Anthracycline cardiotoxicity in childhood cancer. Frequency, risk factors, and early detection
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Summary
Chapter 1.1 reports a systematic review with respect to the frequency and risk factors of clinical heart failure (CHF) after anthracycline therapy in children. A search was made in MEDLINE for studies, published from 1966 to December 2000, that included more than 50 children treated with anthracyclines and reported the frequency of CHF. Information about study features, risk factors, and frequency was abstracted by two reviewers. The potential predictive factors of CHF were analysed both within and across the studies. The frequency of CHF in children was estimated in 30 studies described in 25 articles. All studies have methodological limitations. The frequency varied between 0% and 16%. In the analysis across the studies the type of anthracyclines and the maximal dose in 1 week explain a considerable part of the variation of the frequency of CHF. The predicted frequency of CHF for patients treated with doxorubicin will be 3.1% higher than for patients treated with daunorubicin. (95% confidence interval: 0.6 - 11.2) For patients treated with a maximal dose within 1 week above 45 mg/m² the predicted frequency will be 5.8% higher than for patients treated with a maximal dose below 45 mg/m².(95% confidence interval: 1.7 - 14.1)

Chapter 1.2 presents a cohort study to determine the early and late cumulative incidence of CHF after anthracycline therapy in childhood, and to identify associated risk factors. The cumulative incidence of CHF and risk factors were assessed in a cohort of 607 children who had been treated with anthracyclines between 1976 and 1996. For 96% of the cohort, the clinical status was obtained up to at least January 1997. The cumulative incidence of CHF was 2.8%, after a mean follow-up time of 6.3 years and a mean cumulative dose of anthracyclines of 301 mg/m². A cumulative dose of anthracycline higher than 300 mg/m² was associated with an increased risk of CHF, RR=11.8 (CI: 1.6-59.5) compared with a cumulative dose lower than 300 mg/m². The estimated risk of CHF increased with time after the start of anthracycline chemotherapy, to 2% after 2 years and 5% after 15 years.

Chapter 2.1 presents a systematic review of the frequency and risk factors of subclinical cardiotoxicity after anthracycline therapy in children. The aim of this systematic review was to summarise and appraise the published evidence. A search was made in MEDLINE for studies, published between 1966 and May 2001, that included more than 50 children, and reported on the frequency of measures of subclinical cardiotoxicity. Information about the studies was abstracted by 2 reviewers and a validity score was calculated for each study. The reported frequency of subclinical cardiotoxicity varied between 0% and 57% in 25 included studies. Differences in outcome definitions of subclinical cardiotoxicity and differences in study patients with respect to the dose of anthracycline seemed to explain a part of the wide variance of the frequency of subclinical cardiotoxicity. Fourteen of the 25 studies showed serious methodological limitations.
Chapter 2.2 presents longitudinal echocardiographic data of 113 patients treated with more than 200 mg/m² anthracyclines. In this study the relationship between the shortening fraction (SF) at the end of treatment and the SF at follow-up was evaluated. The frequency of an abnormal SF (SF ≤ 28%) before therapy, at the end of therapy and at a follow-up time was 0%, 3.5%, and 14.2% respectively. The multivariate analysis of the possible risk factors for a lower SF, cumulative dose of anthracycline > 450 mg/m², age at diagnosis, radiation therapy to the heart region, female sex, SF at the end of therapy showed an association between the SF at the end of therapy and the SF at follow-up.

Chapter 3.1 describes a study to determine the value of Indium-111 antimyosin (In-111 AM) scintigraphy in the early detection of myocardial damage in children treated with doxorubicin. Twelve planar scintigrams were made of eight patients. Three scans were made before doxorubicin therapy in three patients and nine scans were made during doxorubicin therapy in seven patients. The heart-to-lung ratio (HLR) was calculated. Left ventricular function was assessed by echocardiography before and during therapy by measuring the shortening fraction (SF). The HLR of the three baseline scans was below 1.5, within the normal range for adults. During chemotherapy six of the seven patients had abnormal HLR values (>1.5). One patient had severe myocyte damage and showed an early increase in the HLR (2.3) after a cumulative doxorubicin dose of 150 mg/m². The SF measured by echocardiography was normal throughout therapy, the final cumulative dose of doxorubicin being 450 mg/m². This patient developed fatal clinical heart failure 3 months after completion of chemotherapy. In one patient, who was pre-treated with the cardioprotective agent dexrazoxane, the HLR remained within normal limits during therapy.

Chapter 3.2 presents the intra- and inter-observer agreement of qualitative and quantitative assessment of 111-In-AM scintigraphy in 23 patients, assessed in 27 111-In-AM scintigrams. The inter-observer agreement of the qualitative assessments expressed as Kappa of ten nuclear medicine physicians was 0.41 (range: 0.21-0.54). To assess the intra- and inter-observer agreement of the quantitative assessment, five independent observers reviewed three times, at 1-week intervals, the HLR of the 27 scintigrams. The intra-observer intra-class correlation coefficients (ICC) for the quantitative assessment was 0.82 and the inter-observer ICC was 0.78. The error sd of one HLR measurement was 0.13 and the error sd of the mean of two measurements was 0.09. The quantitative assessment, using the HLR, showed a better agreement than the qualitative assessment.

Chapter 3.3 describes the role of cardiac troponin T (cTnT), measured in the first 24 hours after the administration of anthracyclines, in the early detection of cardiotoxicity in 38 children. An abnormal cTnT level, defined as a cTnT > 0.010 ng/mL, was measured in only 6 samples of 3 patients. After completion of chemotherapy 7 out of 38 patients
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had left ventricular dysfunction (LV dysfunction). Only 1 of these 7 patients had an elevated cTnT level. Two other patients with elevated cTnT levels did not develop LV dysfunction until 2 and 7 months after the cTnT measurement. These data show that measurement of cTnT, within 24 hours after administration of chemotherapy, seems to be too early to identify patients who are at increased risk of myocardial dysfunction.