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Review

Cumulative incidence and risk factors of mitoxantrone-induced cardiotoxicity in children: a systematic review

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Abstract

Mitoxantrone is believed to maintain anthracycline antitumour activity but be associated with a reduced cardiotoxicity. The aim of this study was to evaluate the evidence for the cumulative incidence of and risk factors for mitoxantrone-induced cardiotoxicity (M-CT) in children treated for childhood cancers. After an extensive literature search, 17 studies were included. The cumulative incidence varied between 0 and 6.7% in the 16 studies evaluating symptomatic M-CT and between 0 and 80% in the 11 studies evaluating asymptomatic M-CT. Risk factors for developing M-CT remain unclear. All studies had serious methodological limitations. In conclusion, children treated with mitoxantrone are at risk of developing M-CT, but due to the low quality of the current evidence, the exact cumulative incidence and risk factors for M-CT remain unclear. It is too early to conclude that in children mitoxantrone is less cardiotoxic than anthracyclines. More well-designed studies are needed to reliably evaluate the incidence of M-CT and its associated risk factors.

Keywords: Cardiotoxicity; Children; Heart failure; Mitoxantrone; Review, academic

1. Introduction

Mitoxantrone is an anthracenedione derivate which is structurally related to the anthracycline derivates. It was synthesised in an effort to maintain or even improve anthracycline antitumour activity, but with reduced side-effects, particularly cardiotoxicity [1]. Similar to cardiotoxicity induced by anthracyclines, mitoxantrone-induced cardiotoxicity (M-CT) can become manifest in patients as either clinical heart failure, cardiac death or asymptomatic cardiac dysfunction. According to the time of presentation, M-CT can be divided into early and late M-CT: early M-CT occurs during mitoxantrone therapy or in the first year after its completion, and late M-CT manifests itself at least 1 year after the completion of mitoxantrone therapy.

Children have a long life-expectancy after a successful antineoplastic treatment. In order to establish adequate follow-up protocols for children treated with mitoxantrone, it is important to know the cumulative incidence of M-CT and to understand which patients are at greatest risk of developing M-CT.

Moreover, many of the children who are receiving mitoxantrone therapy, have had prior anthracycline therapy, and are thus already at risk for developing heart failure. Especially in this group of patients, it is very important to know the impact of M-CT, so adequate decisions about treatment policies can be made.

In this systematic review, an evaluation of the existing evidence is made to obtain more insight into the cumulative incidence and the risk factors of M-CT after treatment for childhood cancer, and, if possible, to compare cardiotoxicity of mitoxantrone with that of the anthracycline derivates.

2. Methods

2.1. Search strategy for identification of studies

The objective of the literature search was to identify all studies reporting on the cumulative incidence of

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mitoxantrone-induced cardiac damage after treatment for childhood cancer. The databases of MEDLINE (from 1966 to October 2002) and EMBASE (from 1980 to October 2002) were searched for potentially relevant articles, combining subject headings and textwords for mitoxantrone, children and heart failure (complete search strategies can be obtained from the corresponding author).

Information on trials not registered in MEDLINE or EMBASE was located by scanning the reference lists of the relevant articles and reviews. In addition, the conference proceedings of the International Society for Paediatric Oncology (SIOP) and the American Society of Clinical Oncology (ASCO) were searched by hand, and so were the following journals: *Annals of Oncology*, *Journal of Clinical Oncology*, and *Medical and Pediatric Oncology*. Both the conference proceedings and the journals were handsearched from 1998 to 2002.

2.2. Selection of articles

Articles were selected on the basis of title and abstract by two independent reviewers (EvD, HvdP) using the following inclusion criteria: (1) study population of children aged 18 years or less treated with mitoxantrone for a childhood malignancy, (2) clinical heart failure, cardiac death and/or asymptomatic cardiac dysfunction as outcome, (3) original research with the exception of case-control studies, case series and case reports, and (4) written in English, Dutch, French or German. To be included in this systematic review, each article had to meet all four criteria.

If the abstract of the article was unavailable electronically or in case it provided insufficient information, full papers were retrieved for more detailed examination. All retrieved articles were screened by the two reviewers to ensure that they met the inclusion criteria. In case of double publications, only one study was included; in case of studies with overlapping data, all studies were included stating the overlap. Inter-observer agreement was calculated.

2.3. Data extraction

From each article, information about the study characteristics, the study population, duration of follow-up, definition and cumulative incidence of M-CT, and the presence of possible risk factors such as prior or concomitant anthracycline chemotherapy and radiotherapy involving the heart region, was abstracted by two independent reviewers (EvD, HvdP). In this systematic review, M-CT was defined as the occurrence of symptoms and/or cardiac abnormalities diagnosed with a cardiac test in patients treated with mitoxantrone as reported by the authors of the included articles. If studies evaluated possible risk factors for M-CT in a multivariate analysis (i.e. adjusted for confounders), we extracted these data.

If in studies including both adults and children only information for the whole study population with regard to treatment with mitoxantrone, anthracyclines and/or radiotherapy involving the heart region was given, we abstracted these data. If important data were lacking, but in the publication the reader was referred to another article on these data, then this reference was retrieved and used for evaluation of the original paper, even if the reference did not fulfil the selection criteria for this review.

2.4. Quality assessment of the included studies

To determine the quality of the selected studies, two independent reviewers (EvD, HvdP) assessed the design and execution of each study. The quality assessment was based on Evidence-Based Medicine criteria [2,3] and focused primarily on the evaluation of the cumulative incidence and possible risk factors of M-CT. Each study was graded on the basis of (not) meeting the criteria.

First, the study population was evaluated: a sample was considered to be well-defined if the mean, median or range of the cumulative mitoxantrone dose was mentioned and when it was described what other (prior) cardiotoxic treatment (i.e. the number of patients treated with anthracyclines and/or radiotherapy involving the heart region including the received dose) was given. A sample was defined as representative for the underlying population if it consisted of more than 95% of the patients treated with mitoxantrone included in the original cohort or if it was a random sample of these patients with respect to important prognostic factors. We defined a cohort as a group of consecutive patients treated with mitoxantrone for childhood cancer. It was also assessed whether the study patients were followed from the start of mitoxantrone treatment onwards or from a fixed point thereafter.

Second, follow-up was evaluated: a minimal follow-up of more than 1 year after the start of treatment or a median or mean follow-up of 2 years after the start of treatment was considered to be long enough to determine the cumulative incidence of M-CT. Follow-up was considered to be complete if the outcome was assessed at the end-date of the study for more than 90% of the study patients. When outcome was assessed for more than 90% of the study patients, but when it was unclear whether this was done at the end-date of the study, we considered this to be adequate.

Third, outcome assessment was evaluated: it was assessed whether an objective definition of outcome criteria was used. In case of clinical heart failure or cardiac death, outcome was considered to be objective if clinical signs and symptoms used for the diagnosis were described and the diagnosis was verified by a diagnostic test. In case of asymptomatic cardiac dysfunction, outcome

was considered to be objective if it was mentioned which test parameters were used and a definition for values considered to be abnormal was given. It was also assessed whether the outcome assessors were blinded with regard to important prognostic factors.

When we abstracted treatment data for the whole study population including both children and adults or when we used data reported in publications referred to in the original paper, these data were not considered for the quality assessment of these studies.

Discrepancies between reviewers occurring during the selection of articles, data extraction or quality assessment of included studies were solved by discussion. If this was impossible, a third reviewer was consulted.

2.5. Data analysis

The cumulative incidence of symptomatic M-CT (including cardiac death) and/or asymptomatic M-CT was calculated as the number of children with clinical heart failure or asymptomatic cardiac dysfunction, respectively, divided by the total number of children treated with mitoxantrone in the study group. The 95% Confidence Interval (CI) of the cumulative incidence of M-CT was calculated using the statistical programme Confidence Interval Analysis (CIA) [4]. If the included studies were of good methodological quality and if the various study groups were comparable with regard to age, gender, tumour diagnosis, treatment, definition used for M-CT and length of follow-up, a pooled analysis of the cumulative incidence of M-CT and the associated risk factors was to be performed.

3. Results

3.1. Selection of articles

The MEDLINE and EMBASE searches identified a total of 111 potentially relevant articles. Screening of the titles and abstracts of these articles excluded 47 studies. The remaining 64 articles were retrieved for more detailed examination. For this selection, the interobserver agreement was 96.4%. Eighteen of the retrieved articles met all the inclusion criteria, including 3 double publications [5–7]. The interobserver agreement for this step of the selection process was 100%. After handsearching the conference proceedings, journals and reference lists of the relevant studies and reviews, 17 additional articles were retrieved for more detailed examination and 2 studies met all the inclusion criteria. The interobserver agreement was 100%.

Thus, after excluding the double publications, 17 studies were included in this systematic review. Consultation of a third reviewer was not needed.

3.2. Description of the included studies

In Table 1, the study characteristics and results of all included studies reporting on symptomatic and/or asymptomatic M-CT are presented.

3.2.1. General

The cumulative incidence of M-CT was evaluated in 17 cohort studies: 15 were prospective and 2 retrospective [11,14]. Sixteen studies reported on symptomatic M-CT [8–11,13–24] and 11 studies reported on asymptomatic M-CT [8,10,12,14,15,17,20–24]. None of the studies was a controlled trial comparing the cardiac toxicity of mitoxantrone therapy with that of other possible cardiotoxic treatments like anthracyclines.

Thirteen studies included children diagnosed with acute leukaemia (i.e. acute lymphoblastic leukaemia (ALL) or acute myeloid leukaemia (AML)) or myelodysplastic syndrome [9–13,15–19,22–24]. In 10 of these studies, the leukaemia was either relapsed or refractory to prior treatment [10,12,13,16–19,22–24]. In the other 4 studies, children with various tumours at different stages of the disease were included.

Ten studies mentioned the gender of the included children [10,12,15–17,20–24]. The percentage of females in the studies varied considerably between 10 and 75%. Fourteen studies mentioned the age at diagnosis, which ranged from 0 to 26 years [9–13,15–18,20–24]. None of the studies reported the age at follow-up.

Ten studies provided data with regard to the cumulative mitoxantrone dose (Table 1) [8,10,12,13,15,17,20,21,23,24]. Fifteen studies reported the maximal mitoxantrone dose administered in 1 week and the maximal single mitoxantrone dose, which ranged from 18 to 80 mg/m^2 (mean 40.87 mg/m^2) and from 6 to 33 mg/m^2 (mean 12.33 mg/m^2), respectively [9–13,15–24].

All studies mentioned the number of children treated with prior or concomitant anthracycline therapy (i.e. daunorubicin, doxorubicin and/or idarubicin), which varied between 0 and 100%. However, 7 of the 17 studies did not mention the cumulative anthracycline dose [12,17,20–24]. In the other 10 studies, the cumulative anthracycline dose ranged between 0 and 500 mg/m^2 [8–11,13–16,18,19]. In 2 studies, children had not received any anthracyclines [8,15]. Only Pratt and colleagues [20] reported that some patients had received radiation therapy involving the heart region: they stated that 15 of the 101 patients (15%) had pulmonary and/or mediastinal radiation therapy, including 1 total body irradiation (TBI). However, the radiation dose was not provided. In all other studies, the presence of radiation therapy involving the heart region was not mentioned.

Data on the duration and/or the completion of follow-up for the assessment of cardiac toxicity were only reported in 5 studies. Three studies mentioned the duration of follow-up (Table 1) [9,15,18]. Four studies

Table 1
Study characteristics and results of all included studies

Author, Publication Year [Ref.]	Original study group		Children treated with mitoxantrone			Symptomatic heart failure[a]		Asymptomatic cardiac dysfunction		Follow-up	
	N	Only children/ all ages	*N*	Cumulative mitoxantrone dose (mg/m^2)	*N* (prior) anthracyclines (%)	Definition Method of detection	*N* (%; 95% CI)	Definition Method of detection	*N* (%; 95%CI)	Duration (years)	*N* (%)
Kremer, 2002 [8]	38	Only children	5	Mean 106	0 (0)	Heart failure due to cardiotoxic chemotherapy. Nm	0 (0; 0–52.2)	SF < 30% or a decline of ⩾15% from baseline. Echocardiography.	4 (80; 28.4–99.5)	Nm	Nm
Creutzig, 2001 [9]	471	Only children	285	Nm	285 (100)	Death due to cardiac insufficiency (and alveolar proteinosis). Nm	1 (0.4; 0.01–1.9)			1.1–6.9 (during continuous CR)	Nm
Dahl, 2000 [10]	68	Only children	68	Max 90	66 (97)	Clinical heart failure. Nm	4 (5.9; 1.6–14.4)	Decreased EF or SF (patients had multifactorial problems). MUGA-scan/echocardiography.	12 (17.6; 9.5–28.8)	Nm	Nm
Riley, 1999 [11]	359	Only children	Max 311	Nm	Max 311 (100)	Death from a cardiac event unrelated to sepsis. Postmortem.	1 (min 0.3; 0.01–1.8)			Nm	Nm
Pourtsidis, 1998 [12]	17	Only children	17	Range 30–100	Min 9 (min 53)			Decreased LVEF. Nm	1 (5.9; 0.2–28.7)	Nm	Nm
Fevzi Ozkaynak, 1998 [13]	15	Only children	15	Max 48	15 (100)	Congestive heart failure. Nm	1 (6.7; 0.17–32)			Nm	Nm
Krischer, 1997 [14]	6493	Only children	92	Nm	92 (100)	Congestive heart failure or sudden death from presumed cardiac causes due to treatment. Signs and symptoms[b]; diagnosis confirmed by cardiologist.	2 (2.2; 0.3–7.6)	Abnormal measurements of cardiac function that prompted discontinuation of therapy. Echocardiography/radio-nuclide scan; diagnosis confirmed by cardiologist.	2 (2.2; 0.3–7.6)	Nm	Nm
Behar, 1996 [15]	108	Only children	106	Max 150	0 (0)	Cardiac death. Nm	0 (0; 0–3.4)	Unexplained SF ⩽28%. Echocardiography.	12 (11.3; 5.3–17.4)	Median 3.5 (range nm)	106 (100)[g]
Wells, 1994 [16]	29	Only children	29	Nm	29 (100)	Cardiac toxicity (associated with allergic drug reaction). Nm	1 (3.4; 0.1–17.8)			Nm	Nm
Vorobiof, 1987 [17]	46	All ages	11	Median 100 (range 30–300)[c]	8 (73)	Heart failure. Clinical signs.	0 (0; 0–28.5)	Absolute fall in LVEF. Resting nuclear ventriculography.	1 (9.1; 0.2–41.3)	Nm	Nm
Steuber, 1987 [18]	21	Only children	21	Nm	Max 20 (max 95)	Congestive heart failure (not due to infection, volume overload, anthracyclines). Nm	0 (0; 0–16.1)			Min 3 weeks after mitoxantrone course	20 (95.2)

(continued on next page)

Table 1 (*continued*)

Author, Publication Year [Ref.]	Original study group		Children treated with mitoxantrone			Symptomatic heart failure[a]		Asymptomatic cardiac dysfunction		Follow-up	
	N	Only children/ all ages	*N*	Cumulative mitoxantrone dose (mg/m^2)	*N* (prior) anthracyclines (%)	Definition Method of detection	*N* (%; 95% CI)	Definition Method of detection	*N* (%; 95%CI)	Duration (years)	*N* (%)
Ritter, 1987 [19]	19	Only children	19	Nm	19 (100)	Cardiotoxicity. Nm	1 (5.3; 0.1–26)			Nm	Nm
Pratt, 1986 [20]	101	All ages[d]	101	Mean 34.4[e] (range 18–144)	92 (91)	Death associated with CMP. Nm	2 (2; 0.2–7)	Asymptomatic abnormal LVEF. Echocardiography/MUGA-scan.	3 (3; 0.6–8.4)	Nm	98 (97)[g]
Ungerleider, 1985 [21]	84	Only children	84	Median 28 (range 10–187)	83 (99)	Congestive heart failure. Signs and symptoms.[f]	3 (3.6; 0.7–10.1)	Decreased LVSF. Echocardiography.	3 (3.6; 0.7–10.1)	Nm	Nm
Starling, 1985 [22]	24	Only children	24	Nm	23 (96)	Cardiotoxicity. Clinical signs.	0 (0; 0–14.2)	Decrease in EF and/or SF. Echocardiography/radio-nuclide scan.	4 (16.7; 4.7–37.4)	Nm	Nm
Ehninger, 1985 [23]	24	All ages	4	Mean 50[e] (range 40–80)	4 (100)	Congestive heart failure. Nm	0 (0; 0–60.2)	Abnormal LV function. Echocardiography/resting nuclear angiography.	0 (0; 0–60.2)	Nm	Nm
Paciucci, 1983 [24]	26	All ages	8	Mean 75[e] (range 60–140)	7 (88)	Mitoxantrone-induced cardiotoxicity. Nm	0 (0; 0–36.9)	Mitoxantrone-induced cardiotoxicity. Nm	0 (0; 0–36.9)	Nm	8 (100)[g]

Public, publication; CMP, cardiomyopathy; N, number; CI, Confidence Interval; nm, not mentioned; SF, shortening fraction; max, maximal; EF, ejection fraction; min, minimal; LV, left ventricular; CR, complete remission; MUGA, multigated angiogram scan.

[a] Including cardiac death

[b] i.e. pulmonary or peripheral oedema, dyspnoea on exertion, poor feeding, increased liver size and deterioration in exercise tolerance treated with anticongestive therapy.

[c] For the whole cohort, no separate value for only the children given.

[d] All patients were less than 25 years of age and had a childhood malignancy.

[e] As calculated by the authors.

[f] i.e. cardiomegaly, tachypnoea, dyspnoea, tachycardia, hepatomegaly supported by cyanosis, oedema or hypertension.

[g] Unclear if followed until end-date of study.

reported the completion of follow-up [15,18,20,24], ranging from 95.2% to 100%. However, only in the study of Steuber and colleagues [18] were the follow-up data complete until the end-date of the study. In all but one study, the beginning of follow-up was the start of mitoxantrone therapy. The other study followed patients from different stages of their treatment [8].

3.2.2. Symptomatic mitoxantrone-induced cardiotoxicity

The cumulative incidence of symptomatic M-CT was reported in 16 of the 17 studies [8–11,13–24]. It varied between 0 and 6.7% (Fig. 1). In 7 of the 16 studies, none of the children developed symptomatic M-CT [8,15,17,18,22–24]. Many different definitions of symptomatic M-CT were used and the methods of detection used also varied among the studies (Table 1). Only Krischer and colleagues [14] stated that the diagnosis of symptomatic M-CT was confirmed by cardiologists.

3.2.3. Asymptomatic mitoxantrone-induced cardiotoxicity

The cumulative incidence of asymptomatic M-CT was evaluated in 11 of the 17 studies [8,10,12,14,15,17,20–24]. It varied between 0 and 80% (Fig. 2). In 2 of the 11 studies, none of the children developed asymptomatic M-CT [23,24]. The definitions of asymptomatic M-CT and the methods of detection used varied among the studies (Table 1). Three studies did not report which test parameters were used to diagnose asymptomatic M-CT [14,23,24]. In only 2 of the 8 studies, a definition for values considered to be abnormal was given [8,15]. The lower limit of normal was 30 or 28%, respectively. Only Krischer and colleagues [14] stated that the diagnosis of asymptomatic M-CT was confirmed by cardiologists.

3.2.4. Risk factors

Only Krischer and colleagues [14] evaluated possible risk factors, although the risk factors were not separately analysed for symptomatic and asymptomatic M-CT. In univariate analyses of children treated with anthracyclines, the risk of cardiotoxicity was significantly increased among children treated with mitoxantrone (RR 3.58; 95%CI 1.32 to 9.76). Higher doses of mitoxantrone (40 mg/m^2 or more) further increased the risk (RR 5.08; 95% CI 1.87 to 13.84). However, in a multivariate model corrected for race, gender, presence or absence of trisomy 21, irradiation of the chest and treatment with amsacrine, cyclophosphamide or anthracyclines, treatment with mitoxantrone did not increase the risk of cardiotoxicity beyond that for anthracyclines. According to the authors, this finding may reflect the small number of children who received mitoxantrone.

3.2.5. Quality assessment of studies evaluating symptomatic mitoxantrone-induced cardiotoxicity

Data on the quality assessment of the 16 studies reporting on symptomatic M-CT are shown in Table 2. This assessment focused primarily on the evaluation of the cumulative incidence and possible risk factors of symptomatic M-CT. All 16 studies were found to have methodological limitations. In none of the studies was the study group well-defined: 7 of the 16 studies did not

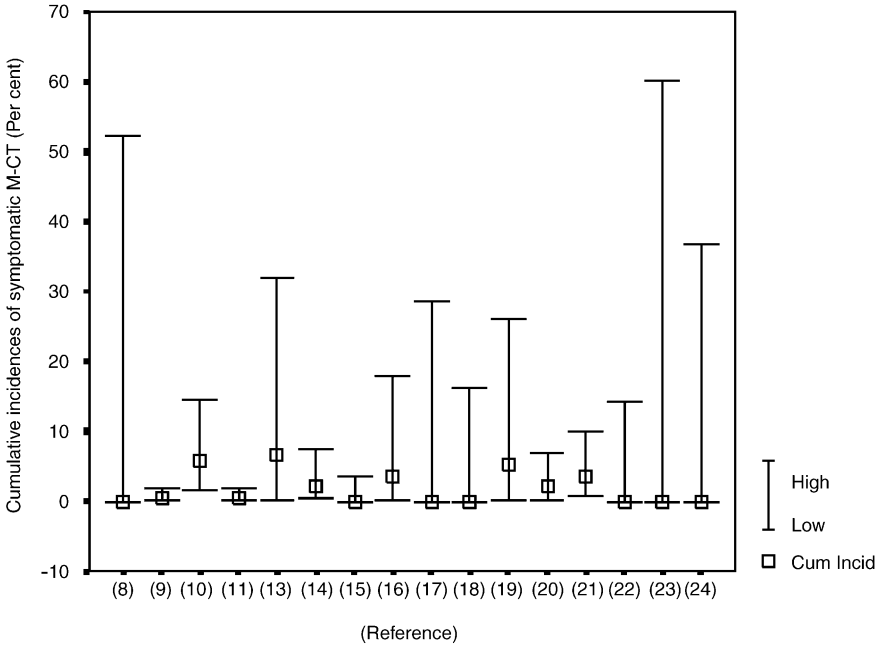

Fig. 1. Cumulative incidences (%) of symptomatic mitoxantrone-induced cardiotoxicity (M-CT). High, upper limit of 95% Confidence Interval (CI); low, lower limit of 95% CI; cum incid, cumulative incidence.

report the cumulative mitoxantrone dose [9,11,14,16,18,19,22]; 6 of the 16 studies did not report the cumulative anthracycline dose [17,20–24] and none of the 16 studies mentioned the dose of radiation therapy involving the heart region. In 15 of the 16 studies, the study group consisted of the whole cohort of children treated with mitoxantrone [8–10,13–24]. In 15 of the 16 studies, the beginning of follow-up was the start of mitoxantrone therapy [9–11,13–24]. Only 3 of the 16 studies mentioned the duration of follow-up [9,15,18], of which 2 had an adequate length [9,15]. Four of the 16 studies reported having a complete follow-up [15,18,20,24], but

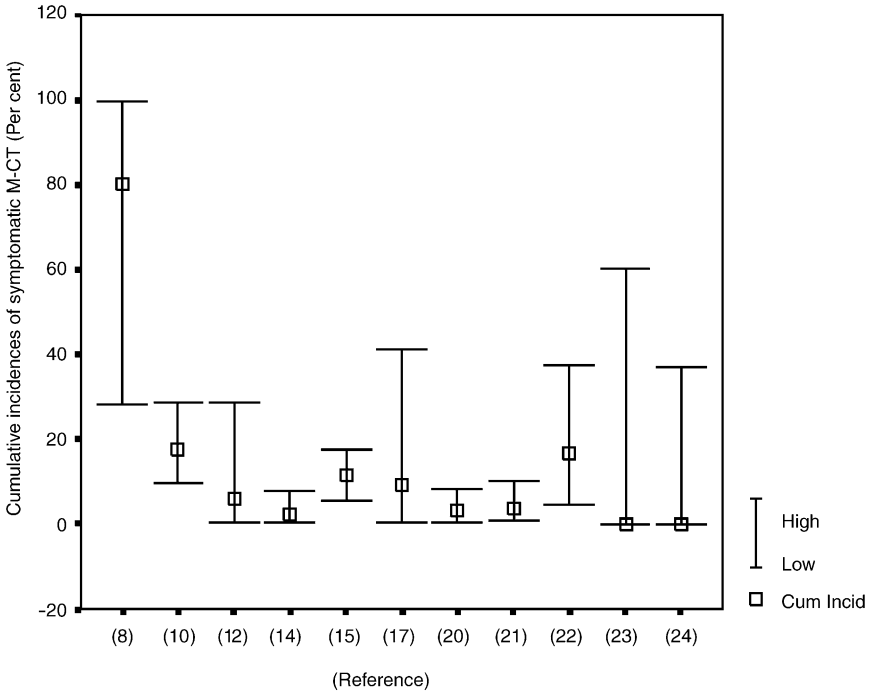

Fig. 2. Cumulative incidences of mitoxantrone-induced cardiotoxicity (M-CT). High, upper limit of 95% CI; low, lower limit of 95%CI; cum incid, cumulative incidence.

Table 2
Quality assessment of studies evaluating symptomatic M-CT

Author, year [Ref.]	Study group			Follow-up		Outcome	
	Well defined	Whole cohort/random sample	Follow-up start of treatment or fixed point thereafter	Long enough	Complete[a]	Objective	Blind
Kremer, 2002 [8]	–	+	–	Nm	Nm	–	Nm
Creutzig, 2001 [9]	–	+	+	+	Nm	–	Nm
Dahl, 2000 [10]	–	+	+	Nm	Nm	–	Nm
Riley, 1999 [11]	–	Nm	+	Nm	Nm	+	Nm
Fevzi Ozkaynak, 1998 [13]	–	+	+	Nm	Nm	–	Nm
Krischer, 1997 [14]	–	+	+	Nm	Nm	+	Nm
Behar, 1996 [15]	–	+	+	+	+	–	Nm
Wells, 1994 [16]	–	+	+	Nm	Nm	–	Nm
Vorobiof, 1987 [17]	–	+	+	Nm	Nm	–	Nm
Steuber, 1987 [18]	–	+	+	–	+ +	–	Nm
Ritter, 1987 [19]	–	+	+	Nm	Nm	–	Nm
Pratt, 1986 [20]	–	+	+	Nm	+	–	Nm
Ungerleider, 1985 [21]	–	+	+	Nm	Nm	+	Nm
Starling, 1985 [22]	–	+	+	Nm	Nm	–	Nm
Ehninger, 1985 [23]	–	+	+	Nm	Nm	–	Nm
Paciucci, 1983 [24]	–	+	+	Nm	+	–	Nm

+, yes; –, no; nm, not mentioned. M-CT, mitoxantrone-induced cardiotoxicity.
[a] In this column: + + complete and + adequate.

the data were complete until the end-date of the study in only 1 of these studies [18]. Only 3 of the 16 studies used an objective outcome definition [11,14,21] and none of the studies mentioned that the outcome assessor was blinded for important prognostic factors.

3.2.6. Quality assessment of studies evaluating asymptomatic mitoxantrone-induced cardiotoxicity

Data on the quality assessment of the 11 studies reporting on asymptomatic M-CT are shown in Table 3. Again, this assessment focused primarily on the evaluation of the cumulative incidence and possible risk factors of asymptomatic M-CT. All 11 studies were found to have methodological limitations. In none of the studies was the study group well-defined: 2 of the 11 studies did not report the cumulative mitoxantrone dose [14,22]; 7 of the 11 studies did not report the cumulative anthracycline dose [12,17,20–24] and none of the 11 studies mentioned the dose of radiation therapy involving the heart region. All studies described a whole cohort of patients. In 10 of the 11 studies, the beginning of follow-up was the start of mitoxantrone therapy [10,12,14,15,17,20–24]. Only 1 of the 11 studies reported on follow-up: the length and completion were adequate, but it was unclear if these data were complete until the end-date of the study [15]. Only 2 of the 11 studies used an objective outcome definition [8,15] and 1 of these 2 studies reported that the outcome assessor was blinded for important prognostic factors [8].

3.3. Pooled analysis

Many studies did not report all of the data needed to adequately evaluate the comparability of the various study groups. Furthermore, the methodological quality of all included studies was low. Due to the associated high risk of bias, we decided not to perform a pooled analysis of the cumulative incidence of M-CT and associated risk factors.

4. Discussion

This systematic review demonstrates that patients treated with mitoxantrone for childhood malignancies are at risk of developing M-CT. However, the exact cumulative incidence of M-CT in children is difficult to estimate due to the low methodological quality of the studies. The reported cumulative incidence of M-CT varied between 0 and 6.7% for clinical heart failure and between 0 and 80% for asymptomatic cardiac dysfunction. In reviews regarding anthracycline-induced cardiotoxicity (A-CT), the cumulative incidence of symptomatic A-CT varied between 0 and 16% [25] and that of asymptomatic A-CT varied between 0 and 57% [26]. But all studies included in these reviews on A-CT and M-CT had serious methodological limitations and no study evaluated the cardiotoxic effects of mitoxantrone and anthracycline derivates in a controlled manner. As a result, it is not possible to correctly compare these data and it is too early to conclude that mitoxantrone is less cardiotoxic than anthracyclines in patients treated for childhood cancer. Furthermore, the risk factors for developing M-CT remain unclear.

A limitation of this systematic review is that the presence of language bias can not be completely ruled out. Although we included all studies reported in the English, Dutch, French and German languages, studies reported in other languages may have been missed.

Table 3
Quality assessment of studies evaluating asymptomatic M-CT

Author, year [Ref.]	Study group			Follow-up		Outcome	
	Well defined	Whole cohort/random sample	Follow-up start of treatment or fixed point thereafter	Long enough	Complete[a]	Objective	Blind
Kremer, 2002 [8]	–	+	–	Nm	Nm	+	+
Dahl, 2000 [10]	–	+	+	Nm	Nm	–	Nm
Pourtsidis, 1998 [12]	–	+	+	Nm	Nm	–	Nm
Krischer, 1997 [14]	–	+	+	Nm	Nm	–	Nm
Behar, 1996 [15]	–	+	+	+	+	+	Nm
Vorobiof, 1987 [17]	–	+	+	Nm	Nm	–	Nm
Pratt, 1986 [20]	–	+	+	Nm	+	–	Nm
Ungerleider, 1985 [21]	–	+	+	Nm	Nm	–	Nm
Starling, 1985 [22]	–	+	+	Nm	Nm	–	Nm
Ehninger, 1985 [23]	–	+	+	Nm	Nm	–	Nm
Paciucci, 1983 [24]	–	+	+	Nm	+	–	Nm

+, yes; –, no; nm, not mentioned; M-CT, mitoxantrone-induced cardiotoxicity.
[a] In this column: ++ complete and +adequate.

After assessing the quality of the included studies, which includes both the internal and external validity, it was obvious that all studies were of a low quality. However, it should be clear that this assessment focused primarily on the evaluation of the cumulative incidence and risk factors of M-CT and, as a result, we can only judge the quality of the included studies with regard to these items.

Internal validity gives an indication of the bias present in a study and thus how valid the results of a certain study are. It includes the following points: random sample, completion of follow-up and blinding of the outcome assessor. Since 16 of the 17 studies described the whole cohort of patients, there is only a small risk of selection bias in this systematic review. On the other hand, since 13 of the 17 studies did not mention the completion of follow-up at all and only 1 of the 4 studies who did report on the completion of follow-up mentioned that it was complete until the end-date of the study, there is a large risk of attrition bias in this review. This will lead to an over-estimation if the reason for being lost-to-follow-up is that the patients are in excellent health and therefore refuse to visit their physician. On the other hand, it will lead to an under-estimation if the reason for the lack of data is that the patients are suffering from M-CT and therefore not able to make the visit. Finally, since only 1 of the 11 studies evaluating asymptomatic M-CT reported that the outcome assessor was blinded for important prognostic factors, whereas none of the studies evaluating symptomatic M-CT stated that the outcome assessor was blinded, there is also a large risk of detection bias in this systematic review. This can lead to an over-estimation of the cumulative incidence of M-CT, since knowledge of prognostic factors can increase the possibility of classifying a patient as having M-CT.

The external validity of a study indicates how well the results of the study can be extrapolated to individual patients treated with mitoxantrone. It includes the following points: well-defined study group, follow-up from the start of treatment or a well-defined point thereafter, a long enough follow-up and an objective outcome definition. In none of the studies was the study group well-defined, which makes it difficult to interpret the results correctly. In 15 of the 17 studies [9–14,16–24], patients had received anthracycline therapy, of which the cumulative doses varied. As a result, it is difficult to comment on the degree of cardiotoxicity attributable to mitoxantrone alone. In 16 of the 17 studies, patients were followed from the start of treatment onwards, thus representing the true cumulative incidence of M-CT. Furthermore, with a longer follow-up more patients will be at risk of developing M-CT. In this review, only 3 of the 17 studies reported the duration of follow-up, of which 2 had an adequate length and most of the studies which did not report on the duration of follow-up described children with relapsed and/or refractory leukaemia, who have a short life-expectancy. It is difficult to extrapolate the results found in these studies to children with a longer life-expectancy, who might be at risk for late M-CT. Finally, only 3 of the 16 studies evaluating symptomatic M-CT and only 2 of the 11 studies evaluating asymptomatic M-CT used an objective outcome definition. When an objective outcome definition is lacking, it is impossible to relate a study finding to individual patients treated with mitoxantrone.

Other items that are important for the extrapolation of study results to individual patients, although not included in our quality assessment, are tumour diagnosis, gender and age at diagnosis. Many studies included in this systematic review did not mention the gender and age at diagnosis of the study patients. In studies of children treated with anthracyclines these were found to be risk factors for the development of A-CT [25,26]. Only 1 study included in this systematic review evaluated risk factors for M-CT, but, unfortunately, none of these earlier mentioned possible risk factors were evaluated. As a result, it is as yet unknown what the effect of these factors is on the risk of developing M-CT.

More well-designed cohort studies are needed to reliably evaluate the cumulative incidence of M-CT and its associated risk factors. To compare the cardiotoxic effects of mitoxantrone and anthracyclines, randomised controlled trials with a long-term follow-up are needed. The Medical Research Council-Acute Myeloid Leukaemia-12 (MRC-AML-12) study, in collaboration with the SNWLK (Stichting Nederlandse Werkgroup Leukemie bij Kinderen), has randomised both children and adults to either mitoxantrone or daunorubicin during the induction phase in order to evaluate the cardiotoxicity of these agents. Patient inclusion has finished and at the moment, we are awaiting the results of this study. Accurate and transparent reporting of findings will make it possible for readers to critically appraise the results of these studies.

As more data become available, clinicians will be able to make well-informed decisions about mitoxantrone therapy for childhood malignancies and adequate follow-up protocols for children treated with mitoxantrone. At this moment, we can only advise clinicians to carefully monitor children treated with mitoxantrone, in order to make it possible to diagnose cardiac dysfunction early and to prevent any further damage.

In conclusion, children treated with mitoxantrone are at risk for developing M-CT, but due to the low quality of the current available evidence, the exact cumulative incidence and risk factors for M-CT remain unclear. It is too early to conclude that mitoxantrone is less cardiotoxic than anthracyclines in patients treated for childhood cancers.

5. Conflict of interest statement

None of the authors have competing interests.

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