Anthracycline cardiotoxicity in childhood cancer. Frequency, risk factors, and early detection
Kremer, L.C.M.

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General discussion
The results of the follow-up study of a cohort of children treated with anthracyclines presented in this thesis show that clinical heart failure after anthracycline therapy is a considerable and serious problem among young patients who survive childhood cancer. These young patients have a long life expectancy and clinical heart failure will influence their quality of further life.

The systematic reviews show that the frequency of clinical heart failure varies between 0% and 16%, and the frequency of subclinical cardiotoxicity between 0% and 57%. A part of this variation can be explained by the type of anthracyclines used, dose within one week, cumulative dose, definition of the outcome, and methodological validity of the studies. Most studies published to date had serious methodological limitations.

In the longitudinal study in children treated with a dose above 200 mg/m² an abnormal left ventricular shortening fraction was measured in 3.5% of the patients at the end of treatment and in 14.2% of the patients at follow-up. The shortening fraction at the end of anthracycline therapy was related to the shortening fraction at follow-up.

With respect to the early detection of cardiotoxicity antimyosin scintigraphy seems to be a promising radionuclide method to detect cardiotoxicity before asymptomatic cardiac dysfunction occurs and before clinical heart failure becomes manifest. Unfortunately, radionuclide labelled antimyosin is currently not commercially available. Troponin T is a new early marker of cardiotoxicity. However, measurement of Troponin T within 24 hours after administration of chemotherapy, seems too early to identify patients at increased risk of myocardial dysfunction.

**Recommendations for practice**

Guidelines for cardiac monitoring during and after anthracycline therapy should be critically reviewed. The clinician should be aware of the huge variation in echocardiographic measurement by observer variation, and the current lack of evidence with regard to the clinical consequences of echocardiographic results. Selection of high risk patients for long-term follow-up is currently possible only based on cumulative dose. The importance of end treatment echocardiography is yet to be established, and at present no recommendations can be made with regard to selection of patients for follow-up. Therefore, follow-up should not be done outside the context of well designed cohort studies.
Recommendations for future research

Several areas of future research can be identified.

Impact of cardiotoxicity on further life of survivors
The natural course of patients with subclinical heart failure after anthracycline therapy and the consequence of clinical heart failure on the survival and quality of life have to be investigated in cohort studies that follow the full cohort or may be random sample of survivors at fixed time points after the end of therapy and with accurate and precise outcome measurements relevant to the patients.

Identification of patients with a higher risk for cardiotoxicity
Knowledge about which patients are at increased risk is important for future treatment strategies, for preventive measurements before and during anthracycline therapy, and for follow-up of patients treated with anthracyclines. Cohort studies of representative groups of survivors should be focussed on the importance of different types of anthracyclines, cumulative dose of anthracyclines, dose intensity.

Prevention before treatment
In most treatment protocols for childhood cancer the anthracyclines have been introduced without performing randomised clinical trials. For those tumours with current doubt about the benefit of anthracyclines on the survival, the need for anthracycline therapy childhood cancer should be re-evaluated in randomised controlled trials. In such studies the impact on the survival should be weighted against the impact of cardiotoxicity. Attempts to develop analogues of anthracyclines that retain their anti-tumour activity without causing cardiotoxicity appears warranted. Better understanding of the pathophysiological mechanism could lead to cardioprotective treatment regimes. The impact of dexrazoxane and other possible cardioprotective agents on the cardiotoxicity related to the survival should be further evaluated in randomised controlled trials in children.

Prevention during anthracycline treatment
Investigations into the possibilities of early detection of cardiotoxicity, i.e. of the accuracy of detecting cardiotoxicity, reliability of the measurement, and predictive value for subsequent clinical heart failure, are needed, because preventive measurements can be taken during anthracycline therapy. The actual benefit of such preventive measurements needs further evaluation in randomised controlled trials. The role of angiotensin converting enzyme inhibitors in the prevention of further deterioration of the cardiac function in patients with asymptomatic cardiotoxicity during and after anthracycline therapy have to be evaluated in randomised controlled trials in survivors of childhood cancer.