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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,

cyclophosphamide and/or radiotherapy involving the heart region. The hazard ratio (HR) for each risk factor was estimated with Cox regression analysis.[14] If the HR for each risk factor did not change over time (*i.e.* they fulfilled the proportional hazards assumption), it was allowed to use the HR as the relative risk (RR). We performed both univariate and multivariate Cox regression analyses. Statistical significance ($P < 0.05$) was determined with the Wald test. The cumulative risk of A-CHF was estimated as a function of the follow-up time from the first dose of anthracycline therapy by the Kaplan–Meier method.[15] Survival curves were constructed and confidence intervals were calculated. Analyses were performed using the statistical software SPSS for Windows 11.5.1 (release 2003; SPSS, Inc., Chicago, IL).

3. Results

3.1. *Study population*

The study population consisted of 830 out of 831 eligible patients. The data of 817 of 831 children were collected directly from the medical records. For 13 patients whose medical records were missing, we obtained information by means of the registry charts kept by the Registry of Childhood Cancer. No data were available for 1 child. We succeeded in obtaining information on the clinical status up to at least January 2002 (or date of death) for 795 patients (95.8% of the cohort) including information from general practitioners for 38 patients. For the other 35 patients (including 20 patients who emigrated or returned to their home country), we used the data of the last known follow-up date.

The clinical characteristics of the study population are listed in Table 1. The mean age at the first dose of anthracycline therapy was 8.8 years (median 8.7 years; range 0.1–18.0 years). The mean cumulative dose of anthracyclines was 288 mg/m^2 (median 280 mg/m^2; range 15–900 mg/m^2): 435 children received only doxorubicin (52.4%), 66 children received only daunorubicin (8.0%), 152 children received only epirubicin (18.3%), 1 child received only idarubicin (0.1%) and 176 children received a combination of doxorubicin, daunorubicin, epirubicin and/or idarubicin (21.2%). The exact cumulative dose of anthracyclines of 19 patients is unknown. Different durations of anthracycline infusion were used, both bolus and continuous infusion (uptil 48 h). The daily anthracycline dose varied between 13 and 150 mg/m^2 and the maximal peak dose varied between 15 and 180 mg/m^2. Further treatment is described in Table 1. For patients who received additional treatment with mitoxantrone, ifosfamide and/or cyclophosphamide, the mean cumulative dose of mitoxantrone was 21.8 mg/m^2 (median 12 mg/m^2; range 12–108 mg/m^2), the mean cumulative dose of ifosfamide was 31.3 g/m^2 (median 18.0 g/m^2; range 1.8–132 g/m^2) and the mean cumulative dose of cyclophosphamide was 6.3 g/m^2 (median 5.8 g/m^2; range 0.3–73.5 g/m^2).

The mean follow-up time after the first dose of anthracycline therapy for the whole group was 8.5 years (median 7.1 years; range 0.01–28.4 years). For 272 patients (32.9%), the follow-up was more than 10 years, for 140 patients (16.9%) it was more than 15 years and for 51 patients (6.1%) it was more than 20 years. The mean age of the patients at the end of the

Table 1 – Clinical characteristics of 830 children treated with anthracyclines for childhood cancer

Characteristic	N (%)
Sex	
Male	476 (57.3)
Female	354 (42.7)
Diagnosis	
Haematological malignancies	
ALL	169 (20.4)
AML	76 (9.2)
Hodgkin's disease	78 (9.4)
Non-Hodgkin's disease	170 (20.5)
Solid tumours	
Osteosarcoma	108 (13.0)
Ewing's sarcoma	73 (8.8)
Rhabdomyosarcoma	45 (5.4)
Wilms' tumour	54 (6.5)
Hepatoblastoma	17 (2.0)
Other	40 (4.8)
Age at first anthracycline dose (years)	
<2	76 (9.2)
2–6	257 (30.9)
7–11	224 (27.0)
12–16	251 (30.2)
>16	22 (2.7)
Cumulative dose of anthracycline (mg/m^2)	
<150	101 (12.2)
150–299	318 (38.3)
300–449	242 (29.1)
450–600	135 (16.3)
>600	15 (1.8)
Unknown	19 (2.3)
Mitoxantrone	
Any	34 (4.1)
<40 mg/m^2	29 (85.3)
⩾40 mg/m^2	5 (14.7)
None	793 (95.5)
Unknown	3 (0.4)
Ifosfamide	
Any	226 (27.2)
⩽10 g/m^2	54 (23.9)
>10 g/m^2	162 (71.7)
Unknown	10 (4.4)
None	601 (72.4)
Unknown	3 (0.4)
Cyclophosphamide	
Any	456 (55.0)
⩽10 g/m^2	351 (77.0)
>10 g/m^2	83 (18.2)
Unknown	22 (4.8)
None	372 (44.8)
Unknown	2 (0.2)
Dexrazoxane	
Any	47 (5.7%)
None	782 (94.2%)
Unknown	1 (0.1%)
Radiotherapy involving the heart	
Any	176 (21.2%)
None	653 (78.7%)
Unknown	1 (0.1%)

N, number; %, percentage; ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia.

follow-up was 17.3 years (median 16.7 years; range 0.3–42.7 years). At last contact 297 patients (35.8%) had died: 287 due to tumour-related causes, 4 due to other causes (traffic accidents, dengue virus infection, hepatitis B infection), and there were 6 cases of cardiac death (5 due to A-CHF and 1 due to pericarditis with cardiac tamponade).

3.2. *Incidence and outcome of anthracycline-induced clinical heart failure*

The cumulative incidence of A-CHF at a mean follow-up time of 8.5 years (median 7.1 years; range 0.01–28.4 years) after the first dose of anthracycline therapy was 2.5% (21 patients; 95% CI 1.6–3.8%). The characteristics of the patients with A-CHF are shown in Table 2. Sixteen cases of A-CHF (76.2%) occurred during or within the first year of therapy, *i.e.* early A-CHF. The mean time between the first dose of anthracycline therapy and the occurrence of A-CHF was 3.7 years (median 0.84 years; range 0.1–20.9 years). For 19 patients, an echocardiographic measurement of the LVSF at the onset of A-CHF was available: the mean LVSF was 19.4% (median 20.0%; range 5–32%).

Sixteen of the 20 cases of A-CHF were already identified in our earlier study[9]; after re-evaluation 1 of the 17 patients diagnosed with A-CHF during pregnancy in that study could not be confirmed by the cardiologist. The 5 newly diagnosed cases of A-CHF in this study can be divided in 2 cases of late A-CHF in patients also included in our earlier study (patients 19 and 20 in Table 2) and 3 cases of early A-CHF in patients treated with anthracyclines since 1996 (patients 8, 13 and 14 in Table 2).

The mean age of the patients with A-CHF at the first dose of anthracycline therapy was 8.6 years (median 9.8 years; range 1.3–15.9 years). The mean cumulative anthracycline dose these patients received at the onset of A-CHF was 434 mg/m^2 (median 413 mg/m^2; range 225–810 mg/m^2): 13 children received only doxorubicin (61.9%), 3 children received only epirubicin (14.3%) and 5 children received a combination of doxorubicin, daunorubicin and/or epirubicin (23.8%). Different durations of anthracycline infusion were used, both bolus and continuous infusion (uptil 6 h). The daily anthracycline dose varied between 25 and 150 mg/m^2 and the maximal peak dose varied between 25 and 180 mg/m^2. Further treatment is described in Table 2. For patients who received additional treatment with ifosfamide (7 patients; 33.3%) and cyclophosphamide (9 patients; 42.9%), the mean cumulative dose of ifosfamide at the onset of A-CHF was 39.9 g/m^2 (median 42 g/m^2; range 12–72 g/m^2), and the mean cumulative dose of cyclophosphamide at the onset of A-CHF was 7.3 g/m^2 (median 7.4 g/m^2; range 0.5–18.2 g/m^2). One patient (4.8%) received additional treatment with 12 mg/m^2 mitoxantrone at the onset of A-CHF. Three patients (14.3%) received RT involving the heart region.

The mean follow-up time after the first dose of anthracyclines was 7.9 years (median 3.9 years; range 0.5–22.1 years). The mean age of the patients at the end of follow-up was 16.6 years (median 15.7 years; range 5.5–30.1 years). Five patients (23.8%) died from A-CHF within 0–5.5 years after the onset of symptoms (mean 1.4 years; median 0.04 years). Nine patients (42.9%) died from tumour-related causes; all but 1 still received anticongestive treatment at the time of death. Seven patients (33.3%) are still alive; 3 are still receiving anticongestive therapy whereas the other 4 are not.

One of the patients still receiving anticongestive treatment at the time of our earlier study does not at the moment (patient 18 in Table 2), whereas in another patient the anticongestive therapy was restarted since then (patient 11 in Table 2).

The risk of developing A-CHF as a function of the follow-up time after the first dose of anthracyclines based on Kaplan–Meier estimates is shown in Fig. 1. The estimated risk of A-CHF 2 years after the first dose of anthracyclines was 2% (95% CI 1–3%), 5 years after the first dose of anthracyclines it was 2.4% (95% CI 1.3–3.5%), 10 years after the first dose of anthracyclines it was 2.6% (95% CI 1.4–3.9%), 15 years after the first dose of anthracyclines it was 3.7% (95% CI 1.8–5.5%) and 20 years after the first dose of anthracyclines it was 5.5% (95% CI 1.5–9.5%).

The risk of developing A-CHF was dose-dependent (see Fig. 2). In patients treated with less than 150 mg/m^2 of anthracyclines it was 0% (95% CI 0–3%), in patients treated with 150–299 mg/m^2 it was 0.6% (95% CI 0.1–2.3%), in patients treated with 300–449 mg/m^2 it was 3.3% (95% CI 1.4–6.4%), in patients treated with 450–600 mg/m^2 it was 5.9% (95% CI 2.6–11.3%) and finally in patients treated with more than 600 mg/m^2 it was 14.3% (95% CI 1.8–42.8%).

3.3. *Risk factors for anthracycline-induced clinical heart failure*

The results of the univariate Cox regression analyses of the different risk factors for the occurrence of A-CHF are shown in Table 3. The univariate analyses showed a statistically significant increase in the occurrence of A-CHF associated with the cumulative anthracycline dose: treatment with a cumulative anthracycline dose of 300 mg/m^2 or more showed a statistically significant increase in the occurrence of A-CHF as compared to a cumulative anthracycline dose of less than 300 mg/m^2 (RR = 8.66, 95% CI 2.01–37.35, $P = 0.004$). Additional treatment with ifosfamide with a cumulative dose of more than 10 g/m^2 also showed a statistically significant increase in the occurrence of A-CHF as compared to the treatment with no or 10 g/m^2 or less ifosfamide (RR = 2.67, 95% CI 1.05–6.82, $P = 0.04$). The other possible risk factors for A-CHF (*i.e.* female sex, age at first anthracycline dose 2 years or younger, RT involving the heart region, additional treatment with mitoxantrone and additional treatment with more than 10 g/m^2 of cyclophosphamide) were not associated with an increased risk of A-CHF.

In the multivariate Cox regression analysis, a cumulative anthracycline dose of 300 mg/m^2 or more was the only independent risk factor (Table 4).

Since the HR for each risk factor did not change over time, we present the HR as the RR.

The risk of developing A-CHF as a function of the follow-up time after the first dose of anthracyclines based on Kaplan–Meier estimates for patients treated with a cumulative anthracycline dose of less than 300 mg/m^2 or 300 mg/m^2 or more is shown in Fig. 3. For patients treated with a cumulative

Table 2 – Characteristics, treatment and follow-up of 21 patients with anthracycline-induced clinical heart failure

Pt	Sex	Tumour	Age at first anthra dose (years)	Cum anthra dose (mg/m^2) ¶	Anthra derivate	Mitoxantrone (mg/m^2) ¶	Ifosfamide (g/m^2) ¶	Cyclophosphamide (g/m^2) ¶	RT on heart ¶	Dexrazoxane ¶	Time to A-CHF after therapy	Outcome of A-CHF	LVSF (%)
1	M	NHL	7.1	300	Doxo	N	N	Y (⩽10)	N	N	During A	T*	20
2	F	AML	12.1	300	Doxo/Dauno	N	N	N	Y	N	During A	T*	27
3	F	Osteo	10.5	225	Doxo	N	N	N	N	Y	During A	T*	32
4	M	Rhabdo	5.7	600	Epi	N	Y (>10)	N	N	N	During A	T*	22
5	F	NHL	3.5	?	Doxo	?	?	?	N	N	During A	T*	16
6	M	Osteo	10.6	375	Doxo	N	Y (>10)	N	N	N	During A	No T	20
7	M	Osteo	15.9	450	Doxo	N	Y (>10)	N	N	N	0.1	Death	11
8	F	AML	7.9	230	Doxo/Dauno	?	N	Y (⩽10)	N	N	0.1	No T*	21
9	M	NHL	6.6	700	Doxo	N	N	Y (>10)	N	N	0.1	Death	16
10	F	NHL	10.3	520	Doxo/Dauno/Epi	N	N	Y (⩽10)	N	N	0.1	No T	26
11	M	Osteo	9.8	450	Doxo	N	Y (>10)	N	N	N	0.2	T	9
12	F	NHL	10.1	350	Doxo	N	N	Y (>10)	N	N	0.2	No T	18
13	M	Rhabdo	3.4	600	Epi	N	Y (>10)	N	N	N	0.2	T*	23
14	F	Osteo	11.0	450	Doxo	N	N	N	N	N	0.2	Death	5
15	F	AML	3.2	570	Doxo/Dauno	N	N	Y (⩽10)	Y	N	0.4	T*	25
16	F	Ewing	14.5	360	Doxo	N	Y (>10)	N	N	N	0.4	T*	21
17	M	AML	12.1	810	Doxo/Dauno/Epi	N	N	Y (⩽10)	N	N	1.4	Death	20
18	M	Ewing	15.4	480	Doxo	N	Y (>10)	N	N	N	6.7	No T	?
19	F	NHL	6.2	300	Epi	Y (<40)	N	Y (⩽10)	N	N	13.5	T	8
20	F	Wilms	3.5	300	Doxo	N	N	N	Y	N	13.8	T	28
21	M	Rhabdo	1.3	300	Doxo	N	N	Y (⩽10)	N	N	20.2	Death	?

Pt, patient; M, male; F, female; NHL, non-Hodgkin lymphoma; AML, acute myeloid leukaemia; osteo, osteosarcoma; rhabdo, rhabdomyosarcoma; Ewing, Ewing's sarcoma; Wilms, Wilms tumour; anthra, anthracycline; cum, cumulative; A-CHF, anthracycline-induced clinical heart failure; doxo, doxorubicin; dauno, daunorubicin; epi, epirubicin; N, no; Y, yes; ?, data missing; A, anthracycline; LVSF, echocardiographic left ventricular shortening fraction; T, anticongestive treatment; no T, no anticongestive treatment at time of last follow-up, but anticongestive treatment previously; T*, used anticongestive treatment until time of death (died from tumour progression or from medical conditions related to tumour treatment excluding A-CHF); no T*, no anticongestive treatment at time of death, but anticongestive treatment previously (died from tumour progression or from medical conditions related to tumour treatment excluding A-CHF); ¶, at time of diagnosis A-CHF.

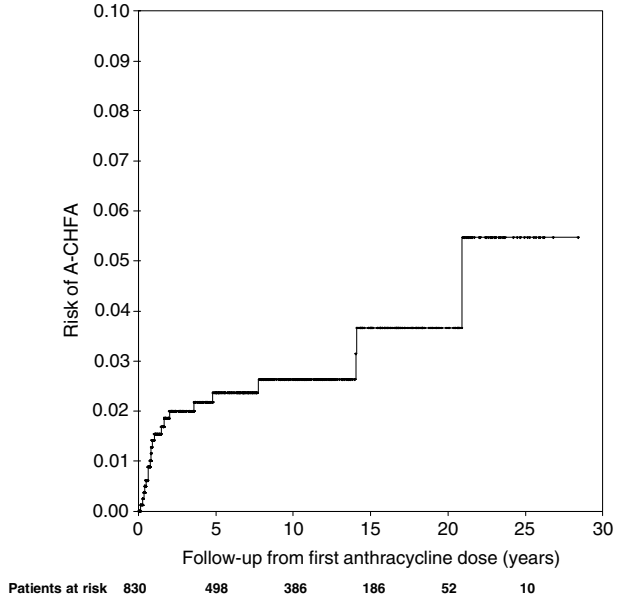

Fig. 1 – Kaplan–Meier plot of the estimated risk of anthracycline-induced clinical heart failure (A-CHF) as a function of the follow-up time after the first dose of anthracyclines.

Table 3 – Risk factors for the occurrence of anthracycline-induced clinical heart failure (univariate Cox regression analyses)

Risk factor	RR	95% CI	P-value
Female sex	1.46	0.62–3.43	0.39
Age at first anthra dose ⩽2 years	0.28	0.04–2.09	0.22
Cum anthra dose ⩾300 mg/m^2	8.66	2.01–37.35	**0.004**
RT on heart	0.67	0.20–2.29	0.53
Treatment with mitoxantrone	1.38	0.18–10.37	0.76
Cum ifosfamide >10 g/m^2	2.67	1.05–6.82	**0.04**
Cum cyclophosphamide >10 g/m^2	0.73	0.17–3.20	0.68

RR, relative risk; CI, confidence interval; anthra, anthracycline; cum, cumulative; RT, radiotherapy.

Table 4 – Risk factors for the occurrence of anthracycline-induced clinical heart failure (multivariate Cox regression analyses)

Risk factor	RR	95% CI	P-value
Cum anthra dose ⩾300 mg/m^2	7.78	1.76–34.27	**0.007**
Cum ifosfamide >10 g/m^2	1.65	0.64–4.26	0.30

RR, relative risk; CI, confidence interval; anthra, anthracycline; cum, cumulative.

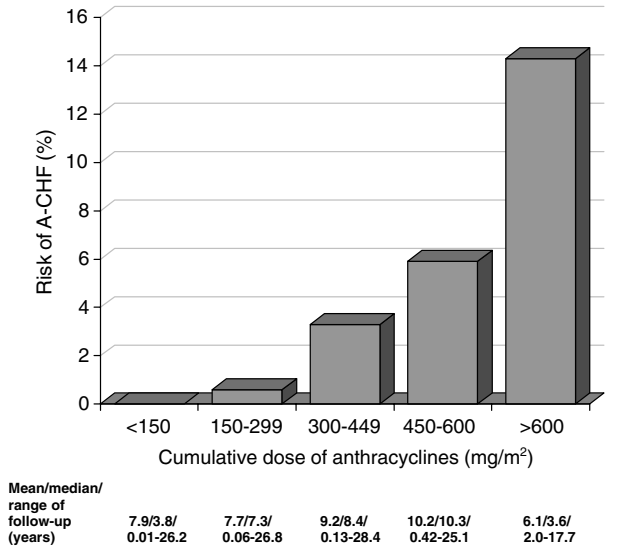

Fig. 2 – Risk of anthracycline-induced clinical heart failure (A-CHF) according to cumulative anthracycline dose.

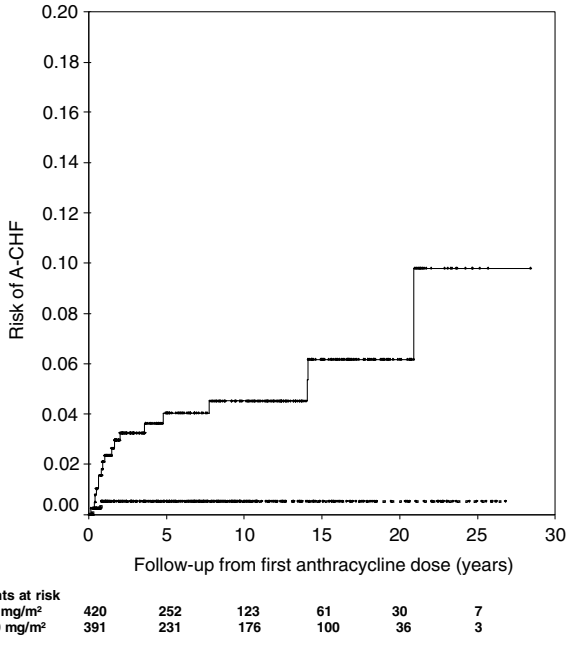

Fig. 3 – Kaplan–Meier plot of the estimated risk of anthracycline-induced clinical heart failure (A-CHF) as a function of the follow-up time after the first dose of anthracyclines for patients treated with a cumulative anthracycline dose of less than 300 mg/m^2 (lower line) or 300 mg/m^2 or more (upper line).

anthracycline dose of less than 300 mg/m^2, the estimated risk of A-CHF 2 years after the first dose of anthracyclines was 0.5% (95% CI 0.0–1.23%). This risk did not increase any further with a longer duration of follow-up. For patients treated with a cumulative anthracycline dose of 300 mg/m^2 or more, the estimated risk of A-CHF 2 years after the first dose of anthracyclines was 3.3% (95% CI 1.4–5.1%), 5 years after the first dose of anthracyclines it was 4.1% (95% CI 1.9–6.2%), 10 years after the first dose of anthracyclines it was 4.5% (95% CI 2.2 to 6.8%), 15 years after the first dose of anthracyclines it was 6.2% (95% CI 3–9.4%) and 20 years after the first dose of anthracyclines it was 9.8% (95% CI 2.2–17.4%).

4. Discussion

This study in a large cohort of patients with a very long and complete follow-up demonstrates that the risk of A-CHF increased over time and that it was strongly dose-dependent. The estimated risk of A-CHF increased from 2% at 2 years after the start of anthracycline therapy to 5.5% at 20 years. For patients treated with a cumulative anthracycline dose of 300 mg/m^2 or more, the estimated risk at 20 years after the start of anthracycline therapy was nearly 10%. This means that 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, especially considering the fact that presently some treatment protocols still include 300 mg/m^2 or more of anthracycline therapy and that this study describes a young patient population.

In the whole cohort of 830 patients, the cumulative incidence of A-CHF after a mean follow-up of 8.5 years (median 7.1 years; range 0.01–28.4 years) after the first dose of anthracycline therapy for childhood cancer was 2.5%. The cumulative incidence of early A-CHF was 1.9%. An explanation for this high cumulative incidence of early A-CHF in comparison with the cumulative incidence of late A-CHF could be that the clinical condition of children during chemotherapy, when they often suffer from anaemia, acidosis, cachexia, fever or overhydration from intravenous fluid, possibly lowers the threshold for A-CHF. The cumulative incidence of late A-CHF was 0.6%. At the moment, it is unclear what the incidence of late A-CHF will be with a follow-up beyond 20 years, but it is seems appropriate to assume that there will be a further increase in the incidence of late A-CHF with time. Green and colleagues[8] reported that the risk of A-CHF increased with a longer follow-up and several studies have reported an increase in the asymptomatic cardiac dysfunction with a longer follow-up.[5,16] It is very likely that asymptomatic abnormalities will progress to a clinically significant impairment of cardiac function. Also, when the childhood cancer survivors become older, aging of the heart will become important.

A part of this cohort (607 patients, 73%) has been evaluated before[9] and for this subgroup we now have the results of a 5-year additional follow-up. Therefore, we are able to present the estimated risk of A-CHF 20 years after the start of anthracycline therapy, confirming the increase of the risk of A-CHF beyond 15 years after the start of anthracycline therapy. Two of the 607 patients developed late A-CHF (respectively, at 13.5 and 13.8 years after the cessation of anthracycline therapy) since our earlier study.

As stated in earlier reports, the occurrence of A-CHF is a dose-dependent phenomenon.[4,7,8] This was confirmed in this study. Even more seriously, for patients treated with a cumulative anthracycline dose of 300 mg/m^2 or more an 8-fold higher risk of A-CHF was found as compared to patients treated with a cumulative anthracycline dose of less than 300 mg/m^2 ($P = 0.007$). Only 2 cases of A-CHF occurred in patients treated with less than 300 mg/m^2 (225 and 230 mg/m^2, respectively). For patients treated with a cumulative anthracycline dose of less than 300 mg/m^2, the estimated risk of A-CHF 2 years after the first dose of anthracyclines was 0.5%. This risk did not increase any further with a longer duration of follow-up. On the other hand, for patients treated with a cumulative anthracycline dose of 300 mg/m^2 or more (47% of our cohort), the estimated risk of A-CHF 2 years after the first dose of anthracyclines was 3.3%, and this risk increased to 9.8% 20 years after the first dose of anthracyclines, which is extremely high. And it is even possible that we underestimated the true incidence of A-CHF, since we used a very strict definition of A-CHF, *i.e.* congestive heart failure treated with anticongestive therapy not attributable to other known causes including valvular disease.

In contrast with other studies, we could not identify other risk factors for the development of A-CHF. However, the identification of risk factors for A-CHF has not been univocal in the literature.[7,10]

At the moment, many treatment protocols still include 300 mg/m^2 or more of anthracycline therapy and many children diagnosed with a relapse will receive additional anthracycline therapy. The results of this study reinforce the need of re-evaluating the cumulative anthracycline dose used in different treatment protocols. Also, strategies to prevent anthracycline-induced cardiotoxicity should be implemented in treatment protocols. For example, even though there is some suggestion that patients treated with the cardioprotectant dexrazoxane might have a lower response rate,[17] in children who will receive a cumulative anthracycline dose of 300 mg/m^{2}or more it might be justified to use it. Furthermore, it is important not to forget that, although the risk of A-CHF is significantly increased with a cumulative anthracycline dose of 300 mg/m^2 or more, both A-CHF and asymptomatic cardiac dysfunction can occur with a lower cumulative anthracycline dose.[5] At present, there is no effective therapy to prevent further deterioration of asymptomatic cardiac dysfunction. Both treatment with ACE-inhibitors[18] and growth hormone therapy[19] did not lead to a lasting improvement in cardiac structure and function.

In conclusion, the risk of A-CHF 20 years after the start of anthracycline therapy was estimated to be approximately 10% in patients treated with a cumulative anthracycline dose of 300 mg/m^2 or more. The patients treated with a lower cumulative anthracycline dose had a relatively low risk of 0.5%. It remains unclear what the cumulative incidence of A-CHF will be with a longer follow-up, but it is likely to increase even further with time.

Conflict of interest statement

None of the authors have competing interests.

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