for AML. All of our patients would have been either considered at very high risk for cardiotoxicities due to preceding cardiovascular morbidities and/or were ineligible for anthracyclines due to concern for exceeding cumulative dose limits. Baseline LVEF in five out of six patients was borderline and ranged from 40% to 50%. Of note, half of these patients had AML characterized by favorable karyotype at diagnosis whose disease would be expected to potentially benefit from standard intensive 7 + 3 chemotherapy. Use of dexrazoxane allowed for the key provision of anthracycline in their treatment regimens. Five of the six patients had stable/recovered LVEF back to baseline pre-chemotherapy levels following concomitant dexrazoxane and chemotherapy. This includes two patients who experienced a transient drop in LVEF in the setting of sepsis. Although four patients have since died, cardiotoxicity was not the leading factor in their demise. Importantly, two patients who received induction chemotherapy with dexrazoxane had preserved LVEF afterwards and were able to successfully undergo allogeneic hematopoietic stem cell transplant at the time of relapse. Both are still alive.

Characterizing the precise clinical effects of dexrazoxane in patients with AML can be difficult because of concurrent use of cardiotoxic agents other than anthracyclines, the general aggressiveness of AML, and the presence of cardiac and non-cardiac comorbidities in older adults. For example, cases 3 and 6, encountered a drop in LVEF in the context of ongoing sepsis, which has been shown to result in global left-ventricular hypokinesis (defined as LVEF < 45%) within 72 h of presentation in the majority of patients [13]. However it is notable that one patient (case 3) who had a stable/improved LVEF of 50% following dexrazoxane and anthracycline chemotherapy subsequently developed progressive heart failure with a drop in the LVEF of 30% following administration of additional anthracycline therapy without cardioprotection.

Although the cardioprotective benefits of dexrazoxane have been clearly demonstrated in both pediatric (mostly hematologic malignancies) and adult (mostly breast cancer) patients, this agent is not currently approved for AML patients receiving anthracycline therapy. One concern was the possibility of dexrazoxane decreasing chemotherapeutic efficacy based on preclinical data showing that dexrazoxane can antagonize the cytotoxicity induced by topoisomerase II directed drugs, daunorubicin and etoposide, in AML cells [14]. More recent reports have shown that dexrazoxane itself may exert anti-leukemic effects. Although dexrazoxane exhibits only weak cytotoxicity against leukemia cells, synergistic anti-tumor effects were reported following combination therapy with dexrazoxane plus anthracycline or dexrazoxane plus daunorubicin and cytarabine in multiple human AML cell lines (HL60, HL60/dox, OCI/AML3, AML-193, CRF-SB, and Molt-4) [15,16]. Similarly, another study showed that dexrazoxane sensitized K562 and

Table 1
Summary of adult patients with AML treated with dexrazoxane.

Case	Age, Sex	Diagnosis, chemotherapy regimen	Prior cardiac history	Anthracycline dose (mg/m^2)		LVEF		Clinical outcomes following DEX
				Prior to DEX	with /after DEX	Prior to DEX	After DEX	
1	59, F	Relapsed AML, HiDAC + Mito	None	300	160	50%	20% - > 55%	Transient decreased LVEF, Died of relapsed disease
2	64, F	Relapsed AML, CLAG-M	None	340	132	55%	55%	Died from treatment related complications
3	67, M	Relapsed and refractory AML, ADE	CAD s/p stent placement	None	338	40%	50% - > 30%*	Decreased LVEF after additional anthracycline without DEX, died from refractory AML
4	55, M	*De novo* AML, ADE	CAD s/p CABG, HTN	None	310	40%	50%	Relapsed AML, alive after alloSCT
5	57, F	*De novo* AML, ADE	Viral cardiomyopathy	None	270	40%	30%- > 66%	RBBB and Mobitz type II block 3 yrs later, relapsed AML, alive after alloSCT
6	71, F	Relapsed AML, HiDAC + Mito	None	370	158	50%	40%	Decreased LVEF and global hypokinesis, died of sepsis and refractory AML

All anthracycline doses have been converted to daunorubicin equivalent. Abbreviations: AML: Acute myeloid leukemia; ADE: Cytarabine, Daunorubicin, Etoposide; AlloSCT: allogeneic stem cell transplantation; CAD: coronary artery disease; CABG: coronary artery bypass graft; DEX: dexrazoxane; HiDAC: high-dose cytarabine; HTN: hypertension; LVEF: left ventricular ejection fraction; LVH: left ventricular hypertrophy; Mito: Mitoxantrone; RBBB: right bundle branch block

Table 2
Temporal changes of left ventricular function (LVEF) in patients with improvement in LVEF post dexrazoxane.

Case 1	Case 4	Case 5
Baseline LVEF of 70%	Baseline LVEF = 40%	Baseline LVEF = 40%
Post-transplant LVEF of 50%, day 1561	Dexrazoxane on days 1–3	Dexrazoxane on days 1–3
Dexrazoxane on days 1561–1563	LVEF of 55% on day 33	LVEF of 30% on days 7, 14
LVEF of 20% on day 1692	LVEF of 50% on day 728	LVEF of 41% on day 538
LVEF of 55% on day 2119	LVEF of 50% on day 839	LVEF of 30% on day 656
	Post-transplant LVEF of 50% on days 866, 873, 944	LVEF of 44% on day 694
		Post-transplant LVEF of 55% on days 781, 832
		LVEF of 66% on day 1084

Day 1 is the day of first anthracycline administration in the patient's overall treatment course of acute myeloid leukemia. Abbreviations: LVEF: left ventricular ejection fraction

HL60 cells to daunorubicin treatment [17]. Dexrazoxane may also prevent the acquisition of the multi-drug export receptor, MDR1, in K562 AML cell lines following doxorubicin, thereby delaying the emergence of multidrug resistance [18]. Another issue was the potentially increased incidence of secondary malignant neoplasms (SMNs), specifically AML and MDS, in patients receiving dexrazoxane. Although one study reported a statistically significantly increased risk of SMNs following dexrazoxane therapy, this study has since come under scrutiny because of the controversial statistical methodology leading to the conclusions [19–21]. Moreover a recent meta-analysis of 1561 patients (mostly adults with breast cancer) enrolled in eight trials showed that dexrazoxane significantly prevented the development of heart failure (RR = 0.18; 95%-CI: 0.10–0.32) [14] without any increased risk of SMNs or negative effects on treatment response, progression-free or overall survival. Several other major studies have similarly not shown any association between dexrazoxane and SMNs or poor treatment outcomes [22,23]. In sum, the available preclinical and clinical data not only support the safety of dexrazoxane as cardioprotective therapy for AML patients but also offer the tantalizing possibility that this agent may enhance anti-leukemic effects. Overall, the potential benefits of dexrazoxane therapy appear to far outweigh the risks, particularly in patients with life threatening malignancies such as AML.

Aside from this report, only two other studies of dexrazoxane use in adult AML patients have been published. In a series of seven patients with AML, Lemez and Maresova reported that the administration of dexrazoxane 30 min before daunorubicin (dose 8-13x higher than daunorubicin) or mitoxantrone (dose 40-60x higher than mitoxantrone) allowed them to give cumulative anthracycline doses in the range of 550–1300 mg/m^2 of daunorubicin without signs of cardiac toxicity [24]. Complete remission was achieved in all patients with relapsed AML treated with high dose cytarabine, anthracycline, and dexrazoxane. However, almost all of these patients were significantly younger (ages 21–58, median 35 years) than our cases (ages 55–71, median 61.5 years), and all had much higher baseline LVEF (62–70%) than our patients (LVEF 40–50%). In another study, Woodlock and colleagues safely administered dexrazoxane to two AML patients: prior to mitoxantrone in a 70 year old patient with ischemic heart disease (LVEF 30%), and prior to idarubicin in a 43 year old patient with concurrent myocardial infarction (LVEF 70%) [11]. Both patients had preserved LVEF after therapy but died shortly thereafter. Dexrazoxane was not thought to be the culprit agent.

Strategies to mitigate the cardiac toxicities of anthracycline therapy are urgently needed to allow for the safe administration of effective, intensive chemotherapy regimens in adult AML patients. A recent cooperative group trial demonstrated that higher daunorubicin doses (90 mg/m^2 vs. 45 mg/m^2) during induction therapy improved clinical outcomes for AML patients across cytogenetic and molecular subgroups [25]. In another large multicenter study, higher-dose daunorubicin (90 mg/m^2 vs. 45 mg/m^2) improved complete remission rate (52% vs. 35%, $p < 0.001$) in adults over the age of 60 years and overall survival (38% vs. 23%, $p < 0.001$) for those aged 60–65 years [26]. Older individuals who constitute the majority of new diagnoses are at particular risk for cardiotoxic complications. Based on our clinical experience and the current data, we believe that the use of dexrazoxane as standard cardioprotection during intensive chemotherapy should be further investigated in large randomized controlled clinical trials. Until such high-quality evidence emerges, we would suggest strongly considering dexrazoxane in adults with known significant cardiac comorbidities and/or who are fit for intensive anthracycline-containing therapy but are approaching or have crossed their lifetime cumulative dose of anthracycline. Dexrazoxane should be administered intravenously 15 min before every dose of mitoxantrone/idarubicin (50:1

dexrazoxane: anthracycline) or daunorubicin (10:1 dexrazoxane: daunorubicin). It is important to note that dexrazoxane is renally eliminated and therefore would require a 50% dose reduction in the setting of renal insufficiency. Other approaches to limit cardiotoxicity in such patients should also be utilized when possible. These include concomitant beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and statins, all of which have previously been shown in various studies to improve a variety of cardiac outcomes in patients receiving anthracyclines [27]. Of note, in patients with metastatic breast cancer, liposomal doxorubicin conferred similar efficacy but significantly less cardiotoxicity than standard doxorubicin [28]. It remains to be seen whether CPX-351, a new liposomal formulation of cytarabine: daunorubicin which has shown improvement in response and overall survival in older patients with secondary AML, represents a safer, less cardiotoxic, induction choice than standard 7 + 3 [29].

5. Conclusion

Anthracyclines constitute the backbone of standard intensive therapies for AML. Cardiotoxicity is one of its most serious adverse effects though, occasionally precluding its usage even in potentially curative cases. Dexrazoxane is a cardioprotective agent that could be used in conjunction with anthracycline therapy. There is preclinical evidence in AML cell lines demonstrating that it may even have anti-leukemic effects. However, there is limited data of its usage in adult AML patients. Of our six cases of older adults (ages 55–71, median 61.5 years) at high risk of anthracycline-induced toxicity who received dexrazoxane as cardioprotective therapy during their therapy for AML, five had preserved/recovered LVEF at or above baseline following treatment while two patients proceeded onto subsequent allogeneic stem cell transplantation. Dexrazoxane should be considered especially in adults with known significant cardiac comorbidities and who are fit for intensive anthracycline-containing therapy but are approaching or have crossed their lifetime cumulative dose of anthracycline. Additional clinical investigation of dexrazoxane in adult leukemia therapy is warranted to better define its role particularly in older individuals at highest risk for cardiovascular mortality.

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Conflict of interest disclosure

The authors have no relevant conflicts of interest to report.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.lrr.2017.04.001.

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