Anthracycline cardiotoxicity in childhood cancer. Frequency, risk factors, and early detection
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Introduction
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Anthracyclines, like daunorubicin, epirubicin, and doxorubicin, have been used in the treatment of childhood cancer for more than 30 years. The antineoplastic effect is caused by binding of anthracyclines to DNA which decrease DNA, RNA and protein synthesis.

The introduction of anthracyclines has contributed to the improvement in the survival rates in childhood cancer from a 5-year survival rate in the 1970s of less than 30% to an 8-year survival rate of more than 70% between 1989 and 1997. Nearly 60% of children treated for childhood cancer are treated with anthracyclines. In the Netherlands, nowadays, approximately 1 out of 750-800 young adults is survivor of childhood cancer. However, since the early trials, cardiotoxicity caused by anthracyclines has been observed. Initially, incidental cases of clinical heart failure were reported. Later on, clinical heart failure was described in previously healthy long-term survivors of childhood cancer. In the early 1990s, two studies reported an unexpectedly high percentage up to 57% of children who showed abnormalities measured by echocardiography.

Pathogenesis

To date, the precise mechanism underlying the cardiotoxicity caused by anthracyclines is not known.

Alterations in the metabolism of calcium have been observed in the presence of anthracyclines which lead to mitochondrial dysfunction, depletion of high-energy phosphates, increased stiffness of the muscle, impaired muscle contractility and cell death. Anthracyclines have been shown to alter the metabolism of histamine, platelet-activated factor and arachidonic acid and thus, that of prostaglandins, thromboxanes and leukotrienes. In addition, there is evidence for a role of the C-13 alcohol metabolite of anthracyclines in the development of cardiotoxicity following the treatment with these agents. A major role, however, has been ascribed to the generation of free radicals by anthracyclines and recently, the alteration of fatty-acid oxidation by mitochondria has been proposed. Damaged myocardial cells can not regenerate.

Symptomatology of cardiotoxicity

Cardiotoxicity after anthracycline therapy in children can be divided in clinical cardiotoxicity, defined on the basis of symptoms of clinical heart failure (CHF), and subclinical cardiotoxicity, defined on the basis of abnormalities of surrogate indicators of CHF in asymptomatic patients. The frequency of clinical cardiotoxicity, after anthracycline
therapy in children has been reported to be as high as 16%. The number of studies that have focussed on clinical cardiotoxicity several years after anthracycline therapy is limited. The term subclinical cardiotoxicity is used to describe various cardiac abnormalities, diagnosed with different diagnostic methods in asymptomatic patients. The prevalence of subclinical cardiotoxicity, defined in terms of echocardiographic parameters such as contractility or afterload, has been reported to be as high as 57%. According to the time of presentation, cardiotoxicity can also be sub-divided into acute, early and late cardiotoxicity. The rare acute form of cardiotoxicity becomes manifest during or immediately after the administration of anthracycline and presents with transient arrhythmia's, a pericarditis-myocarditis syndrome, or heart failure. Early cardiotoxicity can become manifest within one year after anthracyclines treatment, and late cardiotoxicity becomes manifest after the first year of treatment. It is unclear whether a different pathogenesis for these 3 types of cardiotoxicity or individual sensitivity for cardiotoxicity could explain the difference in time of presentation.

**Diagnosis and monitoring**

**Endomyocardial biopsy**
Endomyocardial biopsy is considered to be the 'gold standard' to evaluate myocardial damage after anthracycline therapy. The grade of histologic injury correlates with the cumulative dose of anthracyclines, and has been shown to be predictive for subsequent subclinical cardiotoxicity measured by radionuclide left ventricular ejection fraction (EF), and the development of clinical cardiotoxicity. However, biopsy is an invasive procedure, false negative results can be caused by sampling error, and there is a considerable variability in pathological interpretation.

**Radionuclide angiography and echocardiography**
In adults, measurement of the EF by radionuclide angiography is the clinical standard for monitoring anthracycline cardiotoxicity. The EF is a measurement of the systolic function. In a study of 51 adults, an absolute decline in the EF of more than 15% preceded the development of CHF. There are, however, limitations in the measurement of the systolic function parameter EF. The EF will detect cardiotoxicity relatively late, because impairment of the EF occurs after a critical number of cells have been damaged. Furthermore, the EF is dependent on left ventricular preload and afterload, as well as contractility. This limits the diagnostic value of these parameters for cardiotoxicity. McKillop found a sensitivity of 53% and a specificity of 75% of the EF for cardiotoxicity, measured by endomyocardial biopsy in adults. Stress testing by means of maximal exercise increased the sensitivity to 89% in this study, but decreased the specificity to 41%.
In children, measurement of the left ventricular shortening fraction (SF) measured by echocardiography is the most widely used tool in the detection of cardiotoxicity, because this is a non-invasive method and echocardiography is available in most paediatric oncology centres. A limitation of the echocardiographic SF is that the interpretation of the SF measurement can vary considerably between different observers. Other limitations of the echocardiographic SF are, like the limitations of the radionuclide EF, that SF will detect cardiotoxicity relatively late and the SF is also dependent on afterload, preload, and contractility. Moreover, there are no reports in the literature of studies that evaluate the predictive value of the measurement of SF during therapy or at the end of therapy with regard to the subsequent development of clinical cardiotoxicity. Other echocardiographic measurements, such as a measurement of afterload and stress velocity index have been used in various studies of long-term survivors. However, the clinical importance of these echocardiographic abnormalities is still unknown. The predictive value for stress echocardiography, induced by exercise or dobutamine, is also not clear.

Troponin
Cardiac troponin, a thin filament contractile protein, has been suggested to be an early marker for cardiotoxicity during anthracycline therapy. In an animal model, troponin T was released from doxorubicin-damaged myocytes. The troponin T levels correlated with the dose of anthracyclines and with the degree of myocardial damage. Troponin levels were found to be increased in patients treated with anthracyclines. Only one study involving 15 children investigated the predictive value of troponin T in the early detection of subsequent cardiotoxicity. This study suggested that troponin T predicts subsequent echocardiographic abnormalities, i.e. left ventricular dilatation and wall-thinning, and recommended further studies.

Indium 111 Antimyosin scintigraphy
Indium 111-Antimyosin binds with intracellular myosin only when the sarcolemma is disrupted. A study in rats treated with doxorubicin showed progressive increase in antimyosin uptake with increasing severity of myocardial damage. In adults the uptake of antimyosin is related to the cumulative dose of doxorubicin and the indium 111- antimyosin uptake preceded changes in ejection fraction.

Other measures of cardiotoxicity
Electrocardiographic abnormalities, such as ST segment and T wave abnormalities or arrhythmia's, are usually transient and do not predict subsequent cardiac systolic dysfunction or CHF. It has been suggested that a prolonged QTc interval can detect cardiotoxicity years after therapy, but no relationship with subsequent systolic dysfunction has been described so far.
Diastolic function parameters, measured by radionuclide angiography or echocardiography, heart rate variability, tissue Doppler imaging, MRI, and biochemical markers such as atrial natriuretic peptide, brain natriuretic peptide, and endothelin 1, have been suggested as markers of anthracycline induced cardiotoxicity.\(^{16,36,37}\) The relationship of these markers with subsequent cardiac dysfunction or CHF is unknown.

**Prevention**

Since the introduction of anthracyclines clinicians and researchers have been looking for ways to prevent cardiotoxicity and to limit the damage.

**Before anthracycline therapy**

Before anthracycline therapy prevention can be achieved either by avoiding anthracyclines, the use of analogues which retain anti-tumour activity but without cardiotoxicity, diminishing the cumulative dose or peak dose, or by adding cardioprotective agents. In adults, studies have reported lower incidence of abnormalities in endomyocardial biopsy specimens after a prolonged and continuous infusion of anthracyclines over 48-96 hours.\(^{38}\) However, preliminary results of a prospective randomised study in children could not confirm this difference.\(^{39}\)

Dexrazoxane (ICRF-187) (cardioxane\(^\circledR\)) is an EDTA-like chelator. The inherent property of anthracyclines to generate free radicals and their ability to interfere with iron metabolism might explain the favourable cardioprotective effects of dexrazoxane. The drug is thought to reduce the cardiotoxic effects of anthracyclines by binding free and bound iron, thereby reducing the formation of antracycline-iron complexes and the subsequent generation of reactive oxygen species. Five randomised trials in adults and one in 38 children demonstrated a cardioprotective benefit with dexrazoxane.\(^{40-45}\) Yet, in one of the 5 randomised trials in adults there was a decrease in tumour response rate.\(^{42}\) The overall survival rates were not significant different. The study in children showed no differences, between the dexrazoxane group and control group, in event free survival or overall survival within the limited power of this small study.\(^{45}\) There are ongoing trials addressing the role of dexrazoxane in paediatric patients with acute lymphoblastic leukaemia, T-cell non-Hodgkin’s lymphoma, and Hodgkin’s disease.\(^{46}\) Other agents like antioxidants or free radical scavengers such as vitamin E, carnitine and probucol are cardioprotective in animal studies.\(^{47-49}\) So far, no evidence in patients exists.

**During anthracycline therapy**

During anthracycline therapy prevention can be achieved by an early detection of cardiotoxicity with early markers that predict subsequent clinical cardiotoxicity. Same preventive measures as mentioned before can be taken if cardiotoxicity is diagnosed, yet
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it is unclear whether these are as effective as primary prevention. For adults guidelines for monitoring of patients during anthracycline therapy have been developed by Schwartz and colleagues.\(^{50}\) These guidelines advice to discontinue anthracyclines in the case of an absolute decrease in LVEF of more than 10 % to a LVEF below 50%. A retrospective study suggested the benefit of these guidelines.\(^{50}\) For children guidelines have been published in 1992.\(^{51}\) These guidelines recommended monitoring by echocardiography before each course accompanied by radionuclide EF for patients before each course above 300 mg/m\(^2\) anthracycline. They advised to discontinue anthracycline therapy with an absolute decrease of the SF of more than 10%, or a SF below 30% or with absolute decrease of the EF of more than 10% or a EF below 55% or a decrease in the EF with stress testing. These recommendations are based on experts opinions and until now there is no evidence in children to support these recommendations. Lipshultz et al criticise these recommendations and recommend only modification of the anthracycline dose when clinical evidence of cardiotoxicity is evident.\(^{52}\) To the present day the situation is not clear.

During and after anthracycline therapy

During and after anthracycline therapy angiotensin converting enzyme inhibitors possibly prevent further deterioration of the systolic function in asymptomatic cardiotoxicity.\(^{53}\) After the occurrence of CHF, angiotensin converting enzyme inhibitors, digoxin, diuretics or \(\beta\)-blockers can prevent further deterioration.\(^{54,55}\) In the end stage of CHF, heart transplantation is the only remaining option.\(^{56}\)
Outline of the thesis

The aim of the thesis is to explore the frequency and risk factors of cardiotoxicity after anthracycline therapy and to evaluate possibilities for early detection of heart damage during anthracycline therapy.

Part 1 focuses on the frequency and risk factors of clinical cardiotoxicity. Chapter 1.1 reports on a systematic review with regard to evidence of the frequency and risk factors of CHF after anthracycline therapy in children. In this review the causes of the wide range in reported frequency of CHF are discussed. Chapter 1.2 presents a long-term follow-up study to determine the cumulative incidence of CHF and related risk factors after anthracycline therapy in a cohort of 607 children treated with anthracyclines in Amsterdam.

Part 2 focuses on the frequency and risk factors of subclinical cardiotoxicity. Chapter 2.1 presents a systematic review of the literature with regard to evidence about the frequency and risk factors of subclinical cardiotoxicity. An overview of the different definitions and different diagnostic tests used to determine a decreased systolic function in the study groups is provided. Chapter 2.2 describes the results of a study of longitudinal echocardiographic data of children treated with anthracyclines. This study evaluates the relation between an echocardiographic shortening fraction at the end of therapy and follow-up echocardiography.

Part 3 focuses on the early detection of cardiotoxicity during anthracycline therapy. Chapter 3.1 reports on a study of the role of antimyosin scintigraphy in the detection of anthracycline cardiotoxicity and its possible predictive value for CHF in children treated with anthracyclines. Chapter 3.2 presents the results of a study on the reproducibility of antimyosin scintigraphy. Finally, Chapter 3.3 describes a study in children on the role of troponin T, measured within 24 hours after the administration of anthracyclines, in the early detection of cardiotoxicity.
References


