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Review

# Dexrazoxane for reducing anthracycline-related cardiotoxicity in children with cancer: An update of the evidence

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ABSTRACT

Advances in treating childhood cancers over the past 40 years have more than doubled 5-year survival rates. More effective use of chemotherapeutic agents has been key to this success. However, the increase has come at a price: chronic conditions are significantly more prevalent in long-term survivors of childhood cancer than they are in the general population, and managing these survivors can be challenging. In patients receiving anthracyclines, cardiotoxicity is the leading cause of morbidity and mortality after relapse and second malignancies. More than 50% of patients exposed to anthracyclines exhibit some form of cardiac dysfunction within 20 years after completing chemotherapy, and about 5% develop heart failure. These conditions greatly reduce the quality of life of the individual and also consume substantial amounts of healthcare resources. Dexrazoxane has been used to reduce anthracycline-related cardiotoxicity in children with cancer, but in 2011, the European Medicines Agency determined, on what it acknowledged were limited data, that dexrazoxane was contraindicated in children. Here, we review the evidence for the clinical effects of dexrazoxane in children. Studies published since 2011 have confirmed the efficacy of dexrazoxane in preventing or reducing anthracycline-related cardiotoxicity in children with cancer, and no new evidence of increased risks for recurrence of primary or second malignancies, or reductions in antitumor efficacy has been reported. As a result, we believe that dexrazoxane should be available to children with high-risk cancers to reduce the risk of cardiotoxicity associated with high-dose anthracycline treatment.



## 1. Introduction

Advances in cancer treatment have markedly improved oncological outcomes for most childhood cancers, to a point where over three-quarters of those treated will still be alive in 5 years. However, one repercussion of this success is a marked increase in health problems related to anthracycline-induced cardiotoxicity that can present even decades after treatment [1]. After cancer relapse and secondary malignancies, cardiovascular-related problems are the leading cause of morbidity and mortality in childhood cancer survivors [2,3]. Cardiotoxicity is a limiting adverse consequence of cancer chemotherapy, and its management is pivotal to the survival, overall quality of life, and well-being of these patients.

Dexrazoxane has been used to reduce anthracycline-related cardiotoxicity in children with cancer. In 2011, the Committee for Medicinal Products for Human Use (CHMP) [European Medicines Agency (EMA)] evaluated what it acknowledged were limited data relating the use of dexrazoxane to prevent anthracycline (such as doxorubicin)-induced cardiotoxicity in children [4]. This risk-benefit assessment was triggered by early reports suggesting an increase in secondary malignancies, myelosuppression, and infection in children treated with dexrazoxane. In particular, the Committee noted that:

- The efficacy of dexrazoxane in children had not been established.
- Acute myeloid leukemia-myelodysplastic syndrome (AML/MDS) was a potential risk of dexrazoxane treatment.
- Second malignant neoplasms (SMNs) were a potential risk of dexrazoxane treatment.

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The Committee concluded that, "the safety and efficacy of dexrazoxane in children have not been established and that dexrazoxane should therefore not be used in children due to the risk of second malignancies and potentially negative pharmacodynamic interactions with anthracyclines." On the basis of these findings, the EMA recommended that the use of dexrazoxane in children and adolescents up to 18 years of age be contraindicated.

In this literature review we re-evaluate the risk-benefit of dexrazoxane in children and adolescents receiving anthracycline therapy using evidence from studies published after the original 2011 EMA appraisal. A MEDLINE search on the use of dexrazoxane in children identified 77 articles published between January 1, 2011 and September 12, 2014, 15[a] of which are included in this review. Also included are 10[b] presentations from major oncology scientific meetings (e.g. American Society of Clinical Oncology [ASCO] and the European Society of Medical Oncology [ESMO]) and key articles from earlier literature.

## 2. Childhood cancers and anthracyclines: balancing efficacy with longer-term safety

Anthracyclines such as doxorubicin are among common chemotherapeutic drugs used to treat solid and hematological malignancies in children [1,5–7]. In a population-based study in the UK between 1960 and 1999, 5-year survival increased from 23% to 70% (for leukemias it increased from 6% to 74%), and anthracyclines were administered to 50% of children (78% of those with leukemia) [5]. Similar figures have been reported in the US. Since the 1960s, advances in treatment have greatly reduced mortality rates from childhood cancers; the 5-year survival rate is now approximately 80% [8] with rates in excess of 90% being reported for diseases such as acute lymphoblastic leukemia (ALL), Hodgkin lymphoma and Wilms tumor [9]. A large proportion of these patients become long-term survivors [10], with an estimated 1 in 530 young adults aged 20- to 39-years-old identified as childhood cancer survivors [8]. The improved longevity of childhood cancer survivors in the US is highlighted by the fact that in the year 2010, 379,112 patients were still alive and, of these, about 70% were 20 years or older [8].

Several long-term studies have focused on the late effects of cancer treatment including anthracycline therapy. Childhood cancer survivors have a significantly higher risk of premature death than that of the general population, and a wide range of health problems that can reduce their overall well-being and quality of life [1,3,5,11–14]. For example, in the Childhood Cancer Survivor Study (Table 1), a retrospective analysis of 10,397 adult survivors of childhood cancer, 62% of patients had at least one chronic condition, and in 28% of these patients the condition was life-threatening (Grade 3 or 4 toxicity) [12].

Clinical and subclinical cardiovascular damage, heart failure, coronary artery disease, and cerebrovascular events are treatment-related health complications in survivors of childhood cancer [3,5,12,15–17]. Cumulative doses of anthracycline of 300 mg/m$^2$ or higher increase the risk of cardiomyopathy, valve disorders, and conduction abnormalities over that of unexposed survivors; radiotherapy is an added risk factor [18–20]. Heart damage resulting from anthracycline chemotherapy is a serious problem because it reduces quality of life and can lead to premature death. This problem is considered in more depth in the section on the cardioprotective effects of dexrazoxane.

## 3. Anthracycline cardiotoxicity

Long-term cardiovascular complications of cancer therapies are a major concern in survivors of childhood cancer. These complications pose a threat to overall quality of life, but more specifically, as it relates to this review, to the cardiotoxicity associated with anthracycline chemotherapy [1,21,22], with or without radiotherapy [2,23,24]. The cardiotoxicity of anthracycline drugs, such as doxorubicin or daunorubicin, is a major drawback for physicians treating children with cancer because these drugs are associated with an irreversible and dose-dependent loss of cardiomyocytes.

**Table 1**
Prevalence and relative risk of selected severe (Grade 3) or life-threatening (Grade 4) health conditions in 10,397 survivors of childhood cancer, compared with their siblings — diagnosed between January 1, 1970 and December 31, 1986 [adapted from Oeffinger et al. 2006 [12]].

| Health condition | Prevalence, % | Relative risk (95% CI) |
|---|---|---|
| Major joint replacement | 1.61 | 54.0 (7.6 to 386.3) |
| Heart failure | 1.24 | 15.1 (4.8 to 47.9) |
| Second malignant neoplasm | 2.38 | 14.8 (7.2 to 30.4) |
| Severe cognitive dysfunction | 0.65 | 10.5 (2.6 to 43.0) |
| Coronary artery disease | 1.11 | 10.4 (4.1 to 25.9) |
| Cerebrovascular events | 1.56 | 9.3 (4.1 to 21.2) |
| Renal failure | 0.52 | 8.9 (2.2 to 36.6) |
| Hearing loss | 1.96 | 6.3 (3.3 to 11.8) |
| Eye problems | 2.92 | 5.8 (3.5 to 9.5) |
| Ovarian failure | 2.79 | 3.5 (2.7 to 5.2) |

Reported risk factors of cardiotoxicity in childhood cancer survivors include cumulative anthracycline doses greater than 300 mg/m$^2$, combination therapy involving anthracyclines with other toxic drugs such as the topoisomerase II inhibitors (e.g. etoposide), female sex, cardiovascular history, previous cytotoxic therapy, concomitant mediastinal or cranial radiotherapy, younger age at diagnosis, longer follow-up, trisomy 21, and African–American race [17]. The correlation between high cumulative doses of anthracyclines and cardiotoxicity is well established, but lower doses can also be cardiotoxic, with no safe dose established [18]. This was clearly shown in a study specifically designed to evaluate the effects of low-dose anthracyclines ($\leq$100 mg/m$^2$) on LV function in 91 children after a mean of 9.8 years from diagnosis, as a significant proportion demonstrated subclinical abnormalities [25].

The interplay between the various factors that can adversely impact the cardiovascular system of children with cancer, and the type of cardiotoxicity they cause is both complex and poorly understood [26]. A more thorough evaluation of anticancer therapies, including radiotherapy, and the specific cardiovascular changes they are responsible for may help determine the most appropriate diagnostic and screening procedures for childhood cancer survivors [26].

### 3.1. Epidemiology

Formal estimates of the prevalence of cardiotoxicity in children treated with anthracyclines are lacking. Some of the most comprehensive epidemiological data come from population-based studies in Europe and the US [3,5,12,15,27,28]. In the US, for example, the number of childhood cancer survivors was almost 380,000 in 2010, an increase of 15% from the estimated number in 2005 [1,27]. More than 20% had survived for more than 30 years after diagnosis. Survivors of childhood cancer have about a 75% chance of experiencing an eventual treatment-related chronic health problem [12]. Compared with control subjects, survivors are:

- 15 times more likely to have heart failure [12]
- 10 times as likely to experience coronary artery disease [12]
- 9 times as likely to have a cerebrovascular event [12]
- 8 times as likely to die from cardiovascular-related disease [28]

In addition, 30 years after diagnosis, cardiac-related deaths exceed those caused by cancer recurrence [3], and 45 years after diagnosis 13% of excess deaths are cardiac related [29].

[a] 15 Dexrazoxane full references: 1,16–18,22,31,40,43,50,60,70,78,82,83,89.
[b] 10 Dexrazoxane abstract references: 19,35,45,51,52,59,71–73,79.