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DOI

[10.1056/NEJMp048113](https://doi.org/10.1056/NEJMp048113)

Publication date

2004

Published in

The New England journal of medicine

[Link to publication](#)

Citation for published version (APA):

Kremer, L. C. M., & Caron, H. N. (2004). Anthracycline cardiotoxicity in children. *The New England journal of medicine*, 351(2), 120-121. <https://doi.org/10.1056/NEJMp048113>

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epidemics are potentially dire. Prophecies are always hazardous, but in the former Soviet Bloc, the outlook for the next few decades is perhaps best characterized by a Russian neologism invented to describe the adverse effects of the disintegration of the Soviet system: “katastroika.”

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Anthracycline Cardiotoxicity in Children

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More than 70 percent of children who are treated for childhood cancer can be cured. For long-term survivors, possible late effects of treatment and their consequences for the quality of life are a major concern. Cardiotoxic effects of anthracyclines are among the most frequent and serious adverse effects of the treatment of childhood cancer. Anthracyclines such as daunorubicin, epirubicin, and doxorubicin have been used for more than 30 years, and nearly 60 percent of children with cancer are currently being treated with such agents.

The mechanisms behind cardiotoxic effects are not fully understood, but lipid peroxidation and the generation of free radicals by anthracycline-iron complexes are thought to play major roles. Clinical cardiotoxic effects are defined as symptoms of clinical heart failure, and subclinical cardiotoxic effects as cardiac abnormalities detected in asymptomatic persons by means of various diagnostic methods. Cardiotoxic effects may occur early — during therapy or within the first year after therapy; late cardiotoxic effects are defined as those occurring one year or more after the end of treatment.

What is known about the frequency of cardiotoxic effects and associated risk factors? The reported frequency of clinical cardiotoxic effects in children treated with anthracyclines varies from 0 to 16 percent. Differences in study populations, treatment regimens, and the duration of follow-up could account for this wide variability. The risk of clinical cardiotoxic effects' occurring as long as 15 years

after treatment with a mean cumulative dose of anthracyclines of 300 mg per square meter of body-surface area is estimated to be approximately 5 percent. The frequency of late subclinical cardiotoxic effects, defined in terms of abnormal findings on echocardiography, has been reported to be as high as 57 percent among survivors of childhood cancer. Important risk factors for clinical and subclinical cardiotoxic effects are a higher cumulative dose, receipt of mediastinal radiation therapy, female sex, and younger age at diagnosis; the risk increases over time. In a cohort study in which we followed 607 patients for a mean of 6.3 years after treatment, no clinical cardiotoxic effects developed in patients who had received a cumulative dose of anthracyclines less than or equal to 300 mg per square meter. However, studies have shown that even after a lower dose of anthracyclines, subclinical abnormalities may be detected.

Can the cardiotoxic effects of anthracyclines be prevented? There are several possible ways to do this. First, avoiding anthracyclines would be an option. In most treatment protocols for childhood cancer, anthracyclines have been introduced without data from randomized, controlled trials that would support their use. For tumors for which no survival benefit of anthracyclines has been established, the need for anthracycline therapy should be reevaluated.

Second, cardiotoxic effects may be prevented by lowering the cumulative dose, lowering the peak

dose through the use of a different treatment schedule, or using alternative anthracycline derivatives. Currently, treatment protocols for childhood cancer limit the maximal cumulative dose of doxorubicin to 450 mg per square meter. Liposomal anthracycline may be less cardiotoxic than other types of anthracyclines, but it has not yet been evaluated in children.

A third preventive strategy may be the early detection of subclinical cardiotoxic effects, followed by reductions in the dose of anthracyclines. Serial monitoring of left ventricular function by means of echocardiography (through measurement of the shortening fraction) or radionuclide angiography (assessment of the ejection fraction) has been advocated. Analysis of these measurements, however, will permit the detection of cardiotoxic effects only when many cardiomyocytes have already been damaged. Moreover, the ejection fraction and the shortening fraction are influenced not only by contractility, but also by the loading conditions of the heart. Variability in the results of measurement may be another limitation of the shortening fraction as an early indicator of toxic effects.

Echocardiographic assessments such as the measurement of afterload, the stress-velocity index, and diastolic function have been used in various studies involving long-term survivors of childhood cancer. The clinical implications of changes in these echocardiographic variables during anthracycline therapy are still unknown. The histologic grade of injury in endomyocardial-biopsy specimens has been shown to be predictive of subsequent clinical cardiotoxic effects, but the routine use of this method of assessment is limited by its invasiveness. Because of the lack of evidence to support the reliability of any potential early marker of cardiotoxic effects, some experts recommend modifying the dose of anthracyclines only when there is evidence of clinical cardiotoxic effects.

Finally, cardioprotective agents such as dexrazoxane may be beneficial when used in combination with anthracyclines in children. Dexrazoxane is thought to reduce the cardiotoxic effects of anthracyclines by binding free and bound iron, thereby

reducing the formation of anthracycline-iron complexes and the subsequent generation of reactive oxygen species. Dexrazoxane has cardioprotective effects in adults who are treated with anthracyclines. Data suggesting a decrease in the tumor-response rate in the dexrazoxane group in one randomized trial involving patients with breast cancer, together with uncertainty about possible adverse hematologic or gastrointestinal effects, have delayed the introduction of dexrazoxane in adults. The randomized, controlled trial described by Lipshultz et al. in this issue of the *Journal* (pages 145–153) is an important step toward effective cardioprotection in children. In this study, dexrazoxane — when given to children who were to receive doxorubicin — was associated with a reduction in myocardial injury as measured in terms of the troponin T level. This finding supports the cardioprotective effects of dexrazoxane.

Questions remain, however. Is a small elevation in the troponin T level an accurate predictor of cardiotoxic effects in patients treated with anthracyclines? The predictive value of low-level elevations of troponin T has to be validated in a large cohort of patients treated with anthracyclines. In addition, does dexrazoxane diminish the response of the tumor to anthracyclines? In the current study, no differences in survival were found. However, information about the statistical power of the study to detect a specific difference in survival is lacking.

In conclusion, anthracycline-induced cardiotoxic effects are a serious problem among young patients who survive childhood cancer, and there is an urgent need to prevent such effects. Research in this field is complicated by the infrequency of clinical cardiotoxic effects as an outcome. Valid surrogate end points are needed if we are to gain insight into the risk of cardiotoxic effects in individual patients and into the benefits and risks of preventive measures. We need evidence from this research in order to make informed clinical decisions regarding children who are treated with anthracyclines for cancer.

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