

ORIGINAL RESEARCH

The efficacy and toxicity of dexrazoxane use in children with cancer: A population-based study from Maritimes, Canada

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Abstract

Anthracycline induced cardiotoxicity is a well-recognized complication in pediatric oncology. The use of the cardio-protective drug dexrazoxane has gained traction despite its unclear efficacy and toxicity. A retrospective, population-based study was completed using chart and database information on children treated with anthracycline at the IWK Health Centre from 2009-2015 (n=178). The efficacy of dexrazoxane was defined as a lack of undesirable deviations in identified cardiac parameters on echocardiogram. Toxicity of dexrazoxane was defined as chemotherapy delays from any of decreased absolute neutrophil count (ANC), decreased platelets, increase in viral/bacterial episodes and febrile neutropenia (FN) episodes. Patients were stratified into groups based on the total amount of anthracycline received and whether they received dexrazoxane. Regardless of anthracycline dose, we found no significant relationships regarding cardiac function in the untreated and dexrazoxane treated groups. However, we found that patients who were treated with >250mg/m² of anthracycline and received dexrazoxane experienced significantly more platelet delays but no cardiac benefit (p=0.007). When classified by diagnosis, we also found that dexrazoxane treated patients diagnosed with low-risk acute lymphocytic leukemia (LR-ALL) were likely to experience a delay in treatment due to both low ANC (p=0.0001) and the development of FN (p=0.02) whereas high-risk acute lymphocytic leukemia (HR-ALL) patients were likely to experience treatment delays due to thrombocytopenia (p=0.03), low ANC (p=0.0001) and FN (p=0.0001). Despite finding no significant differences regarding the efficacy of dexrazoxane as a cardio-protectant, we have shown that its use induces non-cardiac toxicities in children with cancer that contribute to treatment delays.

Introduction

In Canada, approximately 1700 children are diagnosed with cancer each year¹. Observed 5-year survival rates are approximately 78%^{1,2}. Therapies used to treat children with cancer can have long-lasting effects that cause serious health complications during survivorship and efforts are ongoing to try and minimize the consequences of delayed treatment toxicities³. Of particular significance, is the effect of cumulative dose of anthracyclines on cardiac function⁴.

Doxorubicin and daunorubicin were among the first anthracyclines to be incorporated into clinical use⁵. Since their discovery, these agents have been used to treat a number of cancers with curative intent. Although effective, anthracyclines are the primary cause of chemotherapy induced cardiotoxicity whose mechanism remains only partially understood with free

radical formation an important contributor^{6,7}. In 2014, Top2 β was shown to be the key mediator of anthracycline induced cardiomyocyte apoptosis and deletion of Top2 β prevented defective mitochondrial biogenesis and reactive oxygen species formation ultimately protecting cardiomyocytes⁸. This process is currently thought to occur at the time of exposure, beginning first at the level of cardiomyocytes and eventually leading to overt heart failure⁹. Therefore, clinical presentation may occur much later than the initial exposure highlighting the importance of either early detection or prevention.

To date, multiple cardio-protectant strategies have been proposed. Some of which include using smaller divided doses of anthracycline, administering concurrent antioxidant drugs or administering medications such as beta-blockers and calcium channel blockers¹⁰⁻¹⁴.

Many of these strategies have minimal efficacy in either primary prevention or improving anthracycline-induced cardiotoxicity¹⁵⁻¹⁷. To date, the only clinically approved cardio-protective agent is dexrazoxane which is a cyclic derivative of ethylenediaminetetraacetic acid (EDTA).

Dexrazoxane readily penetrates cell membranes where it is subsequently hydrolyzed into two active compounds which chelate iron and prevent cardiomyocyte damage by reducing the release of free radicals¹⁸. Multiple studies have evaluated the cardio-protective efficacy of dexrazoxane¹⁹⁻²¹. Chow et al. 2016 found that long-term survivors who received dexrazoxane had more preserved systolic function and reduced myocardial wall stress compared with those who did not receive dexrazoxane²². Others have questioned the safety of dexrazoxane, arguing that it may not only lack cardioprotective properties but may also increase a patient's chance of developing a secondary malignancy or cause delays in treatment due to myelosuppression²³. Whether or not dexrazoxane should be used as a cardioprotective agent remains unclear.

To determine the relative risks and benefits of dexrazoxane use as a cardioprotectant, we retrospectively analyzed pediatric patients who received anthracyclines with or without dexrazoxane at the IWK Health Centre.

Methods

To assess the efficacy and toxicity associated with dexrazoxane, a retrospective, population-based cohort study was completed using chart and database information on children treated with anthracyclines at the IWK Health Centre from 2009-2015. The IWK Health Centre is the only Children's Cancer Centre in Maritime Canada. In 2012, there was a policy change stating dexrazoxane was no longer to be administered to children receiving less than 300 mg/m² cumulative dose of anthracycline. Prior to this change, all patients receiving >150 mg/m² cumulative anthracycline dose and all those less than 5 years old received dexrazoxane. The cardiotoxic index, or doses of anthracycline used was daunorubicin and doxorubicin 1:1, mitoxantrone 4:1 and idarubicin 5:1.

Data was collected from several databases including, 1) the IWK oncology patient database 2) the IWK pharmacy drug database and chart system; used to collect information on anthracycline and dexrazoxane exposure and 3) the IWK cardiology echocardiography database; used to provide information on cardiac size and function measurements for the participants identified.

Toxicity of dexrazoxane was defined as chemotherapy delays (by 3 days or more) from any of: decreased

absolute neutrophil count (ANC), decreased platelets, increase in viral/bacterial episodes and febrile neutropenia (FN) episodes. Viral/bacterial episodes are defined by a positive culture or PCR positive. ANC is defined as the sum of the counts of mature neutrophils and band forms. Febrile neutropenia is defined as an absolute neutrophil count (ANC) less than 0.5 x 10⁹/L and a fever of 38.3°C or oral or tympanic temperature greater than or equal to 38°C for 1 hour or more. The efficacy of dexrazoxane was defined as a lack of undesirable deviations in identified cardiac parameters on echocardiogram (ECHO) associated with anthracycline toxicity. These included decreased ejection fraction (LVEF), decreased fractional shortening (LVFS), increased LV mass (g/m²) and increased z-scores (>2) for left ventricular internal diameter at end diastole and systole (LVIDd, LVIDs) or decreased z-scores (<-2) for left ventricular posterior wall thickness at end diastole (LVPWD). A reduction in left ventricular ejection fraction (<55%) or shortening fraction (<30%) or the presence of symptomatic cardiotoxicity was used as a threshold for defining cardiac toxicity of anthracyclines.

We collected all available information regarding the outcomes listed above. Information was available on a total of 136 patients which were stratified into groups based on the total dose of anthracycline received.

All efficacy outcomes were measured either 1) after anthracycline treatment (LV mass, LVEF, LVFS) or, 2) both before and after anthracycline treatment (LVIDd, LVIDs, LVPWD). The outcomes measured after treatment were plotted using the raw scores reported by echocardiography databases. The outcomes measured before and after treatment were plotted using z-scores to determine whether there was a significant change from baseline in these variables post anthracycline treatment.

Statistics

All graphs were made using GraphPad Prism 4 Software. In all cases where efficacy is analyzed a non-parametric Wilcoxin-Mann-Whitney t-test was used comparing patients who received solely anthracycline (either <150, 150-250 or >250mg/m²) and those who received both anthracycline and dexrazoxane. Stars indicate the strength of the relationship (p<0.05*, p<0.01**, p<0.001***).

Toxicity information was available for a total of 177 patients (including the 136 used for efficacy analysis). First, we analyzed all 177 patients regardless of dexrazoxane administration to look for toxic effect differences between patients receiving various doses of anthracycline. Next, we separated the patients into, 1) patients who received dexrazoxane as well as anthracy-

cline (<150mg/m², 150-250mg/m² or >250mg/m²) and 2) those who received anthracycline only (<150mg/m², 150-250mg/m² or >250mg/m²) to isolate whether patients receiving dexrazoxane experienced significantly more toxic effects than those who did not.

All graphs were made using GraphPad Prism 4 Software or Excel. In all cases where toxicity is analyzed between two or more groups a Kruskal-Wallis ANOVA test with a Dunn's post hoc test was used. To analyze whether patients diagnosed with LR-ALL and HR-ALL exposed to dexrazoxane experienced significantly more treatment delays than dexrazoxane naïve patients, a one-sample Wilcoxon signed rank t test was conducted comparing the number of patients who experienced delays against the null hypothesis which states patients who are treated with dexrazoxane do not experience more treatment delays compared to their untreated counterparts. Stars indicate the strength of the relationship (p<0.05*, p<0.01**, p<0.001***).

Results

The patients included in this study total 178, with a M:F ratio of 41:48. The average age at diagnosis between patients who received dexrazoxane, and those who did not was similar at 7.9 and 7.6 years, respectively. Most patients included in this study were diagnosed with either high-risk or low-risk acute lymphocytic leukemia (HR-ALL, LR-ALL) (Table 1).

We analyzed the efficacy and toxicity of dexrazoxane for patients who received: 1) less than 150mg/m², 2) between 150-250mg/m² and 3) more than 250mg/m² of anthracycline. For statistical strength, multiple diagnoses were included in each group. For example, most patients who received between 150-250mg/m² of anthracycline were diagnosed with HR-ALL, lymphoma, neuroblastoma, or a Wilms tumor. Of all the patients included, 45% received dexrazoxane and 55% did not. Most patients who received dexrazoxane were treated with either 150-250mg/m², or more than 250mg/m² of anthracycline whereas patients who did not receive

dexrazoxane were mostly treated with <150mg/m² of anthracycline.

To analyze the cardioprotective-related efficacy of dexrazoxane, the cumulative amount of anthracycline per patient was obtained and plotted against the following cardiac parameters: 1) LVEF, 2) LVFS, 3) LVID-d/s, 4) LVPWD, and 5) LV mass. All efficacy readouts were recorded during follow-up appointments which occurred 2.4 years, and 3.4 years in the dexrazoxane-naïve and dexrazoxane treated patients, respectively (Table 1). We expected to see better long-term cardiac outcomes in patients who received dexrazoxane but found no significant relationships regarding cardiac function in the dexrazoxane-naïve and dexrazoxane treated groups (Figure 1).

To analyze the toxicity of dexrazoxane administration, we monitored 1) platelet counts, 2) neutrophil counts, 3) development of febrile neutropenia, and 4) development of infection during each patient's chemotherapy regimen. Based on the cumulative anthracycline dose received, we found no significant difference regarding neutrophil counts, the development of either febrile neutropenia or infection between patients who received dexrazoxane and those who did not (Figure 3). We did, however, find regardless of whether a patient has received dexrazoxane, as the dose of anthracycline increases, there are more platelet delays (Figure 2Ai). Whether this was an effect of anthracycline or dexrazoxane remained unclear. Therefore, we analyzed these groups separately. Patients who received both anthracycline and dexrazoxane had significantly more platelet delays (Figure 2Aii). This relationship did not hold true for patients who received solely anthracycline suggesting that dexrazoxane could be the cause of platelet delays (Figure 2Aiii). These results also show that there are significantly more platelet delays between patients who received 150-250mg/m² and those who received >250mg/m² when dexrazoxane is administered (Figure 2Aii). However, this relationship does not exist when patients are treated with anthracycline alone (Figure

Table 1. Patient Demographics.

	Treated with Dexrazoxane (n=79)	Untreated with Dexrazoxane (n=99)
Female	44/96 (46%)	52/96 (54%)
Male	35/82 (43%)	47/82 (57%)
Average Age at Diagnosis	7.9 years	7.6 years
Average Follow Up Time	2.4 years	3.4 years
Diagnosis:		
HR-ALL	26/48 (54%)	22/48 (46%)
LR-ALL	12/48 (25%)	36/48 (75%)
AML	4/11 (36%)	7/11 (63%)
NHL/HL	6/31 (19%)	25/31 (81%)
Neuroblastoma/WILMS	6/14 (43%)	8/14 (57%)
Sarcoma	25/26 (96%)	1/26 (4%)

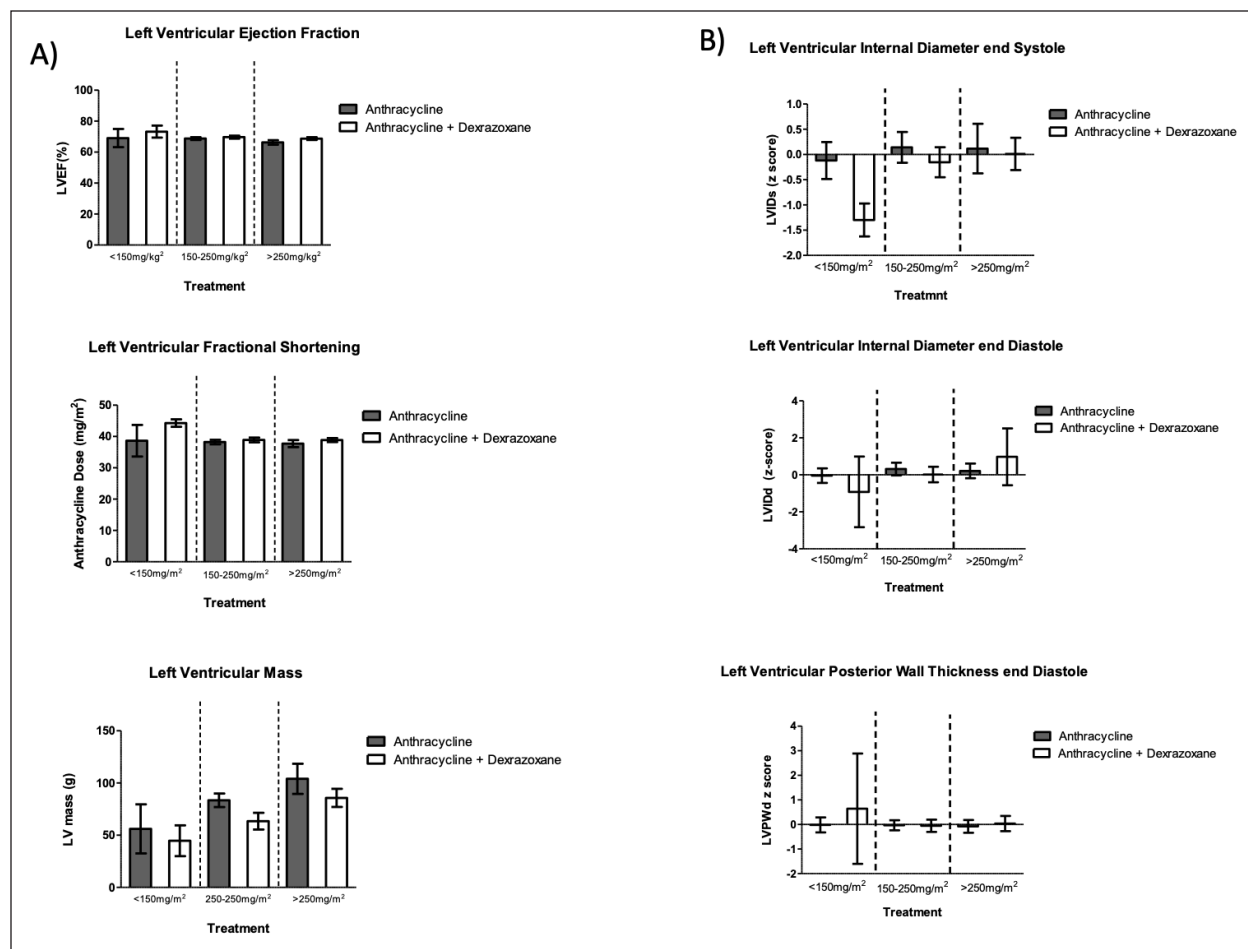


Figure 1. Pediatric patients who receive dexrazoxane do not have better long-term cardiac outcomes compared to patients who did not regardless of total anthracycline dose. (A) Left ventricular ejection fraction (LVEF), left ventricular fractional shortening (LVFS) and left ventricular mass values were recorded from patient charts over time. Patients were stratified into groups based on total anthracycline received. The average LVFS, LVEF and LV mass were plotted (ntotal=136; n<150=39, n150-250=56, n>250=41). (B) Left ventricular internal dimension at end systole (LVIDS), left ventricular internal dimension at end diastole (LVIDd) and left ventricular posterior wall thickness at end diastole (LVPWd) were recorded before and monitored overtime post-treatment. Z-scores were plotted against the total dose of anthracycline received (ntotal=136; n<150=39, n150-250=56, n>250=41).

2Aiii). We also found that patients receiving >250mg/m² anthracycline as well as dexrazoxane have significantly more cases of thrombocytopenia leading to treatment delays than their untreated counterparts (Figure 2B).

We also analyzed toxicity read outs based on diagnosis. The most common diagnoses in this patient cohort were LR-ALL (n=48) and HR-ALL (n=48). Of all patients in the LR-ALL group that were treated with anthracycline and dexrazoxane, 83% and 75% of patients experienced a treatment delay due to low ANC and the development of FN, respectively (Table 2). In the HR-ALL group, we find similar results where 84% and 80% of patients treated with anthracycline and dexrazoxane experienced treatment delay due to low ANC or the development of FN, respectively (Table 3).

Discussion and Conclusion

Anthracyclines have been shown to increase the risk of congestive heart failure and dilated cardiomyopathy in pediatric patients^{10,24,25}. Despite this, they remain the drug of choice for many cancer types due to their efficacy²⁶. Due to an increase in the number of children expected to live decades post-anthracycline exposure, there has been an emphasis on developing methods to reduce and/or prevent anthracycline-induced cardiotoxicity^{27,28}.

To date, dexrazoxane is the only cardioprotective agent that has been shown to protect against long-term anthracycline induced cardiotoxicity²⁹. In children, dexrazoxane was contraindicated mainly due to concerns regarding the development of second primary malignancies which was refuted in 2017^{30,31}. Currently, it is suggested that children aged 0-18 expected to

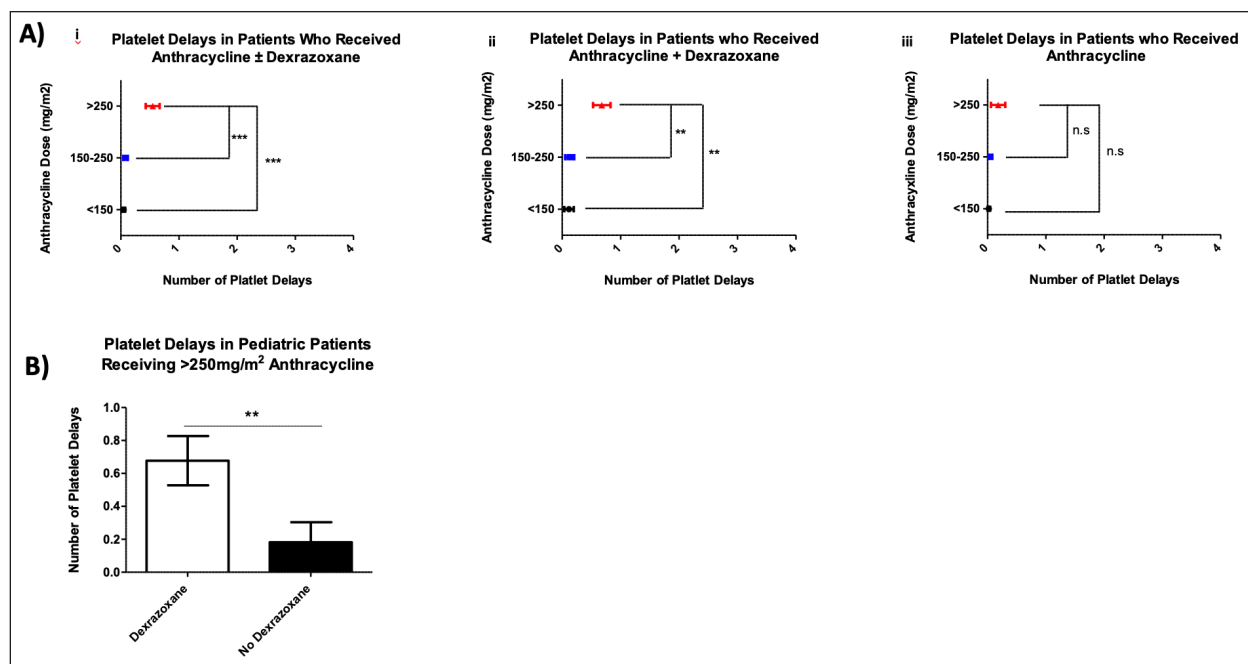


Figure 2. Pediatric patients who receive dexrazoxane are more likely to experience platelet delays compared to their untreated counterparts. (Ai) Platelet counts were recorded from patients receiving anthracyclines with or without dexrazoxane. Platelet delays were then plotted based on cumulative anthracycline dose, (ntotal=178; n<150=63, n150-250=73, n>250=42). (Aii) Platelet counts were recorded solely from patients receiving anthracycline with dexrazoxane. Platelet delays were then plotted based on cumulative anthracycline dose, (ntotal=79; n<150=17, n150-250=31, n>250=31). (Aiii) Platelet counts were recorded from patients receiving anthracycline only. Platelet delays were then plotted based on cumulative anthracycline dose, (ntotal=98; n<150=46, n150-250=41, n>250=11). (B) The number of platelet delays experienced by patients receiving >250mg/m² anthracycline who did and did not receive dexrazoxane (ndex=31; nnodex=11). Platelet delays were defined as counts < 75,000, p<0.05=*, p<0.01=**, p<0.001=***.

receive a cumulative dose of anthracycline >300mg/m² should receive dexrazoxane. There is limited long-term data regarding the impact of dexrazoxane on cardiac and non-cardiac function with many arguing for its use in children and the minority cautioning it^{19,20,22,23,32-38}. In this study, we focused specifically on the efficacy and toxicity of dexrazoxane use in pediatric cancer patients at the IWK Health Centre.

Dexrazoxane has been shown to be cardioprotective when administered in conjunction with >300mg/m² cumulative anthracycline in adults with breast, non-small cell lung cancer, and sarcomas³⁹⁻⁴². We found no significant differences in cardiac function (measured by LVEF and LVFS) between dexrazoxane treated and dexrazoxane-naïve patients despite the cumulative dose of anthracycline received. Lipshutz et al. 2015 showed that the use of dexrazoxane in addition to doxorubicin in ALL patients resulted in a more normal end-systolic dimension and end diastolic thickness-to-dimension at 2- and 3-year follow-up respectively. Although not significant due to the number of patients analyzed, we found that end-systolic and diastolic dimension may be improved using dexrazoxane in patients who receive <150mg/m² of anthracycline but not in those receiving more. Like Lipshutz et al. 2015 we found no significant differences regarding LV mass or LVFS.

Studies regarding non-cardiac toxicities of dexrazoxane have focused on the risk of hepatotoxicity, myelosuppression and pulmonary fibrosis⁴³. Furthermore, a phase II trial studying dexrazoxane in children suggests that studies looking at the cardioprotective effects of dexrazoxane use much lower doses than the maximum tolerated dose which is often given depending on the institution and clinical context. Therefore, non-cardiac toxicities may be underreported.

We add to this literature showing that pediatric patients who receive dexrazoxane and >250mg/m² of anthracycline are more likely to experience severe thrombocytopenia. This finding can be supported by the BC Cancer Agency which states that approximately 10% of patients treated with dexrazoxane will experience severe thrombocytopenia⁴⁴. Toxicities often effect the timing of treatment administration. Our study shows the toxicity associated with dexrazoxane use impacts the timing of chemotherapy administration. Children who receive dexrazoxane are more likely to have a treatment delay due to thrombocytopenia induced by dexrazoxane. In patients diagnosed specifically with LR and HR-ALL we show that the use of dexrazoxane may lead to a higher risk of developing febrile neutropenia as well as low ANC counts leading to delays in treatment.

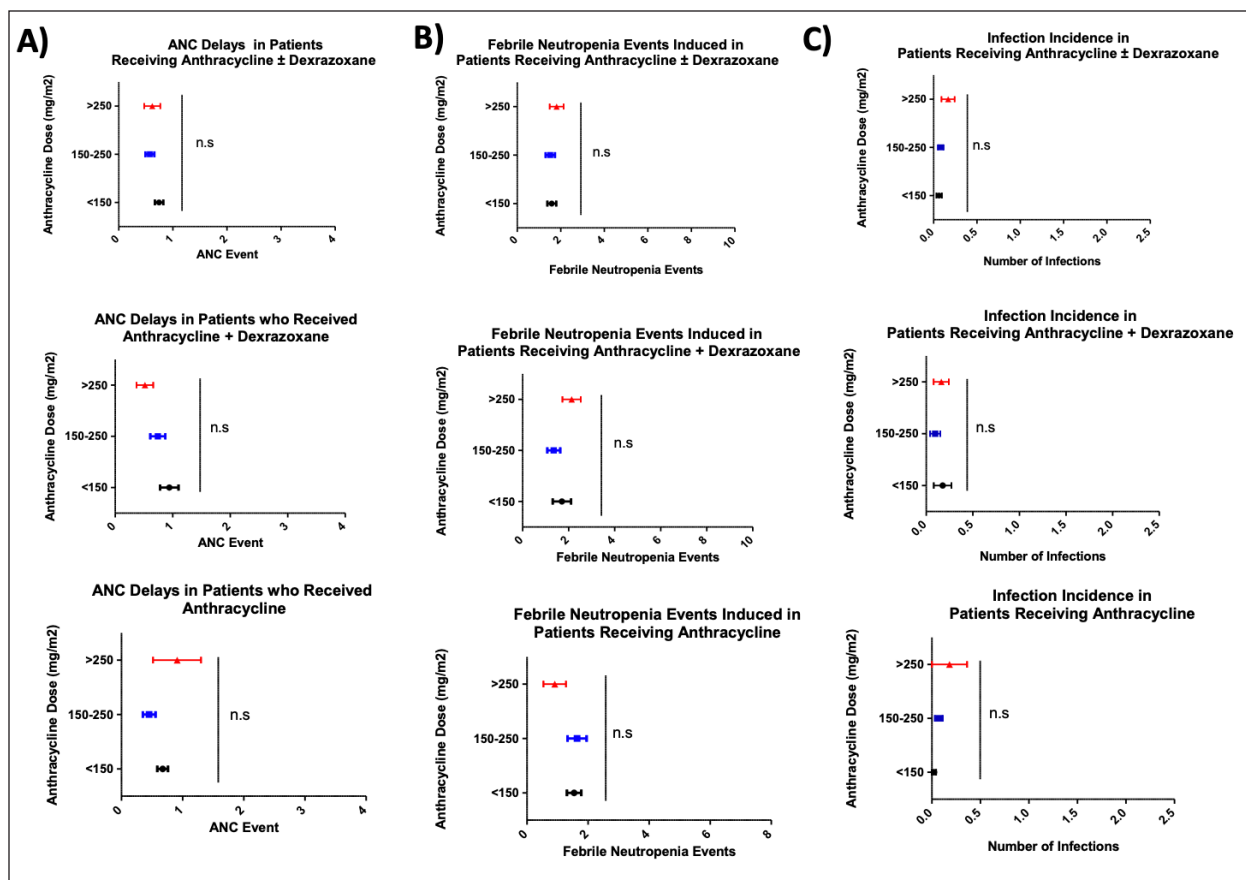


Figure 3. Pediatric patients who receive dexrazoxane are more likely to experience platelet delays compared to their untreated counterparts. (Ai) Platelet coPatients receiving dexrazoxane and anthracycline did not experience more treatment delays due to low ANC, FN or infection. (A) Neutrophil counts were recorded from patients receiving anthracyclines with or without dexrazoxane. Neutrophil delays were then plotted based on cumulative anthracycline dose, (ntotal=178; n<150=63, n150-250=73, n>250=42). Platelet/Neutrophil counts were recorded solely from patients receiving anthracycline with dexrazoxane. Platelet delays were then plotted based on cumulative anthracycline dose, (ntotal=79; n<150=17, n150-250=31, n>250=31). Platelet/Neutrophil counts were recorded from patients receiving anthracycline only. Neutrophil delays were then plotted based on cumulative anthracycline dose, (ntotal=98; n<150=46, n150-250=41, n>250=11). Neutrophil delays were defined as <100, 000. (B/C) The number of times a patient experienced febrile neutropenia/got an infection were recorded from patients receiving anthracycline with or without dexrazoxane. The number of febrile neutropenia events/infections were then plotted based on cumulative anthracycline dose, (ntotal=178; n<150=63, n150-250=73, n>250=42). The number of times a patient experienced febrile neutropenia/got an infection were recorded from patients solely receiving anthracycline with dexrazoxane. The number of febrile neutropenia events/infections were then plotted based on cumulative anthracycline dose, (ntotal=79; n<150=17, n150-250=31, n>250=31). The number of times a patient experienced febrile neutropenia/got an infection were recorded from patients solely receiving anthracycline. The number of febrile neutropenia events/infections were then plotted based on cumulative anthracycline dose, (ntotal=98; n<150=46, n150-250=41, n>250=11), p<0.05=*, p<0.01=**, p<0.001=***.

Table 2. Patients diagnosed with LR-ALL and treated with dexrazoxane experience more delays in treatment due to low ANC count and the development of FN.

	Delay	No Delay	p-value
Platelet	1/12 (8%)	11/12 (92%)	0.3388
ANC	10/12 (83%)	2/12 (17%)	<0.0001
FN	9/12 (75%)	3/12 (25%)	0.02
Infection	2/12 (17%)	10/12 (83%)	0.1661

A one-sample Wilcoxon signed rank t test was conducted comparing the number of patients who experienced delays against the null hypothesis which states patients who are treated with dexrazoxane do not experience more treatment delays compared to their untreated counterparts, <0.05=*, p<0.01=**, p<0.001=***.

Table 3. Patients diagnosed with HR-ALL and treated with dexrazoxane experience more delays in treatment due to low ANC count and the development of FN.

	Delay	No Delay	p-value
Platelet	5/25 (20%)	20/25 (80%)	0.03
ANC	21/25 (84%)	4/25 (16%)	<0.0001
FN	20/25 (80%)	5/25 (20%)	<0.0001
Infection	2/25 (8%)	23/25 (92%)	0.1615

A one-sample Wilcoxon signed rank t test was conducted comparing the number of patients who experienced delays against the null hypothesis which states patients who are treated with dexrazoxane do not experience more treatment delays compared to their untreated counterparts, <0.05=*, p<0.01=**, p<0.001=***.

In conclusion, we argue that 1) the benefits of dexrazoxane administration need to be more clearly elucidated depending on the cumulative dose of anthracycline received and 2) more follow up studies should be done in patients who experienced a treatment delay due to dexrazoxane toxicity to assess long term outcomes. In this study however, we suggest that the use of dexrazoxane should be cautioned in pediatric oncology patients especially those receiving >250mg/m² of cumulative anthracycline.

Limitations

A limitation of this study is the use of echocardiogram (ECHO) which shows subjective changes and is reliant on the reporter. Nonetheless, ECHO remains the best method of measuring cardiac dysfunction. LVEF and LVFS are currently used in clinical practice to modify doses of anthracyclines and as such were the parameters that were captured in this study. In addition to this, the heterogeneity of anthracycline choice was not taken into consideration here. Much of the literature supporting the use of dexrazoxane in children focuses on the use of dexrazoxane when administered with doxorubicin. In addition, we only assessed cardiac outcomes 2-3 years post-anthracycline administration. For this reason, it is possible that we are missing patients who ultimately will experience late cardiotoxicity.

Other limitations of this study are that we did not capture concomitant therapies such as chest radiation and cardiac toxic chemotherapy, the study included subjective reporting of patient chart/database information based on the completeness of the available files and due to small sample size, we were unable to capture the effects of dexrazoxane use on solid tumors. We also note that there are multiple variables that limit our ability to make conclusions such as the wide range of patients included. However, we feel that we have contributed to literature that questions the use of dexrazoxane in children with cancer.

Appendix A

Anthracycline dosing of all patients divided by diagnosis. Patients diagnosed with LR-ALL (n=48), HR-ALL (n=48), AML (n=11), lymphoma (n=31), neuroblastoma/Wilms (n=14) and sarcoma (n=25) received differing doses of anthracycline.

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