

Cardioprotection against the toxic effects of anthracyclines given to children with cancer: a systematic review

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Executive summary

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Executive summary

Background

Anthracyclines are potent cytotoxic antibiotics widely used in the treatment of malignancies in children. Their use has improved survival rates, but been limited by cardiotoxic side-effects which may cause myocardial damage and lead to congestive heart failure and risk of death from cardiac causes. Prevention of anthracycline-induced clinical heart failure (A-CHF) and cardiotoxicity is particularly important in children because they can be expected to survive for decades after treatment. Attempts to minimise cardiotoxicity of anthracyclines include dose limitation and schedule modification, and the use of less cardiotoxic analogues and cardioprotective agents. Cardiac markers released by myocyte cells during anthracycline treatment have been suggested as early markers for the quantification of cardiac damage.

Objectives

The main objective of this study was to evaluate the technologies used to reduce anthracycline-induced cardiotoxicity in children. Other objectives included evaluating cardiac markers to quantify cardiotoxicity, and identifying cost-effectiveness studies and future research priorities.

Methods

A systematic review of the evidence was undertaken using a priori methods.

Data sources

Eight electronic databases were searched from inception to January 2006. Bibliographies of related papers were assessed for relevant studies and experts contacted to identify additional published references.

Study selection

Studies were included if they fulfilled the following criteria:

- Interventions: studies that evaluated different dosing schedules for anthracyclines,

anthracycline derivatives or cardioprotective agents were considered for inclusion.

- Participants: studies on children aged up to 18 years being treated for cancer with anthracyclines were included.
- Outcomes: subclinical cardiac failure, clinical (symptomatic) heart failure, arrhythmias and death were the primary outcome measures considered in the systematic review.
- Design: randomised controlled trials (RCTs) were included. For the section considering cardiac markers controlled cohort studies were also included.

Studies identified were assessed for inclusion through two stages with titles and abstracts and full papers of retrieved studies assessed independently by two reviewers, with differences in decisions resolved through discussion or through recourse to a third, independent reviewer.

Data extraction and quality assessment

Data were extracted by one reviewer using a data extraction form developed a priori, and checked by a second reviewer. Any disagreements were resolved through discussion or through recourse to independent assessment by a third reviewer. The methodological quality of the studies included in the systematic review was assessed using recognised quality assessment tools using individual components of methodological quality rather than relying on summary scores. The quality criteria were applied by two reviewers, with any disagreements resolved through discussion or through recourse to a third, independent reviewer.

Data synthesis

Studies were synthesised using a narrative approach with full tabulation of results from all included studies.

Results

Number and quality of studies

Four RCTs met the inclusion criteria of the review, each considering a different cardioprotective intervention; all trials included children with acute lymphoblastic leukaemia, and one also

included children with non-Hodgkin's lymphoma. The RCTs had methodological limitations owing to inadequacy of randomisation and assessment of outcomes, or insufficient details of methods and incomplete reporting of results. No cost-effectiveness studies were identified. One RCT and six cohort studies on the use of cardiac markers met the inclusion criteria of the review. These studies also had methodological limitations.

Summary of clinical effectiveness of technologies for reducing A-CHF

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 the antileukaemic efficacy of doxorubicin. The other reported a protective effect of coenzyme Q₁₀ on cardiac function during anthracycline therapy.

Summary of cardiac markers to quantify cardiotoxicity

One RCT suggested 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 suggested that these chemicals are elevated in some subgroups of children treated with anthracyclines for cancer compared with healthy children. N-terminal B-type natriuretic peptide 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 correspondingly aged children 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.

Conclusions

It is difficult to draw conclusions about the effectiveness of technologies for reducing or preventing cardiotoxicity and about the use of cardiac markers in children as the evidence is limited in quantity and quality. The lack of standardisation 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 generalisation difficult.

Implications for service provision

Increasing numbers of survivors of childhood cancer treated with anthracyclines will experience cardiac damage and require long-term surveillance and management. This will have an impact on cardiac services and costs. Diverse medical problems and other late sequelae which affect cardiac outcome will have an impact on other specialist services. Mechanisms to reduce or prevent cardiotoxicity from anthracycline therapy and cardiac markers to improve monitoring could alter the extent of this impact on service provision.

Recommendations for research

RCTs of the different methods for reducing or preventing cardiotoxicity in children treated with anthracyclines for cancer with long-term follow-up are needed to determine whether the technologies influence the development of cardiac damage. It is likely that the studies will require a range of outcomes, including event-free survival in terms of the whole treatment protocol, cardiac measurements such as echocardiographic findings and potential cardiac markers, side-effects and measures of anthracycline antitumour efficacy. Cost-effectiveness research is also required.

Publication

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NIHR Health Technology Assessment Programme

The Health Technology Assessment (HTA) programme, now part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the costs, effectiveness and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care, rather than settings of care.

The research findings from the HTA Programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the 'National Knowledge Service'.

The HTA Programme is needs-led in that it fills gaps in the evidence needed by the NHS. There are three routes to the start of projects.

First is the commissioned route. Suggestions for research are actively sought from people working in the NHS, the public and consumer groups and professional bodies such as royal colleges and NHS trusts. These suggestions are carefully prioritised by panels of independent experts (including NHS service users). The HTA Programme then commissions the research by competitive tender.

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Some HTA research projects, including TARs, may take only months, others need several years. They can cost from as little as £40,000 to over £1 million, and may involve synthesising existing evidence, undertaking a trial, or other research collecting new data to answer a research problem.

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Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reported in this monograph was commissioned by the HTA Programme as project number 05/34/01. The contractual start date was in September 2005. The draft report began editorial review in March 2006 and was accepted for publication in February 2007. As the funder, by devising a commissioning brief, the HTA Programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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