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Clinical heart failure in a cohort of children treated with anthracyclines: A long-term follow-up study

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ABSTRACT

The cumulative incidence of anthracycline-induced clinical heart failure (A-CHF) in a large cohort of 830 children treated with a mean cumulative anthracycline dose of 288 mg/m^2 (median 280 mg/m^2; range 15–900 mg/m^2) with a very long and complete follow-up after the start of anthracycline therapy (mean 8.5 years; median 7.1 years; range 0.01–28.4 years) was 2.5%. A cumulative anthracycline dose of 300 mg/m^2 or more was the only independent risk factor (relative risk (RR) = 8). The estimated risk of A-CHF increased with time to 5.5% at 20 years after the start of anthracycline therapy; 9.8% if treated with 300 mg/m^2 or more.

In conclusion, 1 in every 10 children treated with a cumulative anthracycline dose of 300 mg/m^2 or more will eventually develop A-CHF. This is an extremely high risk and it reinforces the need of re-evaluating the cumulative anthracycline dose used in different treatment protocols and to define strategies to prevent A-CHF which could be implemented in treatment protocols.

1. Introduction

Anthracyclines have gained widespread use in the treatment of numerous childhood malignancies: nearly 60% of children diagnosed with a malignancy receive anthracyclines. The introduction of anthracyclines has contributed to the improvement in the survival rates of childhood cancer: from 30% in the 1960s to 70% nowadays.[1,2] As a result, a rapidly growing number of children will have survived childhood cancer. In the Netherlands, nowadays, approximately 1 out of every 750–800 young adults has survived childhood cancer.[3]

Unfortunately, the use of anthracyclines is limited by the occurrence of cardiotoxicity. It can become manifest as either clinical heart failure[4] or asymptomatic cardiac dysfunction,[5] which can not only develop during anthracycline therapy, but also years after the cessation of treatment.[6] Several studies have evaluated the incidence and risk factors for the anthracycline-induced clinical heart failure (A-CHF) in children,[7–9] but the majority of these studies have serious methodological limitations: small study populations, only subgroups were described, and/or a short follow-up period. The reported incidence of A-CHF varies widely between 0%

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and 16%. Several risk factors, like a higher cumulative anthracycline dose, different anthracycline derivates, peak dose (*i.e.* maximal dose received in one week), radiation therapy involving the heart region, female sex, younger age at diagnosis, black race, additional treatment with amsacrine, cyclophosphamide, ifosfamide or mitoxantrone and the presence of trisomy 21, have been identified, although not univocal in all studies.[7,10] The risk of developing anthracycline-induced cardiotoxicity remains a lifelong threat. In one of our earlier studies, the estimated risk of A-CHF increased with time to 2% at 2 years and 5% at 15 years after the start of treatment.[9] Other studies also reported that the incidence of cardiac abnormalities increased with time.[8,11]

The consequences of A-CHF are extensive. It impairs the quality of life in childhood cancer survivors, it involves long-term treatment and thus high medical costs and it causes premature death. The excess mortality due to cardiac disease is 8-fold higher than that expected for long-term survivors of childhood cancer compared to the normal population.[11] In order to establish adequate follow-up protocols for these patients, who should have a long life expectancy after a successful antineoplastic treatment, it is important to estimate the risk and risk factors of A-CHF in those patients.

In this study, we evaluated the cumulative incidence of A-CHF and associated risk factors in a large cohort of patients with childhood cancer treated with anthracyclines between 1976 and 2001.

The patients treated with anthracyclines between 1976 and 1996 have been evaluated before,[9] so for this subgroup we are able to give the results of a 5-year additional follow-up.

2. Patients and methods

2.1. Patients

All children who where treated with anthracyclines in the Emma Children's Hospital/Academic Medical Center (EKZ/AMC) for childhood cancer between 1st January 1976 and 31st December 2000 were eligible for this study. The patients were identified using the Registry of Childhood Cancer of the EKZ/AMC. This registry was established in 1966 and contains data on all children treated for childhood cancer in the EKZ/AMC with regard to diagnosis, treatment and follow-up. We decided to include only patients who received their first treatment with anthracyclines after 1976, because the chemotherapeutic treatment was not specified in the early years of registration. According to the registry, 831 patients were eligible, including the 609 children treated between 1976 and 1996 who have been evaluated before.[9]

2.2. Treatment and follow-up data

If possible, data were collected directly from the medical records of the clinical surveillance of patients at the department of paediatric oncology and/or the late effects outpatient clinic (PLEK) of the EKZ/AMC by one of the authors (EVD). For the patients whose medical records were missing, we obtained information by means of the registry charts kept by the Registry of Childhood Cancer of the EKZ/AMC. Attempts were made to establish the clinical status of patients who were lost to follow-up by sending a questionnaire to their general practitioners.

For each patient the following information was recorded: (1) date of birth, (2) sex, (3) type of malignancy, (4) date of tumour diagnosis, (5) chemotherapeutic protocol, including the cumulative doses of administered anthracycline derivates (*i.e.* doxorubicin, daunorubicin, epirubicin and/or idarubicin), mitoxantrone, ifosfamide, cyclophosphamide and the cardioprotectant dexrazoxane, (6) characteristics of the anthracycline therapy (date of the first and last dose of anthracycline therapy and for each anthracycline derivate: infusion duration, maximal daily dose, maximal dose received in 1 week (peak dose)), (7) concurrent radiotherapy (RT) involving the heart region (*i.e.* on the mediastinum, left part of the upper abdomen, left part of the thorax, thoracic spinal cord and total body irradiation), (8) last follow-up date, (9) date and cause of death, (10) signs and symptoms of clinical heart failure and, if that was the case, aetiology, time of occurrence, treatment and clinical outcome and (11) for patients diagnosed with A-CHF the value of echocardiographic left ventricular shortening fractions (LVSF) measured at the onset of A-CHF.

2.3. Definition of anthracycline-induced clinical heart failure

A case of A-CHF was defined as a congestive heart failure, not attributable to other known causes, such as direct medical effects of the tumour, septic shock, valvular disease or renal failure. We defined congestive heart failure as the presence of the following clinical signs and symptoms: dyspnoea, pulmonary oedema, peripheral oedema and/or exercise intolerance which were treated with anticongestive therapy. A cardiologist (WK) confirmed the diagnosis in patients with cardiac events that may or may not have met this definition of clinical cardiotoxicity. The cardiologist was unaware of the cumulative anthracycline dose received by the patients. The clinical outcome of A-CHF was either 'death', 'alive with anticongestive treatment' or 'clinical recovery without current requirement for anticongestive therapy, but anticongestive treatment previously'. Depending on the time of onset, A-CHF was classified as early A-CHF, *i.e.* during anthracycline chemotherapy or within the first year after the end of treatment, or as late A-CHF, *i.e.* more than 1 year after the completion of anthracycline chemotherapy.[6]

2.4. Statistical analysis

The main outcome event was defined as the occurrence of A-CHF. The 95% confidence interval (CI) of the cumulative incidence of A-CHF was calculated using the statistical program confidence interval analysis.[12] If no cases of anthracycline-induced cardiotoxicity were identified, we used the 'Rule of Three' as described by Hanley and Lippman-Hand.[13]

Event-free survival was defined as the time from the start of anthracycline therapy until the development of A-CHF, or until the latest follow-up evaluation, or until death. The following risk factors for A-CHF were evaluated: sex, age at the first dose of anthracycline therapy, cumulative anthracycline dose, additional treatment with mitoxantrone, ifosfamide,