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Use of cardiac markers to assess the toxic effects of anthracyclines given to children with cancer: A systematic review ☆

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ABSTRACT

Aim: To evaluate the effectiveness of cardiac markers to quantify anthracycline-induced cardiotoxicity in children with cancer.
Methods: Systematic review using a priori methods.
Results: Seven studies, all with methodological limitations, were identified. One RCT suggests that cardiac troponin can be used to assess the effectiveness of the cardio-protective agent dexrazoxane. Cohort studies suggest that atrial natriuretic peptide and brain (B-type) natriuretic peptide are elevated in some subgroups of patients compared with healthy children; NT-pro-BNP levels are significantly elevated in children with cardiac dysfunction compared with those without; serum lipid peroxide is higher in children who have received doxorubicin compared with children not receiving doxorubicin; there are no differences in carnitine levels between children treated with doxorubicin and a healthy control group.
Conclusions: The limited evidence makes conclusions difficult. Research is needed to fill this important evidence gap and link short-term changes in cardiac markers to longer-term cardiac damage.

1. Introduction

Cytotoxic antibiotics, known as anthracyclines, are highly potent chemotherapeutic agents and are widely used in the treatment of solid and haematological malignancies in children. Their introduction has contributed to the successful treatment of childhood cancer with long-term survival rates now approaching 75%.[1] There are an estimated 270,000 survivors of childhood cancer in the United States (USA)[2] and more than 20,000 in the United Kingdom (UK),[3] half of whom are likely to have been treated with anthracyclines. However, the use of anthracyclines has been limited by their dose-dependent cardiotoxic side-effects during and after treatment.[4–6] Many survivors of anthracycline treatment have long-term problems because of myocardial damage such as impaired left ventricular contractility and cardiomyopathy,

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which may lead to overt heart failure and an increased risk of cardiac death or the need for cardiac transplantation.

Anthracycline-induced clinical heart failure (A-CHF) is a major public health concern within the exposed population as it may not be manifested for many years and remains a life long threat. It is a particular problem in children treated for cancer because it is hoped that they will survive for several decades after treatment. As survival rates continue to improve the resources needed to monitor and care for survivors will also continue to increase.

Due to the importance of anthracyclines in chemotherapy protocols for childhood cancer and the fact that toxicity varies considerably between individuals, a method of quantifying cardiotoxicity before cardiac damage becomes apparent would be invaluable. Various serum cardiac markers have been suggested as potentially important in treatment planning and monitoring to allow maximum anthracycline dosages without sustaining severe cardiac damage and in the development of preventative strategies to limit cardiomyopathy in later life. Such cardiac markers are attractive because samples can be obtained in a minimally invasive way and are easily analysed. Also they can potentially allow quantitative assessment of the severity of the cardiac insult.

Several possible markers of cardiac damage have been identified. Since anthracyclines cause disruption of cardiac myocyte cell membranes, resulting in the release of intracellular proteins such as lactate dehydrogenase (LDH), creatine phosphokinase (CPK) and cardiac troponin (cTnT), these substances have been used to assay for the presence and extent of myocyte injury. In the absence of myocardial injury, cTnT levels are usually below the limit of detection of current analytical methods.[7] It has been demonstrated that low level elevations of cTnT induced by the anthracycline doxorubicin are associated with histologic evidence of myocardial injury, which may be clinically meaningful.[8] Other potential markers include plasma levels of circulating natriuretic peptides, such as atrial/A-type natriuretic peptide (ANP) and brain/B-type natriuretic peptide, which are elevated in left ventricular dysfunction and heart failure. N-terminal pro BNP (NT-pro-BNP) has been shown to be secreted from the cardiac ventricles in response to volume expansion and pressure overload.[9] The clinical presentation of carnitine deficiency includes cardiomyopathy which improves after carnitine replacement, suggesting a relationship between serum carnitine concentrations and cardiac dysfunction.[10] Elevated serum lipid peroxide levels have been shown in animals given doxorubicin. It has been suggested that this increase reflects a release of lipid peroxide from heart tissues exposed to doxorubicin[11] which could also be useful for assessing cardiotoxicity. Markers, such as BNP and NT-pro-BNP, have been shown to be useful for diagnosis, prognosis and assessing severity of heart failure in adults.

Due to the uncertainty about the effectiveness of cardiac markers to quantify anthracycline-induced cardiotoxicity in children and the importance of trying to limit the impact of this cardiotoxicity in terms of cost to the children receiving anthracyclines for cancer and their carers, and to the UK National Health Service (NHS), we were commissioned by the NHS Health Technology Assessment Programme to assess the evidence in the literature. We conducted a systematic review of the use of cardiac markers to quantify anthracycline-induced cardiotoxicity in children and this paper summarises our findings and discusses their implications.

2. Patients and methods

Eight electronic databases (including Medline, Cochrane Database of Systematic Reviews, Cochrane Controlled Trials Register and Embase) were searched from inception for periods up to January 2006. Additional studies were identified through searching bibliographies of related publications and through contact with experts. Further details are available elsewhere.[12,13]

This review evaluated the effectiveness of cardiac markers to quantify cardiac damage in children receiving anthracyclines for cancer by seeking the highest level of evidence available. Studies were included if they considered the use of a cardiac marker in children receiving anthracyclines, and had a control or comparison group.

Inclusion criteria, decisions about quality criteria and data extraction were applied independently by two reviewers, with any differences in opinion resolved through discussion. Studies of clinical effectiveness were combined through narrative synthesis with full tabulation of included studies. Quality assessment of included studies was undertaken using criteria developed by Spitzer.[14]

3. Results

3.1. *Quantity of research available*

One RCT[7] and six cohort studies[9–11,15–17] met the inclusion criteria for this review (see Table 1).

The RCT was conducted to determine whether dexrazoxane therapy reduces myocardial injury as measured by serum cardiac troponin T (cTnT) levels in children with newly diagnosed acute lymphoblastic leukaemia being treated with doxorubicin.[7]

Of the six cohort studies, two measured plasma atrial natriuretic peptide (ANP) levels to determine if these levels could indicate cardiac damage.[15,16] One of these also measured brain natriuretic peptide (BNP) levels.[16] One study examined BNP levels alone,[17] one measured plasma levels of NT-pro-BNP and cardiac troponin I,[9] another serum lipid peroxide levels[11] and one serum carnitine levels.[10]

3.2. *Quality of research available*

The quality of the studies included in the review is shown in Table 2.

The RCT[7] was described as randomised but it is not known if treatment allocation was concealed as no details are given. Eligibility criteria were specified and treatment groups were similar at baseline in terms of prognostic factors. Outcome assessors were blinded to treatment allocation; withdrawals and drop-outs were incompletely described.

Sampling, blind assessment, objective eligibility criteria and sample attrition were not discussed or reported in any

Table 1 – Summary details of cardiac marker studies

Study details	Design	Cardiac markers and outcomes	Intervention group	Control group
Lipshultz et al.[7]	RCT	cTnT and echocardiographic studies	DZX 300 mg/m^2 followed by DOX 2 × 30 mg/m^2 during induction then 8 × 30 mg/m^2 every 3 weeks (cumulative dose 300 mg/m^2) *n* = 105	DOX alone 2 × 30 mg/m^2 during induction then 8 × 30 mg/m^2 every 3 weeks (cumulative dose 300 mg/m^2) *n* = 101
Bauch et al.[15]	Cohort	ANP and LVEF	Combination chemotherapy, including DOX (ADR); total cumulative dose 80–480 mg/m^2 *n* = 16	(1) *Treatment controls*: oncology patients, undergoing chemotherapy but never received doxorubicin, *n* = 10 (2) *Untreated controls*: healthy volunteers, *n* = 11
Hayawaka et al.[16]	Cohort	ANP and BNP levels; Echocardiographic cardiac dysfunction; correlation between systolic and diastolic functions of LV and ANP and BNP	In complete remission, receiving combination chemotherapy including DOX *n* = 34	Healthy control group *n* = 19
Horino et al.[11]	Cohort	Serum lipid peroxide	Various types of neoplasms treated with chemotherapeutic regimens including DOX *n* = 21	Did not receive DOX *n* = 44
Pinarli et al.[17]	Cohort	BNP and Cardiac functions	Asymptomatic having received DOX, DAUN, and EPI for solid tumours *n* = 34	*Healthy volunteers*: (1) echo controls *n* = 12; (2) BNP controls *n* = 16
Yaris et al.[10]	Cohort	Serum carnitine levels and relationship with cardiac dysfunction	NHL given combination chemotherapy including DOX *n* = 15	Healthy volunteers *n* = 20
Soker et al.[9]	Cohort	NT-pro-BNP and cardiac toponin I (cTnI) levels, and echocardiographic cardiac dysfunctions	In complete remission receiving chemotherapy regimens including DOX. Total cumulative dose 30–600 mg/m^2 *n* = ALL 27, AML 2, HD 1 and NHL 1	Healthy volunteers *n* = 31

ADR: adriamycin (doxorubicin), ALL, acute lymphoblastic leukaemia, AML: acute myeloblastic leukaemia, ANP: atrial or A-type natriuretic peptide, BNP: brain or B-type natriuretic peptide, cTnI: cardiac troponin I, cTnT: cardiac troponin T, DZX: Dexrazoxane (ICRF-137), DOX: Doxorubicin, EPI: Epirubicin, HD: Hodgkins disease, LVEF: left ventricular ejection fraction, NHL: non-Hodgkin lymphoma.

of the cohort studies. In addition, none of the studies achieved an adequate sample size[9–11,15–17] and no inclusion criteria were stated explicitly. Different patient groups were included in the studies and some details were not reported. One cohort study did not report what types of cancer patients had, or whether they were in remission.[15] In two studies, the patients were in complete remission,[9,16] and in one of these most patients had acute lymphoblastic leukaemia.[9] In a third study patients were described as asymptomatic with no evidence of residual malignancy.[17] A fourth study described patients with non-Hodgkin lymphoma[10] and the fifth as 'patients with various types of neoplasms'.[11] In each of the cohort studies, the groups were incomparable at baseline, or the comparability of the groups was uncertain. All cohort studies used some healthy volunteers as part of the control groups. Age ranges of healthy controls were not given in all the studies, and in one study the healthy volunteers were adults aged 24–38 years.[15] In one study patients receiving chemotherapy without doxorubicin and with unrelated disorders were grouped with healthy volunteers.[11]

A large range of cumulative anthracycline dose was given to patients in four of the six cohort studies: 80–480 mg/m^2,[15] 42–696 mg/m^2,[16] 90–490 mg/m^2,[17] and 30–600 mg/m^2.[9] In another study the regimen administered was doxorubicin every 4–7 weeks in a dose of 15–30 mg/m^2.[11] In the remaining study, all patients had received a total cumulative doxorubicin dose of 300 mg/m^2 at the end of the study.[10] The median cumulative dose of doxorubicin in the RCT was 300 mg/m^2.[7]

The timing of blood sampling for cardiac markers may not have been comparable between the studies. Serum was collected daily after induction doses of doxorubicin, 7 days after a dose of doxorubicin during induction therapy and at the completion of therapy in the RCT.[7] In one cohort study[15] samples were taken when children came to the outpatient clinic or when they were admitted to hospital for chemotherapy administration. As different treatment protocols were fol-

Table 2 – Quality assessment of cardiac marker studies

Criteria	Lipshultz et al.[7]	Bauch et al.[15]	Hayakawa et al.[16]	Pinarli et al.[17]	Soker et al.[9]	Horino et al.[11]	Yaris et al.[10]
Proper random assignment	U (no details)	n/a	n/a	n/a	n/a	n/a	n/a
Proper sampling	Y	NR	NR	NR	NR	NR	NR
Adequate sample size	U	N	N	N	N	N	N
Objective outcomes	Y	Y	Y	Y	Y	Y	Y
Blind assessment	Y	NR	NR	NR	NR	NR	NR
Objective eligibility criteria	Y	NR	NR	NR	NR	NR	NR
Reported attrition	I	NR	NR	N	NR	NR	NR
Comparability of groups	Y	N	N	U	N	N	U
Generalisability	U	U	U	U	U	U	U

Y: yes; n/a: not applicable; NR: not reported, U: uncertain, N: no, I: incomplete.

lowed there was variation in the time interval between administering a dose of doxorubicin and obtaining blood samples for ANP levels.[15] The last dose of anthracycline was more than one month previously in two studies,[9,16] and 1–7 weeks before in another.[11] One study reported that blood sampling was 3–4 weeks after cumulative doses of doxorubicin[10] and another that the mean time between the last dose of anthracycline and cardiac evaluation was 45.7 ± 27.9 months (range 3–122 months).[17]

Due to the factors discussed above, the generalisability of the studies was difficult to determine.

3.3. *Assessment of effectiveness of cardiac markers*

The effectiveness of cardiac markers in the included studies is summarised in Table 3.

3.4. *cTnT*

The RCT[7] found that patients who had been treated with moderate dose doxorubicin (or total cumulative dose 300 mg/m^2) alone were significantly more likely to have elevated cTnT levels than those treated with dexrazoxane and doxorubicin. No significant differences in echocardiographic indices of left ventricular performance between the groups were found and event free survival was similar in both groups.

3.5. *ANP, BNP and NT-pro-BNP*

One study[15] found that 37% of children treated with doxorubicin had transiently elevated ANP levels, three weeks after treatment, which were associated with high cumulative doses of doxorubicin. No statistically significant differences in left ventricular ejection fraction were found and no children had abnormal left ventricular ejection fraction. Both ANP and BNP levels, measured after the completion of anthracycline treatment, were significantly elevated in a subgroup of patients treated with doxorubicin who had cardiac dysfunction compared with healthy controls or patients with normal cardiac function.[16] ANP and BNP levels were significantly correlated with cardiac systolic function but not with diastolic function.[16] A third study[17] found that BNP levels, measured at a mean period of nearly 4 years after the completion of anthracycline treatment, were significantly higher in patients than healthy controls before exercise testing; echocardiographic indices showed increased systolic wall stress in patients compared to controls, but no significant differences in measures of myocardial shortening. Diastolic filling patterns showed various abnormalities; mitral and tricuspid early and atrial peak filling velocity, LV isovolumic relaxation time and acceleration time were significantly higher than those of controls. Different controls were used for different outcomes. In another study[9] NT-pro-BNP plasma levels, measured after the completion of anthracycline treatment, were elevated significantly in patients with cardiac dysfunction compared with a healthy control group and the patients with normal cardiac function. cTnI levels were under normal value for all patients. No significant correlations were found between any of the echocardiographic parameters with natriuretic peptides and cumulative doxorubicin dose.

3.6. *Serum lipid peroxide*

One study[11] found that younger age groups of patients treated with doxorubicin had significantly higher levels of serum lipid peroxide, measured after the completion of anthracycline treatment, than a correspondingly-aged group not receiving doxorubicin. All echocardiographic findings were normal and no cardiotoxicity was observed. There has been no further published data regarding this marker since 1983.

3.7. *Serum carnitine*

One study[10] found no significant differences in carnitine levels between children treated with doxorubicin and a control group of healthy children. A decrease in serum carnitine levels with higher cumulative doses of doxorubcin was observed but was not statistically significant. There was no correlation between carnitine values and subclinical echocardiographic abnormalities.

4. Discussion

This review, which was guided by an expert advisory panel, considered systematically the evidence on the use of cardiac markers to assess cardiotoxicity in children with cancer who had received anthracyclines. The highest level of evidence

Table 3 – Summary of effectiveness of cardiac marker

Study details	Cardiac marker used	Cardiac marker levels	Cardiac outcomes
Lipshultz et al.[7] RCT	Patients with elevated cTnT %	*Any elevation in cTnT* DZX + DOX group, 21% (95% confidence interval (CI) 13,31) DOX group, 50% (95%CI 38,62) $p < 0.001$ *Many elevations in cTnT* DZX + DOX group, 12% (95%CI 6, 21) DOX group, 37% (95%CI 26, 49) $p < 0.001$	LVFS, LVD, LVC not significantly different between groups LVFS significantly depressed in both groups during and after treatment
Bauch et al.[15] Cohort	ANP pg/ml mean ± SE	DOX group with high ANP, 136.2 ± 23.3* DOX group with normal ANP, 33.3 ± 4.1 No DOX treatment control group, 34.6 ± 7.9 Untreated healthy control group, 25.1 ± 2.4 *$p < 0.01$ higher than any other group	LVEF not significantly different between groups
Hayawaka et al.[16] Cohort	ANP pg/ml mean ± SD	DOX group with cardiac dysfunction, 28.8 ± 14.6* DOX group with normal cardiac function, 17.6 ± 8.6 Control group, 14.8 ± 5.8	Peak E filling velocity m/s not significantly different between groups Peak A filling velocity m/s significantly elevated compared with patients with normal cardiac function and healthy controls ($p < 0.05$)
	BNP pg/ml mean ± SD	DOX group with cardiac dysfunction, 29.0 ± 31.2* DOX group with normal cardiac function, 9.0 ± 14.8 Control group, 5.6 ± 3.8 *$p < 0.01$ compared with control and $p < 0.05$ compared with normal cardiac function DOX group	No other point estimates given
Horino et al.[11] Cohort	Serum lipid peroxide level (malondialdehyde nmol/ml of serum) mean ± SE	DOX group (age 0–2), 2.65 ± 0.37 No DOX group (age 0–2), 1.68 ± 0.44 $p < 0.01$ DOX group (age 3–5), 2.73 ± 0.23 No DOX group (age 3–5), 2.00 ± 0.31 $p < 0.001$ DOX group (age 6–10), 2.23 ± 0.32 No DOX group (age 6–10), 1.78 ± 0.32 $p < 0.01$ DOX group (age 11–15), 1.95; No DOX group (age 11–15), 2.23 ± 0.31 DOX group (16–adult), ND No DOX (age 16–adult), 2.59 ± 0.55	Not reported

(*continued on next page*)

Table 3 – *continued*

Study details	Cardiac marker used	Cardiac marker levels	Cardiac outcomes
Pinarli et al.[17] Cohort	BNP (pg/ml) mean ± SD before exercise testing BNP (pg/ml) mean ± SD after exercise testing	Anthracycline group, 10.56 ± 10.22; Healthy control group, 4.09 ± 2.26 $p < 0.016$ Anthracycline group, 15.70 ± 14.0; Healthy control group, n/a	LVEF % Anthracycline group 72.50 Healthy control group 75.50 No significant difference between groups
Yaris et al.[10] Cohort	Carnitine (μ mol/l) mean ± SD	DOX group, baseline, 31.05 ± 11.54; DOX group, 180 mg/m^2, 29.60 ± 12.85 DOX group 300 mg/m^2, 28.43 ± 11.2 Healthy control group, 32.0 ± 8.2	LVEF % DOX group, baseline, 62.2 ± 3.09; DOX group, 180 mg/m^2, 68.5 ± 4.9 DOX group 300 mg/m^2, 66.0 ± 5.4* Healthy control group, 70.1 ± 4.8 *$p < 0.05$ compared with healthy controls but within normal limits
Soker et al.[9] Cohort	NT-pro-BNP pg/ml mean ± SD	DOX group with cardiac dysfunction, 299.03 ± 264.97*; DOX group with normal cardiac function, 107.55 ± 131.82 DOX group, total, 135.92 ± 166.16 Control group, 47.17 ± 19.48 *$p < 0.008$ compared with DOX normal cardiac function group and $p < 0.001$ compared with control group	LVEF Mean ± SD DOX group with cardiac dysfunction, 55.72 ± 3.63; DOX group with normal cardiac function, 68.16 ± 4.43 DOX group, total, 66.25 ± 6.25

ANP: Atrial or A-type natriuretic peptide, BNP: Brain or B-type natriuretic peptide, cTnT: cardiac troponin T, DOX: Doxorubicin, DZX:Dexrazoxane (ICRF-137), LVEF: left ventricular ejection fraction, LVFS: left ventricular fractional shortening, LVD: left ventricular diastolic dimension, LVC: left ventricular contractility, LVEF: left ventricular ejection fraction, ND: not determined, SD: standard deviation, SE: standard error.

was sought but only one RCT was identified, the remainder being cohort studies with controls.

The evidence is limited not only in quantity but also quality. The cardiac marker studies have a high risk of confounding due to the study type employed and the use of healthy controls. Also, they are small with few participants and generally give preliminary results. They are of short duration and the timing of assessment of outcomes is problematic, being too early for the conditions of interest to have developed. Both control and treatment groups in the studies often comprised mixed groups with different baseline characteristics. Treatment groups received different interventions or dosages, and timings of samples taken after anthracycline therapy varied because patients were on different protocols. Different control groups for different outcome measures were also used. Some of the cardiac marker studies suffer from poor reporting, making them difficult to interpret and understand, and with inappropriate analysis of results, such as post hoc subgroup analysis. These methodological problems make comparisons between groups difficult.

Another difficulty is that the studies of cardiac markers appear to be measuring an association of levels of serum chemicals with anthracycline treatment rather than a statistical correlation with cardiotoxicity. As cardiac outcomes are not always reported, or if reported show no significant difference between groups, or are significant through post hoc analysis, it is difficult to see how these substances can be used as surrogate markers for later cardiac damage without further evaluation. Additionally, it is not known how much levels of cardiac markers may be influenced by other factors apart from anthracycline therapy, such as exercise. The timing of blood samples from last anthracycline dose is also an issue in trying to assess the usefulness of markers of cardiac damage. It is known that echocardiographic abnormalities detected after anthracycline administration can normalise and the precise timing may be important as the heart compensates for the damage. The time taken for a return to normal or the lack of return to normal may be predictive of late cardiac damage.

Although the evidence base for the use of cardiac markers to quantify cardiotoxicity is poor, the need for reliable surrogate measures to predict morbidity and mortality in children with cancer given anthracyclines continues. An increase in the incidence of childhood and adolescent cancers has been demonstrated for a wide range of different cancer diagnoses.[3] Children that have been successfully treated for cancer are likely to have long life-expectancy.[18] They are one of the largest and fastest growing groups of patients at risk from premature cardiovascular disease; this cardiotoxicity can be asymptomatic or symptomatic up to the appearance of congestive heart failure.[19]

Effective markers of acute cardiac damage during treatment could predict long-term cardiac outcomes and allow modification of the treatment protocol, for example by omitting further anthracycline treatment, by the use of a different anthracycline formulation, concomitant cardioprotection or by guiding individual dose limitation to minimise the cardiotoxic effects of anthracyclines. Effective late markers after completion of cancer treatment could inform follow-up advice and treatment of cardiac dysfunction or possible incipient heart failure. One recent study in adults with coronary heart disease suggests that NT-proBNP levels predict cardiovascular morbidity and mortality and identify at-risk individuals even in the absence of cardiac dysfunction by echocardiography.[20]

The use of effective cardiac markers would impact not just on clinical effectiveness but also the cost effectiveness of anthracycline therapy which is an additional important consideration.

In summary, this review was undertaken employing standard a priori methods, and found that evidence on the use of cardiac markers for quantifying cardiac damage is limited in quantity and quality making conclusions problematic. One RCT suggests that cTnT can be used to assess the effectiveness of the cardio-protective agent dexrazoxane, but does not demonstrate that troponin elevation during treatment predicts worse long-term cardiac outcome; cohort studies suggest that ANP (two studies) and BNP (two studies) are elevated in some subgroups of children treated with anthracyclines compared with healthy controls, but not all studies report all appropriate outcomes such as cardiac dysfunction. 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 correspondingly-aged children not receiving doxorubicin, but all echocardiographic results were normal. No differences were found in carnitine levels between children treated with doxorubicin and a healthy control group in one cohort study.

Cancer treatment protocols are dynamic and becoming more complex, with more short-term toxicities and increased potential for delayed side effects such as cardiac damage. As such, serum markers of cardiac damage would be invaluable to improve long-term care of children with cancer. Further research is needed to establish the effectiveness of cardiac markers in children, and their link to anthracycline dose, and their use in predicting individual risk for the development and progression of cardiotoxicity. This research could lead to refinement of detection and monitoring strategies and inform recommendations in guidelines.[21] Studies would need adequate sample sizes and long-term follow-up. Continued follow-up of participants of the single RCT is also important.

Conflict of interest statement

None declared.

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