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Review

Prevention of anthracycline-induced cardiotoxicity in children: The evidence

Elvira C. van Dalen, Huib N. Caron, Leontien C.M. Kremer*

Department of Paediatric Oncology, Emma Children's Hospital/Academic Medical Center, University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands

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ABSTRACT

Anthracycline-induced cardiotoxicity after treatment for childhood cancer is a considerable and serious problem. In this review, important insight into the current state of the evidence on the use of different cardioprotective agents, different anthracycline analogues, and different anthracycline infusion durations to reduce or prevent cardiotoxicity in children treated with anthracyclines is provided. It has become clear that, at the present time, there is not enough reliable evidence for many aspects of the prevention of anthracycline-induced cardiotoxicity in children. More high quality research is necessary. Suggestions for future research have been presented. As the results of these new studies become available, it will hopefully be possible to develop evidence-based recommendations for preventing anthracycline-induced cardiotoxicity in children. Until then, we can only advise care providers to carefully monitor the cardiac function of children treated with anthracyclines. With regard to the use of the cardioprotectant dexrazoxane, it might be justified to use dexrazoxane in children if the risk of cardiac damage is expected to be high. However, for each individual patient, care providers should weigh the cardioprotective effect of dexrazoxane against the possible risk of adverse effects including a lower response rate. We recommend its use in the context of well-designed studies.

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1. Introduction

Anthracyclines have gained widespread use in the treatment of both solid tumours and haematological malignancies in children. Almost 60% of children diagnosed with cancer receive anthracyclines as part of their treatment; the most used types are doxorubicin, daunorubicin and epirubicin.

The introduction of anthracyclines, together with other improvements in childhood cancer treatment, has contributed to the improved survival of many different childhood cancers.[1] As a result, a rapidly growing number of children will have survived childhood cancer. In the Netherlands, at the present time, approximately one out of every 750–800 young adults has survived childhood cancer.[2]

Unfortunately, an important side effect of anthracyclines is heart damage (cardiotoxicity). It can become manifest in patients as either clinical heart failure (i.e. with symptoms)[3] or as asymptomatic heart damage (i.e. without symptoms, but on, for example, an ultrasound of the heart, abnormalities in heart function can be seen).[4] Heart damage caused by anthracyclines cannot only occur during treatment, but also years after the end of treatment.[5]

* *Corresponding author:* Tel.: +31 20 5665697; fax: +31 20 5669021.
E-mail address: e.c.vandalen@amc.uva.nl (E.C. van Dalen).
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Anthracycline-induced cardiotoxicity is a widely prevalent problem. In one of our earlier studies, the estimated risk of anthracycline-induced clinical heart failure increased with time to 5.5% at 20 years after the start of anthracycline therapy. In patients treated with a cumulative anthracycline dose of 300 mg/m^2 or more the risk was even higher, almost 10%.[6] The incidence of anthracycline-induced asymptomatic cardiac dysfunction has been reported to be more than 57% at a median of 6.4 years after treatment.[7] The incidence of anthracycline-induced cardiotoxicity, both clinical and asymptomatic, seems to increase with a longer follow-up period.[6,8,9] With the current improved cancer survival rates, the problem of late-onset cardiotoxicity is increasing.

The consequences of heart damage caused by anthracyclines are extensive. First, it can cause a reduction in the amount of anthracyclines that a patient was supposed to receive and as a result, the chance of survival of that patient can be reduced.[10] Also, cardiotoxicity can lead to long-term side effects, causing severe morbidity and reduced quality of life. It involves long-term treatment and thus high medical costs and it causes premature death. The excess mortality due to cardiac disease is 8-fold higher than expected for long-term survivors of childhood cancer compared to the normal population.[11]

Extensive research has been devoted to the identification of methods or agents capable of ameliorating anthracycline-induced cardiotoxicity. This review provides a compilation of evidence from multiple Cochrane systematic reviews, the quality of which is higher than that of reviews published in paper journals.[12] It covers the existing evidence on (1) the use of cardioprotective agents, (2) the use of possibly less cardiotoxic anthracycline analogues, and (3) the use of different anthracycline dosage schedules to reduce or prevent cardiotoxicity in children treated with anthracyclines.

2. Methods

2.1. *Search methods for identification of Cochrane systematic reviews*

The Cochrane Database of Systematic Reviews (The Cochrane Library; issue 4, 2006) was searched for all systematic reviews examining any intervention to reduce or prevent cardiotoxicity in children treated with anthracyclines. The terms 'anthracycline OR anthracyclines OR doxorubicin OR daunorubicin OR epirubicin OR idarubicin' combined with 'cardiotoxicity OR heart OR cardiac' were entered, restricted to record title, abstract or keyword. This resulted in five Cochrane systematic reviews,[13–17] of which three were included in this review. They either evaluated different cardioprotective agents,[13] different anthracycline analogues,[14] or different anthracycline dosage schedules.[15] The other reviews were excluded, because their study populations consisted of adults with, respectively, breast cancer and prostate cancer.[16,17]

2.2. *Description of Cochrane systematic reviews identified*

2.2.1. *Criteria for including studies*

The criteria for including studies in the identified systematic reviews were: (1) randomised controlled trial (RCT), (2) comparison of any cardioprotective agent with placebo or no additional treatment; comparison of different anthracycline analogues; comparison of different anthracycline dosage schedules (either different peak doses (defined as the maximal anthracycline dose received in 1 week) or different anthracycline infusion durations); therapy other than anthracyclines should be the same in both treatment groups, (3) patients (both adults and/or children) with any type of cancer who received anthracycline chemotherapy, and (4) evaluation of cardiotoxicity.

2.2.2. *Search methods*

The search methods used in the identified systematic reviews were similar. RCTs were identified from different sources. The databases of MEDLINE, EMBASE, CENTRAL (Cochrane Register of Controlled Trials in the Cochrane Library) were searched using sensitive search strategies. In addition, reference lists of relevant publications and the conference proceedings of the International Society for Paediatric Oncology (SIOP) and the American Society of Clinical Oncology (ASCO) were searched. For two systematic reviews, the authors also checked ongoing trials databases (both the ISRCTN Register and the National Institute of Health Register) using www.controlled-trials.com. In none of the systematic reviews was language restriction imposed. The search for the systematic review on different cardioprotective agents[13] was recently updated.

2.2.3. *Description of studies*

All identified Cochrane systematic reviews included studies performed in adults and/or children. However, in this review we will discuss the available evidence in children.

In the systematic review on *cardioprotective agents*[13] only for two agents, coenzyme Q10 and dexrazoxane, was an adequate RCT in children identified.[18,19] After this systematic review was finalised another study evaluating dexrazoxane in children was published;[20] this study was the only eligible RCT in children identified in the recent update of the search for this Cochrane systematic review. See Table 1 for the characteristics of these RCTs.

In the systematic review on *different anthracycline analogues*[14] no adequate RCTs in children were identified.

The systematic review on *different anthracycline dosage schedules*[15] evaluated both different anthracycline peak doses (defined as the maximal received anthracycline dose in 1 week) and different anthracycline infusion durations (for which the reviewers used a cut-off point of 6 hours, i.e. 6 hours or longer versus less than 6 hours). No RCTs adequately addressing different anthracycline peak doses were identified, whereas for different anthracycline infusion durations, two RCTs in children were found.[21,22] See Table 2 for the characteristics of these RCTs.

All included Cochrane systematic reviews evaluated cardiotoxicity (both clinical and asymptomatic), tumour response, survival (both progression-free and overall) and adverse effects. See Table 3 for used definitions of asymptomatic cardiac dysfunction.

Table 1 – Characteristics of randomised controlled trials of cardioprotective agents in paediatric oncology patients treated with anthracyclines

Study	Cardioprotective agent	Total N of pts (intervention/control) Tumour	Age (years)	Prior anthra Prior cardiac RT	Anthra analogue Cum dose (mg/m^2)	Follow-up
Iarussi[18]	Coenzyme Q10	20 (10/10) ALL or NHD	1–15	Nm Nm	Doxo or dauno 210–270	Nm
Wexler[19]	Dexrazoxane (ratio to anthra 20:1)	41 (23/18)[a] Ewing sarcoma family	4–24	No No	Doxo 70–410	Med 39 months
Lipshultz[20]	Dexrazoxane (ratio to anthra 10:1)	206 (105/101) ALL	<18	No No	Doxo Median 300	Med 2.7 years

N: number; pts: patients; ALL: acute lymphoblastic leukaemia; NHD: non-Hodgkin's disease; anthra: anthracycline; RT: radiotherapy; Nm: not mentioned; cum: cumulative; doxo: doxorubicin; dauno: daunorubicin; med: median.
a Three patients received dexrazoxane without randomisation.

Table 2 – Characteristics of randomised controlled trials of different anthracycline infusion durations in paediatric oncology patients

Study	Infusion duration	Total N of pts (intervention/control) Tumour	Age (years)	Prior anthra Prior cardiac RT	Anthra analogue Cum dose (mg/m^2)	Follow-up
Steinherz[21]	Over 48 h versus bolus	44 (22/22) ALL	1 to 19	No No	Dauno 120–585	Med 54+ months
Lipshultz[22]	Over 48 h versus bolus	121 (57/64) ALL	0.4 to 17.9	No No	Doxo 222–360	Med 1.5 years

N: number; pts: patients; ALL: acute lymphoblastic leukaemia; anthra: anthracycline; RT: radiotherapy; cum: cumulative; dauno: daunorubicin; doxo: doxorubicin; med: median.

Table 3 – Used definitions of asymptomatic cardiac dysfunction in randomised controlled trials evaluating cardioprotective methods in paediatric oncology patients treated with anthracyclines

Study	Cardioprotective intervention	Definition of asymptomatic cardiac dysfunction
Iarussi[18]	Coenzyme Q10	Echocardiographic LVSF <28%
Wexler[19]	Dexrazoxane	A reduction in LVEF as measured by MUGA to <45% or a decrease in LVEF as measured by MUGA of >20 percentage points from baseline
Lipshultz[20]	Dexrazoxane	Troponin T elevated above 0.01 ng per ml Differences in different echocardiographic parameters
Steinherz[21]	Infusion duration	A LVSF of <29% or a 10% unit or more decrease from baseline to 29% (borderline function) or median change in LVSF as measured by echocardiography
Lipshultz[22]	Infusion duration	Median fall in left ventricular characteristics as measured by echocardiography

LVSF: left ventricular shortening fraction; LVEF: left ventricular ejection fraction; MUGA: multiple gated acquisition scan.

2.2.4. *Methodological quality of included studies*

The validity of the results of a systematic review depends on the quality of the included studies. All included Cochrane systematic reviews evaluated the methodological quality of the included studies, based on concealment of treatment allocation (for selection bias), blinding of care providers and patients (for performance bias), blinding of outcome assessors (for detection bias) and completeness of follow-up (for attrition bias). All included Cochrane systematic reviews concluded that the methodological quality of the included RCTs in children varied. See Table 4 for the scores per included study.

Table 4 – Quality of randomised controlled trials of different cardioprotective interventions in paediatric oncology patients treated with anthracyclines

Study	Cardioprotective intervention	Allocation concealment	Blinding of care provider	Blinding of patient	Blinding of outcome assessor[a]	Completeness of follow-up (>80%)[a]
Iarussi[18]	Coenzyme Q10	Unclear	No	No	Asympt (echo): unclear	Asympt (echo): unclear
Wexler[19]	Dexrazoxane	Yes	No	No	Clinical: unclear Asympt (MUGA): yes	Clinical: yes Asympt (MUGA): yes
Lipshultz[20]	Dexrazoxane	Yes	No	No	Clinical: unclear Asympt (echo): yes Asympt (troponin T): yes	Clinical: unclear Asympt (echo): no Asympt (troponin T): no
Steinherz[21]	Infusion duration	Unclear	Unclear	Unclear	Asympt (echo): unclear	Asympt (echo): yes
Lipshultz[22]	Infusion duration	Yes	Unclear	Unclear	Clinical: unclear Asympt (echo): yes	Clinical: no Asympt (echo): no

Asympt: asymptomatic; echo: echocardiography; MUGA: multiple gated acquisition scan.
a For cardiotoxicity outcomes.

3. Results

3.1. *Cardioprotective agent coenzyme Q10*

The cardioprotective agent coenzyme Q10 is evaluated in children in one small RCT.[18] Only asymptomatic cardiac dysfunction was assessed, which occurred in none of the children.

Tumour response, survival and adverse effects were not evaluated in this study.

3.2. *Cardioprotective agent dexrazoxane*

The cardioprotective agent dexrazoxane is evaluated in children in two RCTs.[19,20] Since not all studies allowed data extraction for all evaluated outcomes and/or it was not possible to separate the results of the 38 randomised and three non-randomised patients in the study of Wexler and colleagues,[19] we can only provide descriptive results.

Wexler and colleagues[19] identified a significant difference in the occurrence of anthracycline-induced cardiotoxicity: four out of the 20 patients randomised to dexrazoxane developed cardiotoxicity (either clinical or asymptomatic) compared to 10 out of 18 patients in the control group (RR = 0.36; 95% CI 0.14 to 0.95). Objective response rates were identical in both treatment groups, with no significant differences seen in event-free or overall survival (for randomised and non-randomised patients combined). This study did not report the number of patients having suffered an adverse effect.

In the study of Lipshultz and colleagues[20] patients in the control group were more likely than those in the dexrazoxane group to have elevated troponin T levels, which is a marker for heart damage (50% versus 21%; $P < 0.001$). On echocardiographic evaluation there were no significant differences in cardiac function before, during and after therapy. The echocardiographic left ventricular shortening fraction was significantly decreased in both groups during and after therapy. None of the children developed anthracycline-induced clinical heart failure. Nine children (four in the dexrazoxane group (3.8%) and five in the control group (4.9%)) did not have a complete remission. Event-free survival at 2.5 years was 83% in both groups ($P = 0.87$). In both groups there were no dexrazoxane- or doxorubicin-associated dose-limiting adverse effects (definitions of adverse effects were not provided).

3.3. *Different anthracycline infusion durations*

Different anthracycline infusion durations are evaluated in children in two RCTs.[21,22] Since not all studies allowed data extraction for all evaluated outcomes, we can only provide descriptive results.

Steinherz and colleagues[21] did not report on clinical heart failure. Thirty-six of 44 randomised patients underwent an echocardiography: four out of 18 patients in the bolus group developed asymptomatic cardiac dysfunction compared to none out of 18 patients in the continuous infusion group. This was not a significant difference ($P = 0.10$). The median change in left ventricular shortening fraction was −6.5 for the bolus group and +1 for the continuous infusion group. It was not stated if this was a significant difference. No information regarding response rate, survival and adverse effects was provided.

In the study of Lipshultz and colleagues[22] none of the children developed anthracycline-induced clinical heart failure. In this study, asymptomatic cardiac dysfunction was not presented as the number of patients who developed asymptomatic cardiac dysfunction. However, it did provide the median Z score of different echocardiographic parameters (bolus group versus continuous infusion group): diastolic dimension (−0.12 versus −0.23), wall thickness (−0.32 versus −0.28), systolic dimension (0.85 versus 0.38), left ventricular fractional shortening (−2.34 versus −1.77) and mass (−0.65 versus −0.47). None of the differences were significant. Please note that only a small percentage of the randomised patients were evaluated for this outcome (21 to 26%). No information regarding response rate, progression-free and overall survival and adverse effects was provided. No significant difference in 5-year

event-free survival between the treatment groups was identified (89% in the short infusion group and 87.3% in the continuous infusion group; $P = 0.50$).

4. Discussion

Heart damage due to anthracycline chemotherapy is a considerable and serious problem. It reduces the quality of life and can even cause premature death. Also, when heart damage occurs during therapy the maximum cumulative dose of anthracyclines needs to be limited and as a result the efficacy of anthracycline chemotherapy may be reduced. Therefore, it is extremely important to identify methods to reduce or even prevent anthracycline-induced cardiotoxicity. This review provides an important overview of all available evidence on preventing anthracycline-induced cardiotoxicity with regard to the use of different cardioprotective agents, the use of different anthracycline analogues, and the use of different anthracycline dosage schedules to reduce or prevent cardiotoxicity in children treated with anthracyclines.

The overall quality of the included Cochrane systematic reviews was good. Selection of eligible studies was performed by two independent reviewers, as were data-extraction and quality assessment of the included studies. An extensive literature search was performed in order to avoid publication bias. No language restriction was imposed, so the presence of language bias can be ruled out. The quality of the included studies was assessed, and taken into account in the interpretation of the review's results.

The Cochrane systematic review on *cardioprotective agents*,[13] together with the later published study of Lipshultz and colleagues[20] demonstrated that, due to the lack of reliable evidence for other possible cardioprotective agents, only for dexrazoxane some conclusions can be made.

Dexrazoxane significantly reduced the occurrence of heart damage caused by anthracyclines.

However, an important question regarding the use of dexrazoxane during anthracycline therapy is whether it could selectively decrease the heart damage caused by anthracyclines without reducing the anti-tumour efficacy (i.e. tumour response and survival). The suggestion of a lower tumour response rate after treatment with dexrazoxane as identified in the meta-analysis of the adult studies included in the Cochrane systematic review on cardioprotective agents (RR = 0.88; 95% CI 0.77 to 1.01)[13] could not be confirmed in children, but could also not be ruled out. No significant differences in survival were identified, both in children and adults.

Another important question regarding the use of dexrazoxane during anthracycline therapy is whether it could selectively decrease the heart damage caused by anthracyclines without negative effects on toxicities other than cardiac damage, such as alopecia, nausea, and leucopoenia. Unfortunately, the results of this Cochrane systematic review do not allow for a definitive conclusion on adverse effects with the use of dexrazoxane.

It should be noted that both RCTs in children had methodological limitations and that the power of these studies to detect a specific difference in survival was either too low[23] or necessary information was lacking.[24] Also, both studies had a relatively short follow-up and as a result, the possible cardioprotective effect of dexrazoxane beyond these follow-up periods remains unknown. In a non-randomised study in childhood cancer survivors with an 8-year follow-up dexrazoxane seemed to reduce the risk of late asymptomatic cardiac dysfunction, but this needs to be confirmed in a RCT.[25] Finally, the measurement of the left ventricular ejection fraction by MUGA-scan, the echocardiographic measurement of the left ventricular shortening fraction and the measurement of heart damage by measuring troponin T are surrogate markers and their predictive value for the future development of anthracycline-induced clinical heart failure is yet unknown.

In summary, for possible cardioprotective agents other than dexrazoxane, more research is needed before evidence-based recommendations for their use in children can be made. High quality RCTs should be undertaken, evaluating not only cardiotoxicity, but also anti-tumour efficacy and other adverse effects. They should be performed in homogeneous study populations treated for either a haematological malignancy or a solid tumour, using valid outcome definitions. The number of included children should be sufficient to obtain the power needed for the results to be reliable and also, the follow-up should be long enough to identify late-onset cardiotoxic events. Although the results of the dexrazoxane studies in children are promising, there is only a small amount of data in children available. It is uncertain if results obtained in adults can be extrapolated to children and therefore, dexrazoxane should be further evaluated in children. At the moment we have knowledge about six ongoing trials in children.[26–31] To give reliable results, these ongoing studies should meet the above mentioned criteria for high quality RCTs. It will be very interesting to examine long-term survival data from the RCTs (already) performed in children. In a recent paper, the event-free survival of children treated on the DFCI ALL consortium protocol 95-01, including the children included in the study of Lipshultz and colleagues,[20] at a median follow-up of 5.7 years has been presented.[32] Again, no statistically significant difference in event-free survival between children treated with or without dexrazoxane was reported (76% in the dexrazoxane group and 77% in the control group; $P = 0.99$). Although the exact follow-up period of patients randomised to treatment with or without dexrazoxane was not reported, it seems correct to assume that the follow-up presented in this paper is longer than that in the report of the RCT. Another possibility to assess the benefits and risks of treatment with dexrazoxane in children is the performance of individual patient data (IPD) analyses.

Furthermore, in the RCTs evaluating dexrazoxane, different ratios of dexrazoxane to anthracyclines were used. Wexler and colleagues used a ratio of 20:1[19] and Lipshultz and colleagues[20] used a ratio of 10:1. The most optimal dexrazoxane to anthracycline ratio in children remains to be determined.

For clinical practice, evidence-based recommendations for the use of dexrazoxane in children treated with anthracyclines are currently not possible. It might be justified to use dexrazoxane in children if the risk of cardiac damage is expected to be high. However, for each individual patient, care providers should weigh the cardioprotective effect of dexrazoxane against the possible risk of adverse effects including a lower response rate. In our hospital, it was decided to pro-

vide dexrazoxane to children receiving a cumulative anthracycline dose of 300 mg/m^2 or more. We recommend its use in the context of well-designed studies.

The Cochrane systematic review on *different anthracycline analogues*[14] demonstrated the lack of reliable studies in children. A limited number of adult studies were identified, but since data obtained in adults cannot be extrapolated to children, no definitive conclusions about the cardiotoxic effects of different anthracycline analogues in children can be made. More research is needed. High quality RCTs, as described above, should be undertaken. Until the results of these new studies are available, we can only advise care providers to carefully monitor the cardiac function of children treated with anthracyclines.

The Cochrane systematic review on *different anthracycline dosage schedules*[15] demonstrated the lack of reliable studies on the use of different anthracycline peak doses (defined as the maximal dose received in 1 week). Therefore, no conclusions can be made about the difference in cardiotoxicity with the use of different anthracycline peak doses. For different anthracycline dosage schedules two RCTs evaluating bolus versus continuous infusion over 48 h were identified. Clinical heart failure was evaluated in one study in which no difference was identified. In both studies no difference in asymptomatic heart damage was identified. No information regarding tumour response rate, survival and adverse effects could be obtained for children.

It should be noted that both studies had methodological limitations and that the follow-up of the studies was relatively short. As a result, the possible cardioprotective effect of continuous anthracycline infusion duration on heart damage developing beyond these follow-up periods remains unknown. Also, echocardiographic parameters are surrogate markers and their predictive value for the future development of anthracycline-induced clinical heart failure is yet unknown. Finally, it should be kept in mind that the inclusion of studies for this systematic review was limited to RCTs describing cardiotoxicity, and consequently, it is possible that results for tumour response, survival and adverse effects in children are available from RCTs who did not describe anthracycline-induced cardiotoxicity.

In summary, for different anthracycline peak doses (defined as the maximal received dose in 1 week), more research is needed to establish their role in preventing anthracycline-induced cardiotoxicity in children. High quality RCTs, as described above, should be undertaken. Also, more definitions of anthracycline peak doses than the one used in this systematic review are possible, for example, single dose infusion versus consecutive divided daily doses. To evaluate all the available evidence on the exact role of other kinds of peak doses on the occurrence of anthracycline-induced cardiotoxicity in children, one or more new (Cochrane) systematic reviews, evaluating cardiotoxicity, anti-tumour efficacy and other adverse effects, can be initiated. Since there is only a small amount of data in children available, different anthracycline infusion durations should be further evaluated in children. These new RCTs should meet the above mentioned criteria. It will be very interesting to examine long-term survival data from the RCTs (already) performed in children. Another possibility to assess the benefits and risks of different anthracycline infusion durations in children is the performance of individual patient data (IPD) analyses. Furthermore, the two available RCTs in children used a continuous infusion duration of 48 h. It would be interesting to evaluate the cardiotoxic profile of other infusion durations in children (like for example 6 hours or 24 hours). For clinical practice, evidence-based recommendations for the use of different anthracycline dosage schedules in children treated with anthracyclines are currently not possible. Until the results of these new studies are available, we can only advise care providers to carefully monitor the cardiac function of children treated with anthracyclines.

Finally, direct comparisons of dexrazoxane with other cardioprotective strategies, like other possible cardioprotective agents, different anthracycline analogues or possibly less cardiotoxic anthracycline dosage schedules, in a well-designed RCT have not yet been performed, but would provide important additional information.

In conclusion, anthracycline-induced cardiotoxicity after treatment for childhood cancer is a considerable and serious problem. In this review, important insight into the current state of the evidence on different cardioprotective methods is provided. It has become clear that, at the present time, there is not enough reliable evidence for many aspects of the prevention of anthracycline-induced cardiotoxicity in children. More high quality research is necessary. Suggestions for future research have been presented. As the results of these new studies become available, it will hopefully be possible to develop evidence-based recommendations for preventing anthracycline-induced cardiotoxicity in children. Until then, we can only advise care providers to carefully monitor the cardiac function of children treated with anthracyclines. With regard to the use of the cardioprotectant dexrazoxane, it might be justified to use dexrazoxane in children if the risk of cardiac damage is expected to be high. However, for each individual patient, care providers should weigh the cardioprotective effect of dexrazoxane against the possible risk of adverse effects including a lower response rate. We recommend its use in the context of well-designed studies.

Conflict of interest statement

None declared.

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