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# Dexrazoxane decreases the cardiotoxic effects of doxorubicin in osteosarcoma patients without increasing mortality from secondary malignant neoplasms

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**ABSTRACT** A clinical decision report appraising:

Schwartz CL, Wexler LH, Krailo MD, et al. Intensified chemotherapy with dexrazoxane cardioprotection in newly diagnosed nonmetastatic osteosarcoma: A report from the Children's Oncology Group. *Pediatr Blood Cancer*. 2016;63(1):54-615.  
<https://doi.org/10.1002/pbc.25753>

for a patient with osteosarcoma and concerns about the risk of secondary malignant neoplasms that attend use of dexrazoxane.

**Keywords:** dexrazoxane, doxorubicin, cardiotoxicity, osteosarcoma

## Clinical-Social Context

James Stevenson (pseudonym) is a 17-year-old male who presented to the emergency department with his mother after a 2-month history of aching right humerus pain that has suddenly become severe after a basketball game. The pain is unrelieved by ibuprofen and plain radiographs indicate a gross fracture of the proximal humerus with lytic lesions and a raised periosteum despite no reported trauma. MRI revealed a sclerosing mass that was subsequently biopsied which confirmed osteosarcoma which carries a roughly 35% five year all-cause mortality despite best treatment.<sup>1</sup> Further work-up with abdominal and chest CT revealed no metastases. Mr. Stevenson is due to begin chemotherapy with later evaluation for resection. His scheduled chemotherapy medications are: ifosfamide 1.8 g/m<sup>2</sup>/d x5 days (with MESNA rescue), cisplatin 60 mg/m<sup>2</sup>/d x2 days, methotrexate high-dose 12 g/m<sup>2</sup> (with leucovorin rescue), and doxorubicin 37.5 mg/m<sup>2</sup>/d x2 days. Mr. Stevenson is an only child and lives with his single mother. Mr. Stevenson and his mother were counselled on the potential side effects of the medication including the risk of cardiotoxicity of doxorubicin causing late dilated cardiomyopathy. Mr. Stevenson's mother was concerned as Mr. Stevenson's father passed away from an MI at age 54. Moreover, Mr. Stevenson wishes to return to basketball as soon as possible and does not want a failing heart to impair his ability to be active. Mr. Stevenson is academically an A student and wishes to study Kinesiology in university.

Dexrazoxane is a cardioprotective agent against doxorubicin (an anthracycline) by acting as an iron chelator, hence reducing doxorubicin induced free radical damage.<sup>2</sup> However, dexrazoxane can increase the risk of secondary malignant neoplasms (SMN) and is banned in Europe for use in children.<sup>2,3</sup> The healthcare team weigh the harm versus benefit of administering dexrazoxane given a scarce literature on this rare disease. Given his family history and desire for an active lifestyle, the healthcare team is inclined to add dexrazoxane to his chemotherapeutic

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regimen but are unsure given its potential risks. When speaking to the physician about dexrazoxane's potential side-effects, Mr. Stevenson becomes concerned about not being able to play basketball at a competitive level, while his mother worries about the risk of cancer returning should he take dexrazoxane.

## Clinical Question

In reducing the cardiac toxicity of doxorubicin in patients with osteosarcoma, does dexrazoxane increase the chance of secondary malignant neoplasm?

## Research Article

Schwartz CL, Wexler LH, Krailo MD, et al. Intensified chemotherapy with dexrazoxane cardioprotection in newly diagnosed nonmetastatic osteosarcoma: A report from the Children's Oncology Group. *Pediatr Blood Cancer.* 2016;63(1):54-615. <https://doi.org/10.1002/pbc.25753>

## Description of Related Literature

Using the following pub med search terms: "doxorubicin AND dexrazoxane AND osteosarcoma AND [secondary malign\*]", a single article was returned. PMID: 17290056 this raised the possibility of secondary malignancy, but the topic is controversial. PMID: 17634500 The rebuttal by Lipshultz and Lipsitz et al. delves into the statistical gymnastics used to raise the concern for secondary malignancies. Only meta-analysis, retrospective or prospective cohorts and randomized controlled trials (RTC) were considered. Studies that focused exclusively on osteosarcoma cardio protection were prioritized over other childhood malignancies. Case studies and studies that focused on patients with underlying cardiac comorbidities, congenital defects, or genetic abnormalities (Down's Syndrome), were excluded.

The two most recent meta-analyses conducted were in 2018 by Liesse et al.<sup>4</sup> and 2016 by Shaikh et al.<sup>2</sup> In Liesse et al. 2018, the team assessed whether dexrazoxane in combination with anthracyclines will reduce cardiotoxicity in pediatric solid tumor patients. Liesse et al. began with 4213 search results and chose only 22 RTCs, prospective and retrospective cohorts to be included in their study. Of the 22 studies (n=4782), 14 focused on osteosarcoma (n=2813). This study was thorough in its selection criteria and had no evidence of bias. Study outcomes were cumulative anthracycline dose, incidence and early versus late onset of cardiotoxicity, tumor response, overall 5-year survival and event-free survival. Cardiotoxicity was defined as a left ventricular shortening fraction of <28% or a 10% decline from baseline. Liesse et al. found that although dexrazoxane administration did decrease overall rates of cardiotoxicity, the rate of cardiotoxicity increased over 20 years for those treated with and without dexrazoxane. Shaikh et al. yielded 17 RTCs and cohort studies noting that none were blinded as a source of bias. All types of pediatric cancer were included, and outcomes of cardiotoxicity and SMN were measured. Shaikh et al. determined that while dexrazoxane did reduce anthracycline cardiotoxicity, it also had a borderline increase in SMN. Using these meta-analyses and search criteria, other notable studies were identified: Filomena et al. 2020<sup>5</sup>, Huh et al. 2010<sup>6</sup>, Matos Neto et al. 2006<sup>7</sup>, Getz et al. 2020<sup>8</sup>, Kopp et al. 2019<sup>9</sup>, and Schwartz et al. 2016<sup>10</sup>.

Filomena et al. conducted prospective cohort study of 20 patients treated with anthracycline and dexrazoxane and 20 healthy controls. The primary outcome were all-cause mortality and cardiotoxicity (ejection fraction, EF <50%). No statistically significant differences were noted between the two groups. Notably, this study did not include an anthracycline only cohort and was not blinded.<sup>5</sup>

Huh et al. conducted a retrospective cohort study of 63 patients with either Ewing's or osteosarcoma and assessed cardiotoxicity (EF <50%) with and without the administration of dexrazoxane. Huh et al. concluded that dexrazoxane treated patients did have a statistically significant higher EF than those on anthracycline alone (59.1% vs 55%), however these differences may not be clinically significant. The primary limitation of this study is the lack longer term follow up and varying treatment protocols used. Moreover, it does not address any potential risk of SMN.<sup>6</sup>



Matos Neto et al. conducted a prospective non-randomized study of 55 patients with osteosarcoma to assess cardiac dysfunction (shortening fraction, SF<29%) in those treated with and without dexrazoxane. The authors concluded that those who were treated with dexrazoxane did have limited improvements in cardiac function at 3 timepoints.<sup>2</sup> The study did not address SMN and all timepoints were within the same year of treatment and not long-term and hence not useful in answering Mr. Stevenson's case.

Getz et al. completed the most recent trial of dexrazoxane cardioprotection by assessing EF (<55%) and SF (<28%) in 1014 patients with acute myeloid leukemia (AML) in multicenter prospective cohort study. Dexrazoxane treated patients had preserved EF and SF and similar 5 year event free survival as those treated with anthracyclines alone.<sup>8</sup> While this study is of extremely high quality, the lack of osteosarcoma patients limits its use due to differing tumor pathologies and treatment protocols.

Kopp et al. conducted a retrospective study of 2 cohorts assessing dexrazoxane cardioprotection and SMNs in patients with osteosarcoma who were being treated with doxorubicin or trastuzumab. The cohorts were drawn from Schwartz et al.<sup>10</sup> and Ebb et al.<sup>11</sup> Using 316 patients between the two studies, Kopp et al. determined that LV dysfunction was prevented by dexrazoxane and did not see an increase in SMN associated with its use. Due to this study including trastuzumab treated patients, this study would not be appropriate to Mr. Stevenson's case.

Schwartz et al. completed their prospective cohort study of 242 patients with osteosarcoma to assess the effect of dexrazoxane on those treated with high dose anthracycline medication for anti-tumor efficacy (via histology), cardioprotection, and SMNs. They determined that treatment with dexrazoxane did not increase the chance of SMNs and was cardioprotective, with no patients having severe LV dysfunction (grade 3-5).<sup>10</sup> This paper was determined to have a 2B level of evidence according to the Oxford Centre for Evidence-based Medicine Levels of Evidence.<sup>12</sup>

## Critical Appraisal

Schwartz et al. conducted a prospective cohort study of 242 patients being treated for osteosarcoma. The study is a combination of three pilot trials of dexrazoxane being used in combination with MAP or MAPI (methotrexate, doxorubicin, cisplatinum + ifosfamide) chemotherapy. In these pilots, patients were treated for 10 weeks with chemotherapy plus dexrazoxane and subsequently underwent resection at week 11. The resected sample was analyzed histologically for tumor necrosis and those with >2% tumor viability were deemed standard responders (SR) and those with <2% were good responders (GR). Following resection, GR's were given an additional 15 weeks of chemotherapy and the SR's were given 23 weeks of high dose doxorubicin (600 vs 450mg/m<sup>2</sup>) or etoposide/ifosfamide. Patients were monitored for using the previously validated NCI Common Toxicity Criteria V2. Echocardiograms to measure cardiac dysfunction (FS<28%) were done at baseline before chemotherapy, during therapy and 3, 30, and 60 months post therapy.<sup>10</sup>

Event free survival (EFS) and overall survival (OS) were considered as outcomes in addition to the incidence of SMN. The study had a limit of <3 patients among the SR's to be diagnosed with clinical heart failure which would have identified 94% of heart failure if the true rate is 1%. All echocardiograms were remeasured at a central site and FS z scores were calculated with standard age-sex adjusted methods for all patients at 78 weeks post diagnosis.

There was no significant change in FSZ (p=0.85) after induction therapy through week 78 with only 5 patients having mild LV dysfunction and none with heart failure. scores decreased with time since enrollment by a range of 0.9 standardized units per year. Patients on standard therapy versus intensification did not alter the decline in FSZ. Overall, the total incidence of SMNs after 6 years was 0.4%. The 4-year OS was 74% (95%CI: 68–79%) with no statistical difference in OS among the three pilots (p=0.38). OS was 93% (95%CI 83–97%) for GR patients versus 75% for SR (95%CI 67–82%). For Mr. Stevenson, these results are reassuring that an increased doxorubicin dose is not associated with increased cardiotoxicity versus standard dose when combined with dexrazoxane. Moreover, the SMN and treatment efficacy was not associated with dexrazoxane.

With sample size in pediatric cancer being challenging, providing 242 patients in a single study bolsters Schwartz et al.'s use in Mr. Stevenson's case. Furthermore, there is no evidence of selection bias and the reported effect size needed was 12 in the first pilot and 27 in the first 2 pilots. The study also largely patient centered, focusing heavily on symptomatology. Lastly, by remeasuring echocardiograms at a central location, this removes a large degree of inter-rater variability error.



The main limitation of this study in Mr. Stevenson's case is its lack of a doxorubicin only control group. The authors justify this by the already proven response to doxorubicin treatment without dexrazoxane. While this is reasonable, a control group would have given the further strength to the authors conclusions. Moreover, there was a lack of blinding in the echocardiograms and echocardiogram raters may have been biased to patients in the SR and GR arms. Lastly, echocardiograms were used up to 78 weeks after induction therapy but were due to be captured 60 months post therapy. This long-term data has yet to be reported and would provide important long term cardiotoxic data for Mr. Stevenson.

### Clinical Application

17-year-old Mr. Stevenson is an active young man with newly diagnosed osteosarcoma of the proximal right humerus who is unsure if the benefits of dexrazoxane cardioprotection outweigh its harms. The literature seems to indicate that dexrazoxane effectively decreases the likelihood of cardiotoxicity from doxorubicin and does not increase risk of SMN nor alter treatment efficacy. In the case of Mr. Stevenson, the decision to use dexrazoxane cardioprotection for each dose of doxorubicin was made to best preserve his cardiac function and his desire for an active lifestyle.

### New Knowledge Related to Clinical Decision Science

Clinical decision science is based on a patient centered approach and is to be informed by the available literature. In the current case, Mr. Stevenson wishes to continue to play basketball, but the realities of treatment (particularly surgery) make this challenging. Simultaneously, his mother worries about his risks of SMN with dexrazoxane. To balance these risks the oncology team took the approach of open communication, being honest about the uncharted territory, and explaining why they recommend dexrazoxane given Mr. Stevenson's clinical context. Both he and his mother will never be truly free from the anxiety associated with the uncertainty of this diagnosis, but honest communication is in the patient's best interest. We provided them with the reassurance that he was always at the center of the decision-making process. Because basketball is a team sport, we inquired how he wanted to handle the information sharing aspect of his diagnosis with his teammates. Because his family size is small, teammates, friends, and the social organization of high school sports teams are a potential resource to this family as they approach a difficult treatment course.

### Conflict Of Interest Statement

The author reports no conflict of interest. While Dr. Lipshultz is a former faculty member at Wayne State University School of Medicine, he has never worked with the author directly or indirectly. At the time of manuscript creation, Dr. Lipshultz was no longer faculty at Wayne State.

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