



# Dexrazoxane in children receiving anthracyclines: efficacy, safety, and region-specific considerations for Latin America

## Review

**Cite this article:** Goldsman A, Stelmaszewski EV, Gonzalez Ortiz A, Prada Casilimas Mdel P, Arevalo Leal O, Biancolini J, Sardella A, Maza Caneva O, Pignatelli R, and on behalf of the working group on paediatric and adolescent cardio-oncology of the paediatric cardiology and ACHD Council, Inter-American Society of Cardiology (SIAC) (2026) Dexrazoxane in children receiving anthracyclines: efficacy, safety, and region-specific considerations for Latin America. *Cardiology in the Young*, page 1 of 4. doi: [10.1017/S1047951126113729](https://doi.org/10.1017/S1047951126113729)

Received: 21 March 2026 UTC

Revised: 23 May 2026 UTC

Accepted: 30 May 2026 UTC




### Keywords:

dexrazoxane; anthracyclines; cardiotoxicity; paediatric oncology; cardioprotection

### Corresponding author:

Alejandro Goldsman;

Email: [agoldsman@hotmail.com](mailto:agoldsman@hotmail.com)

Alejandro Goldsman<sup>1,2</sup> , Erica Victoria Stelmaszewski<sup>3</sup>, Andres Gonzalez Ortiz<sup>4</sup>, Milena del Pilar Prada Casilimas<sup>5</sup>, Oscar Arevalo Leal<sup>6,7</sup>, Julio Biancolini<sup>8,9</sup>, Angela Sardella<sup>1</sup> , Olga Maza Caneva<sup>10</sup> and Ricardo Pignatelli<sup>11,12</sup> , on behalf of the working group on paediatric and adolescent cardio-oncology of the paediatric cardiology and ACHD Council, Inter-American Society of Cardiology (SIAC)

<sup>1</sup>Cardiology, El Hospital de Niños Ricardo Gutierrez, Argentina; <sup>2</sup>Cardiology, CEMIC, Argentina; <sup>3</sup>Cardiology, Hospital de Pediatría Prof Dr Juan P Garrahan, Argentina; <sup>4</sup>Asociación Medica del Centro Medico ABC, Mexico; <sup>5</sup>Clinica Imbanaco, Colombia; <sup>6</sup>Cardiology, Hospital Pediatrico La Misericordia, Colombia; <sup>7</sup>Hospital Universitario Mayor, Colombia; <sup>8</sup>Pediatric Cardiology, Hospital General de Niños Pedro de Elizalde, Argentina; <sup>9</sup>Sanatorio Sagrado Corazón, Argentina; <sup>10</sup>Cardiology, Organización Clínica General del Norte, Colombia; <sup>11</sup>Texas Children's Hospital, USA and <sup>12</sup>Baylor College of Medicine, USA

### Abstract

**Background:** Anthracyclines are indispensable in paediatric oncology but are associated with well-recognised dose-dependent cardiotoxicity that may result in progressive cardiomyopathy and late heart failure. Dexrazoxane has emerged as a potential primary cardioprotective strategy; however, concerns regarding safety, secondary malignancies, and possible interference with antitumour efficacy have historically limited its widespread adoption. **Objectives:** To critically review current evidence regarding the efficacy, safety, and clinical applicability of dexrazoxane in children receiving anthracycline-based chemotherapy, including region-specific implications for Latin America. **Methods:** Narrative review of randomised controlled trials, observational studies, systematic reviews, meta-analyses, and international guideline statements evaluating cardiac outcomes, survival, toxicity profiles, and second primary malignancy risk. **Results:** Dexrazoxane consistently demonstrates cardioprotective effects, including reduced biomarkers of myocardial injury and improved preservation of left ventricular systolic function, particularly among patients exposed to higher cumulative anthracycline doses. Available data indicate no significant adverse impact on relapse rates, event-free survival, or overall survival. Although early studies raised concerns about increased second primary malignancies, subsequent investigations have yielded inconsistent results, leaving residual uncertainty. **Conclusions:** Dexrazoxane represents an effective cardioprotective strategy in selected high-risk paediatric patients. A risk-adapted approach balancing cardioprotection, oncologic safety, and healthcare resources is warranted.

### Introduction

Improvements in the treatment of childhood cancer represent one of the major medical advances of the past 50 years, with 5-year survival increasing from less than 60% to more than 85% today.<sup>1</sup> These advances are largely attributable to improvements in surgery, radiotherapy, and combined chemotherapy, including anthracyclines.<sup>2</sup>

Cardiomyopathy is the most significant late toxicity associated with anthracycline therapy. The cumulative incidence of clinical heart failure among long-term survivors of childhood cancer reaches approximately 25% by 40 years of age in certain cohorts.<sup>3</sup> Cumulative anthracycline dose is one of the most important predictors of cardiomyopathy.<sup>4</sup> Although overall late mortality and morbidity have improved in children treated during the 1990s compared with those treated in the 1970s, late cardiovascular morbidity has not decreased substantially over this period.<sup>5,6</sup>

For these reasons, it is essential to establish appropriate cardioprotective strategies from the initiation of anthracycline therapy in paediatric and adolescent patients.

Dexrazoxane is a bisdioxopiperazine that has demonstrated cardioprotective properties through iron chelation and reduction of anthracycline-induced oxidative damage.<sup>7</sup> It is administered at a 10:1 mg/m<sup>2</sup> ratio relative to the anthracycline dose as an intravenous bolus prior to each anthracycline infusion. However, long-term data on the cardioprotective efficacy of dexrazoxane in survivors of childhood cancer remain limited, although short- and medium-term data suggest a potential benefit.<sup>8,9</sup>

While international consensus guidelines exist, a stark gap remains in translating these recommendations to Latin America due to regional variations in resource availability, late-stage disease presentation, and disparities in cardiac monitoring infrastructure. This narrative review aims to evaluate global dexrazoxane efficacy data and synthesise them into a pragmatic, region-specific framework tailored for Latin American clinical environments.

### Evolution of global regulatory and guideline landscapes

In 2010, the United Kingdom Medicines and Healthcare products Regulatory Agency requested a formal evaluation by the European Medicines Agency of dexrazoxane's cardioprotective efficacy and its potential association with adverse outcomes, including infection, myelosuppression, and second primary malignancies—particularly acute myeloid leukaemia and myelodysplastic syndrome.

Based on these concerns, the Healthcare Products Regulatory Agency contraindicated dexrazoxane use in children and adolescents in 2011, citing insufficient evidence of benefit and a possible increased risk of secondary malignancies and haematologic toxicity.<sup>10</sup>

Following reevaluation, the European Medicines Agency Committee for Medicinal Products for Human Use revised this position in 2015, restricting the contraindication to children expected to receive cumulative doxorubicin doses below 300 mg/m<sup>2</sup> (or equivalent anthracycline exposure). This regulatory stance has since been adopted across the European Union,<sup>11</sup> reflecting a shift towards risk-adapted decision-making rather than universal avoidance.

According to the 2022 recommendations of the International Late Effects of Childhood Cancer Guideline Harmonization Group:

- Dexrazoxane should not be administered to children expected to receive cumulative doxorubicin or equivalent doses below 250 mg/m<sup>2</sup>, as current evidence is insufficient to determine whether reduced cardiac risk outweighs the potential risk of secondary malignancies.
- Dexrazoxane administration is reasonable in children expected to receive cumulative anthracycline doses  $\geq 250$  mg/m<sup>2</sup>, with shared decision-making between clinicians, patients, and families, based on clinical judgment.<sup>12</sup>

The 2022 Australian and New Zealand consensus similarly recommends dexrazoxane use in high-risk patients, particularly those receiving cumulative anthracycline doses  $> 250$  mg/m<sup>2</sup> or mediastinal radiation  $> 15$  Gy, while advising against its use in low-risk patients due to an unfavourable cost–benefit profile.<sup>13</sup>

## Results

### Safety profile and evaluation of secondary malignant neoplasms

Multiple studies support the cardioprotective efficacy of dexrazoxane in paediatric patients treated with anthracyclines. In a retrospective cohort of 258 children, dose-limiting cardiotoxicity occurred significantly more frequently in patients who did not receive dexrazoxane ( $p = 0.006$ ).<sup>14</sup> Among patients receiving cumulative anthracycline doses of 200–300 mg/m<sup>2</sup>, left ventricular ejection fraction and fractional shortening  $z$ -scores were significantly better preserved in dexrazoxane-treated patients ( $p < 0.04$ ).

In patients with osteosarcoma exposed to very high cumulative doxorubicin doses (600 mg/m<sup>2</sup>), dexrazoxane was associated with

only minimal reductions in fractional shortening and predominantly transient, low-grade ventricular dysfunction.<sup>15</sup>

Notably, long-term data from Chow *et al.* demonstrated that dexrazoxane use was associated with improved ventricular function and lower myocardial stress nearly two decades after cancer diagnosis, particularly among patients exposed to cumulative doxorubicin doses  $\geq 250$  mg/m<sup>2</sup>.<sup>16</sup> These findings suggest not only short-term myocardial protection but also durable long-term benefits.

Concerns regarding second primary malignancies largely originate from a single analysis in paediatric Hodgkin lymphoma, in which a higher number of second primary malignancies was observed in the dexrazoxane arm.<sup>17,18</sup> However, subsequent large observational studies and clinical trials have failed to corroborate this association.

A retrospective analysis of over 15,000 paediatric cancer patients demonstrated lower, not higher, rates of secondary acute myeloid leukaemia among dexrazoxane-exposed patients.<sup>19</sup> Additional cohort studies and meta-analyses likewise failed to show a statistically significant increase in second primary malignancies risk.<sup>20</sup>

The 2022 Cochrane review did, however, conclude that a potential association cannot be definitively excluded in paediatric populations,<sup>21</sup> emphasising ongoing uncertainty rather than confirmed causal risk.

Dexrazoxane is generally well tolerated. While some studies report increased haematologic toxicity, major randomised trials have shown comparable rates of infection, myelosuppression, and neurologic toxicity in dexrazoxane-treated and control patients.<sup>9</sup>

Initial regulatory concerns regarding excess mortality were not substantiated by later analyses. Long-term pooled data from randomised trials demonstrated no adverse effect on 10-year overall survival, a finding corroborated by subsequent meta-analyses and guideline reviews.<sup>9,12,22</sup>

Across multiple randomised trials and systematic reviews, dexrazoxane has not been associated with increased relapse or inferior event-free or overall survival.<sup>12,22,23</sup> These data collectively indicate that dexrazoxane does not attenuate the antitumour efficacy of anthracycline-based chemotherapy.

The cost–benefit profile of dexrazoxane must be interpreted in the context of cumulative anthracycline exposure and expected lifetime cardiovascular risk. Its primary benefit lies in the prevention of subclinical myocardial injury, which may otherwise progress silently for years before manifesting as irreversible heart failure.

Potential risks include uncertain protocol-dependent associations with secondary malignancies and transient haematologic toxicity. However, in patients expected to receive cumulative anthracycline doses  $\geq 250$  mg/m<sup>2</sup>—particularly those with long anticipated survival—the balance increasingly favours cardioprotection.

### Predicament of Latin America

In high-income countries, contemporary paediatric oncology and cardio-oncology guidelines increasingly endorse a risk-stratified use of dexrazoxane in children expected to receive high cumulative anthracycline doses, supported by access to advanced cardiac imaging, biomarker surveillance, and long-term survivorship programs. In contrast, much of Latin America faces structural limitations, including restricted access to serial echocardiography, cardiac MRI, and specialised survivorship care, as well as greater

sensitivity to upfront drug costs within publicly funded health systems. Consequently, while high-income settings may rely on intensive monitoring to detect and manage early cardiotoxicity, Latin American health systems must place greater emphasis on primary prevention strategies that reduce irreversible late cardiac damage in the absence of robust long-term follow-up infrastructure. This divergence highlights the need to interpret international guidelines through a regional lens, adapting recommendations on dexrazoxane use to local clinical capacity, economic constraints, and survivorship realities rather than applying high-income country paradigms uncritically.<sup>24,25</sup>

From a public health perspective, Ministries of Health in Latin America should consider incorporating dexrazoxane into national paediatric oncology protocols for clearly defined high-risk patients, as targeted cardioprotection may reduce long-term heart failure-related morbidity and downstream healthcare costs in survivorship despite higher upfront drug expenditure.

## Discussion

Cardioprotection is desirable for any patient receiving anthracyclines, as even very low doses can induce subclinical cardiotoxicity.<sup>26</sup> Despite consistent evidence that dexrazoxane reduces cardiotoxicity, lingering concerns regarding long-term safety persist, particularly regarding secondary malignancies.<sup>12,27,28</sup>

Children treated with cumulative anthracycline doses  $\geq 250$  mg/m<sup>2</sup> are known to have a high absolute risk of heart failure and represent a population most likely to benefit from primary prevention strategies.

A prospective study of 173 paediatric cancer patients receiving doxorubicin with or without dexrazoxane suggested that cardioprotective effects were more pronounced in those receiving higher cumulative doses ( $\geq 250$  mg/m<sup>2</sup>) compared with lower doses ( $< 250$  mg/m<sup>2</sup>).<sup>29</sup>

The 2024 study by Lo AC et al. evaluating long-term cardiotoxicity (25-year follow-up) in patients with Hodgkin lymphoma concluded that reductions in the proportion of patients receiving mediastinal radiotherapy, the use of smaller radiotherapy target volumes, and the increased use of dexrazoxane were associated with a net reduction in late cardiac disease.<sup>30</sup>

Given the high lifetime burden and cost of anthracycline-related heart failure in childhood cancer survivors, Ministries of Health in Latin America should prioritise the inclusion of dexrazoxane for well-defined high-risk paediatric patients as a cost-saving preventive intervention within national oncology protocols.

## Conclusions

In response to the initial questions, current evidence suggests that the cardioprotective benefits of dexrazoxane outweigh its potential adverse effects, without demonstrating a significant reduction in the antitumour efficacy of anthracyclines.

In paediatric populations, its use is primarily recommended for high-risk patients receiving cumulative anthracycline doses  $> 250$  mg/m<sup>2</sup> or mediastinal radiotherapy.

Although the cost-benefit balance remains debated, dexrazoxane's potential to prevent irreversible cardiac damage supports its selective use. Long-term safety concerns persist, underscoring the need for further studies in children and adolescents.

The challenge moving forward in the Latin American continent will be to balance effective cardiac protection with oncologic safety,

optimising dexrazoxane use without compromising antitumour efficacy.

**Acknowledgements.** None.

**Financial support.** None.

**Competing interests.** None.

## References

- Howlander N, Noone AM, Krapcho M, et al. (eds): SEER Cancer Statistics Review, 1975-2018. National Cancer Institute, Bethesda, MD, 2021.
- Armenian SH, Armstrong GT, Aune G, et al. Cardiovascular disease in survivors of childhood cancer: insights into epidemiology, pathophysiology, and prevention. *J Clin Oncol* 2018; 36: 2135-2144.
- Chow EJ, Chen Y, Kremer LC, et al. Individual prediction of heart failure among childhood cancer survivors. *J Clin Oncol* 2015; 33: 394-402.
- Lipshultz SE, Adams MJ, Colan SD, et al. Long-term cardiovascular toxicity in children, adolescents, and young adults who receive cancer therapy: Pathophysiology, course, monitoring, management, prevention, and research directions: a scientific statement from the American Heart Association. *Circulation* 2013; 128: 1927-1995.
- Armstrong GT, Chen Y, Yasui Y, et al. Reduction in late mortality among 5-year survivors of childhood cancer. *N Engl J Med* 2016; 374: 833-842.
- Gibson TM, Mostoufi-Moab S, Stratton KL, et al. Temporal patterns in the risk of chronic health conditions in survivors of childhood cancer diagnosed 1970-99: a report from the Childhood Cancer Survivor Study cohort. *Lancet Oncol* 2018; 19: 1590-1601.
- Herman EH, Ferrans VJ, Jordan W, et al. Reduction of chronic daunorubicin cardiotoxicity by ICRF-187 in rabbits. *Res Commun Chem Pathol Pharmacol* 1981; 31: 85-97.
- Lipshultz SE, Rifai N, Dalton VM, et al. The effect of dexrazoxane on myocardial injury in doxorubicin-treated children with acute lymphoblastic leukemia. *N Engl J Med* 2004; 351: 145-153.
- Asselin BL, Devidas M, Chen L, et al. Cardioprotection and safety of dexrazoxane in patients treated for newly diagnosed T-cell acute lymphoblastic leukemia or advanced-stage lymphoblastic non-Hodgkin lymphoma: a report of the Children's Oncology Group randomized trial Pediatric Oncology Group 9404. *J Clin Oncol* 2016; 34: 854-862.
- EMA. European Medicines Agency. Assessment report. Dexrazoxane-containing medicinal products (EMA/H/A-31/1275). 2011.
- EMA. European Medicines Agency. Questions and answers on Cardioxane (dexrazoxane: powder for solution for injection: 500 mg). Outcome of a procedure under Article 13 of Regulation (EC) No 1234/2008. 2017.
- Baat EC, van Dalen EC, Mulder RL, et al. Primary cardioprotection with dexrazoxane in patients with childhood cancer who are expected to receive anthracyclines: recommendations from the International Late Effects of Childhood Cancer Guideline Harmonization Group. *Lancet Child Adolesc Health* 2022; 6(12): 885-894. DOI: [10.1016/S2352-4642\(22\)00239-5](https://doi.org/10.1016/S2352-4642(22)00239-5).
- Toro C, Felmingham B, Jessop S, et al. Cardio-oncology recommendations for pediatric oncology patients: an Australian and New Zealand Delphi consensus. *JACC Adv* 2022; 1(5): 100155. DOI: [10.1016/j.jaccadv.2022.100155](https://doi.org/10.1016/j.jaccadv.2022.100155).
- Kang M, Kim KI, Song YC, et al. Cardioprotective effect of early dexrazoxane use in anthracycline treated pediatric patients. *J Chemother* 2012; 24(5): 292-296.
- 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): 54-61.
- Chow EJ, Aggarwal S, Doody DR, et al. Dexrazoxane and long-term heart function in survivors of childhood cancer. *J Clin Oncol* 2023; 41(12): 2248-2257. DOI: [10.1200/JCO.22.02423](https://doi.org/10.1200/JCO.22.02423).
- Tebbi CK, London WB, Friedman D, et al. Dexrazoxane-associated risk for acute myeloid leukemia/myelodysplastic syndrome and other secondary malignancies in pediatric Hodgkin's disease. *J Clin Oncol* 2007; 25(5): 493-500.

18. Hellmann K. Dexrazoxane-associated risk for secondary malignancies in pediatric Hodgkin's disease: a claim without evidence. *J Clin Oncol* 2007; 25(29): 4689–4690.
19. Seif AE, Walker DM, Li Y, et al. Dexrazoxane exposure and risk of secondary acute myeloid leukemia in pediatric oncology patients. *Pediatr Blood Cancer* 2015; 62(4): 704–709.
20. Vrooman LM, Neuberg DS, Stevenson K, et al. The low incidence of secondary acute myelogenous leukaemia in children and adolescents treated with dexrazoxane for acute lymphoblastic leukemia: a report from the Dana–Farber Cancer Institute ALL Consortium. *Eur J Cancer* 2011; 47(9): 1373–1379.
21. Baat EC, Mulder RL, Armenian S, et al. Dexrazoxane for preventing or reducing cardiotoxicity in adults and children with cancer receiving anthracyclines. *Cochrane Database Syst Rev* 2022; 9(9): CD014638. DOI: [10.1002/14651858.CD014638.pub2](https://doi.org/10.1002/14651858.CD014638.pub2).
22. Chow EJ, Asselin BL, Schwartz C, et al. Late mortality after dexrazoxane treatment: a report from the Children's Oncology Group. *J Clin Oncol* 2015; 33(24): 2639–2645.
23. Shaikh F, Dupuis LL, Alexander S, et al. Cardioprotection and second malignant neoplasms associated with dexrazoxane in children receiving anthracycline chemotherapy: a systematic review and meta-analysis. *J Natl Cancer Inst* 2016; 108(4): djv357.
24. Gonzalez-Ramella OC, Freigeiro D, Castellanos M, et al. Joining forces for children with cancer in Latin America. *Lancet Oncol* 2016; 17(6): 701–703.
25. Izurieta Pacheco AC, Noyd D, Challinor J, et al. Childhood cancer survivors in Latin America: insights into health outcomes and information needs. *Pediatr Blood Cancer* 2025; 72(9): e31833.
26. Leger K, Slone T, Lemler M, et al. Subclinical cardiotoxicity in childhood cancer survivors exposed to very low dose anthracycline therapy. *Pediatr Blood Cancer* 2015; 62(1): 123–127.
27. Cvetkovic RS, Scott LJ. Dexrazoxane. A review of its use for cardioprotection during anthracycline chemotherapy. *Drugs* 2005; 65(7): 1005–1024.
28. Van Dalen EC, Caron HN, Dickinson HO, et al. Cardioprotective interventions for cancer patients receiving anthracyclines. *Cochrane Database Syst Rev* 2005; (1).
29. Chow EJ, Aggarwal S, Doody DR, et al. Dexrazoxane and heart function among long-term childhood cancer survivors: a Children's Oncology Group study. *J Clin Oncol* 2020; 38: 10513–10513.
30. Lo AC, Liu A, Liu Q, et al. Late cardiac toxic effects associated with treatment protocols for Hodgkin lymphoma in children. *JAMA Netw Open* 2024; 7(1): e2351062. DOI: [10.1001/jamanetworkopen.2023.51062](https://doi.org/10.1001/jamanetworkopen.2023.51062).