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Title **Cardioprotection against the Toxic Effects of Anthracyclines Given to Children With Cancer: A Systematic Review**

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Aim

To evaluate technologies that can potentially reduce anthracycline-induced cardiotoxicity in children, including: a) different dosage schedules, b) different anthracycline derivatives, c) use of cardioprotective agents, eg, dexrazoxane, and d) use of antioxidant protection, eg, probucol or nutritional supplementation with glutamine. To identify markers to quantify cardiotoxicity in children. To refine outcome measures for use in longer term studies. To identify studies evaluating the cost effectiveness of cardioprotection against the toxic effects of anthracyclines given to children with cancer. To identify priorities for future primary research.

Conclusions and results

Four randomized controlled trials (RCTs) on cardioprotective interventions, and one RCT and six cohort studies on the use of cardiac markers, met the inclusion criteria of the review. All studies had methodological limitations.

Two RCTs considered continuous infusion versus bolus (rapid) infusion. One found that continuous infusion of doxorubicin did not offer any cardioprotection over bolus; the other suggested that continuous infusion of daunorubicin had less cardiotoxicity than bolus infusion. Two studies considered cardioprotective agents. One concluded that dexrazoxane prevents or reduces cardiac injury as reflected in levels of a cardiac marker during doxorubicin therapy without compromising anti-leukemic efficacy of doxorubicin. The other reported a protective effect of coenzyme Q_{10} on cardiac function during anthracycline therapy.

One RCT suggests that cardiac troponin T can be used to assess the effectiveness of the cardioprotective agent dexrazoxane. Two cohort studies considering atrial natriuretic peptide and two considering brain (B-type) natriuretic peptide (BNP) suggest that these chemicals are elevated in some subgroups of children treated with anthracyclines for cancer compared with healthy children. NT-pro-BNP levels were significantly elevated in children treated with anthracyclines who had cardiac dysfunction compared with patients who did not have cardiac dysfunction and healthy controls in one cohort study. One cohort study found that serum lipid peroxide was higher in younger children treated with doxorubicin than in children of corresponding age not receiving doxorubicin. No differences in carnitine levels were found in children treated with doxorubicin and a group of healthy children in one cohort study.

Recommendations

Limited evidence makes it difficult to draw conclusions about the effectiveness of technologies to reduce or prevent cardiotoxicity and about the use of cardiac markers in children. The lack of standardization for monitoring and reporting cardiac performance is problematic. Not all studies report effectiveness in terms of cardiac outcomes and event-free survival with supporting statistical analyses. Studies are mostly small and of short duration, making generalization difficult.

Methods

See Executive Summary link above.

Further research/reviews required

RCTs of the methods to reduce or prevent cardiotoxicity in children treated with anthracyclines for cancer with long-term followup are needed to determine whether the technologies influence the development of cardiac damage. Studies will probably require a range of outcomes, the most important being event-free survival in terms of the whole cancer treatment protocol. Other outcomes include cardiac measurements, eg, echocardiographic findings and potential cardiac markers, side effects, and measures of anthracycline anti-tumor efficacy.

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