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The use of liposomal anthracycline analogues for childhood malignancies: A systematic review

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ABSTRACT

In an effort to prevent or reduce anthracycline-induced cardiotoxicity, liposomal anthracyclines have been developed. The objective of this systematic review was to summarise all available evidence on the benefits and risks of liposomal anthracyclines in children with cancer.

We searched databases (MEDLINE (1966–September 2009), EMBASE (1980–September 2009) and CENTRAL (The Cochrane Library, issue 3 2009)), reference lists of relevant articles and ongoing trial databases for relevant studies. Two reviewers independently performed study selection, data extraction and quality assessment of included studies.

No randomised controlled trials (RCTs) or controlled clinical trials (CCTs) were found. Fifteen observational studies described the use of liposomal anthracyclines in children with cancer. Most patients had been treated extensively in the past. Some patients developed cardiotoxicity, serious allergic reactions, mucositis, infections, hematotoxicities and/or hepatotoxicity after single agent treatment. However, due to the low quality of the currently available research, it is unclear what the exact risks are.

In conclusion, there is no evidence available from RCTs or CCTs about the benefits and risks of liposomal anthracyclines in children with cancer. Limited data from observational studies suggest that children treated with liposomal anthracyclines are at risk for developing cardiotoxicity and other serious toxicities. There is an urgent need for results of well-designed studies which accurately evaluate the benefits and risks of liposomal anthracyclines in children with cancer. Until high quality evidence is available, we recommend monitoring of cardiac function in childhood cancer patients treated with a liposomal anthracycline and awareness of other serious toxicities.

1. Introduction

Anthracyclines have gained widespread use in the treatment of numerous childhood malignancies.[1,2] Unfortunately, their use is limited by the risk of cardiotoxicity. Anthracycline-induced cardiotoxicity can become manifest as either asymptomatic cardiac dysfunction or as clinical heart failure and can occur during but also many years after treatment.[2,3] It is estimated that 20 years after treatment, almost 10% of childhood cancer survivors treated with anthracycline doses of $\geqslant 300\ mg/m^2$ will have developed clinical heart failure.[2] Additionally, asymptomatic cardiac dysfunction is described in up to 57% of anthracycline-treated survivors and is often progressive.[3,4]

In an effort to prevent or reduce anthracycline-induced cardiotoxicity, liposomal-encapsulated anthracyclines have

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been developed.[5] Intravenously administrated liposomes cannot escape the vascular space in sites that have tight capillary junctions, such as in the heart muscle. They do exit the circulatory system in tissues and organs with cells that are not tightly joined or through areas where capillaries are disrupted by, for example, tumour growth. Thus, changes in tissue distribution of liposomal anthracyclines lead to less drug exposure in sensitive organs and more drug activity in tumour cells.[6] Therefore, liposomal anthracyclines are expected to be less cardiotoxic and have at least similar anti-tumour activity compared to conventional anthracyclines. This was confirmed in pre-clinical studies.[7,8] Also, a systematic review of randomised controlled trials (RCTs) showed that in adults with solid tumours liposomal-encapsulated doxorubicin was associated with less cardiotoxicity and no difference in tumour response and survival compared to conventional doxorubicin.[5] In this systematic review no RCTs in children were identified.

Liposomal anthracyclines can also have other side-effects. Common side-effects in adults are allergic reactions and hand-foot syndrome (HFS), a dermatologic toxic reaction that can lead to considerable discomfort.[9,10]

Before promising new drugs such as liposomal anthracyclines can be recommended as standard treatment in children, the treatment efficacy and toxicity in that patient population should be studied and summarised. The different underlying cancers, the different body composition and the developmental changes children undergo make it impossible to reliably extrapolate results from adults to children.[11] For toxicities, this evidence does not have to be derived from RCTs or clinical controlled trials (CCTs) only, since observational study designs can provide credible evidence on the adverse effects of treatment.[12,13] Thus far, an overview of other studies than RCTs in children treated with liposomal anthracyclines is lacking.

The objective of this systematic review was to summarise all available evidence on the benefits and risks of liposomal anthracyclines in childhood cancer patients regarding survival, tumour response, cardiotoxicity and other adverse effects.

2. Methods

2.1. Identification of studies

First, the databases of MEDLINE (1966–September 2009), EMBASE (1980–September 2009) and CENTRAL (The Cochrane Library, issue 3 2009) were searched for potentially relevant articles. The search strategy for MEDLINE is listed in Table 1 (Available online). For the other databases we used adaptations of this strategy. They can be obtained from the corresponding author.

Second, articles were selected on the basis of title and abstract by two independent reviewers (ES, EvD) using the following inclusion criteria: (1) study population contained patients aged $\leqslant$21 years treated with a liposomal anthracycline for any type of childhood malignancy (if patients >21 years were included, the study was only eligible for inclusion if data for patients $\leqslant$21 years were presented separately), (2) original research (all types of study design) and (3) written in English, Dutch, French or German. If the abstract was unavailable electronically or if it provided insufficient information, we retrieved the full text paper for more detailed examination.

Third, all selected articles were assessed in full text by two reviewers (ES, EvD) to ensure eligibility.

Finally, information on studies not registered in the electronic databases was located by scanning the reference lists of relevant articles (ES, EvD) and reviews (ES). We searched for ongoing trials by scanning the ISRTCN and National Institute of Health registers (www.controlled-trials.com; September 2009; ES, EvD).

We calculated inter-observer agreement for the second and third part of the selection process.

2.2. Data extraction

From included studies, two independent reviewers (ES, EvD) abstracted information about design, study population, current treatment, previous cardiotoxic treatment (anthracyclines and/or mediastinal radiotherapy, defined as irradiation of the mediastinum, thorax, spine, left or whole upper abdomen or total body irradiation), duration of follow-up and definition and quantification of outcomes (tumour response, survival and toxicities).

2.3. Quality assessment

To determine the quality of selected studies, two independent reviewers (ES, EvD) assessed the internal and external validity of each study with the exception of case-reports. The used criteria are described in Table 2 and are based on Evidence-Based Medicine criteria.[14,15]

Discrepancies between reviewers during the review process were solved by discussion.

2.4. Data analyses

We planned to perform meta-analyses if the included studies were of good methodological quality and if the various study groups were comparable with regard to age, sex, tumour diagnosis, treatment, used outcome definitions and length of follow-up. Otherwise, we summarised the results descriptively.

We presented data on treatment efficacy (i.e. survival and tumour response) only when RCTs or CCTs were available. Data on toxicities were presented independent of study design.

3. Results

3.1. Identification of studies

The searches in the electronic databases identified 421 potentially relevant articles, of which 359 were excluded based on screening of titles and abstracts. We retrieved 62 articles in full text for more detailed examination (inter-observer agreement 97.9%), of which 13 met all inclusion criteria. During handsearching the reference lists of relevant articles and reviews, we identified seven potentially relevant studies, which we retrieved in full text. Two more studies

Table 2 – Quality assessment criteria.

Internal validity

1. *Selection bias*
   Study design:
   - Adequate (+): if study was a randomised controlled trial

   Study population
   - Representative (+): if the study population consisted of more than 90% of the patients treated with liposomal anthracyclines included in the original cohort or if it was a random sample of these patients with respect to important prognostic factors (cumulative anthracycline dose, radiotherapy involving the heart)

2. *Performance bias*
   Blinding of health care providers:[a]
   - Adequate (+): if health care providers were blinded to the intervention

   Blinding of patients:[a]
   - Adequate (+): if patients were blinded to the intervention

3. *Attrition bias (evaluated for each outcome separately)*
   Follow-up assessment:
   - Complete (++): if the outcome was assessed at the end date of the study for more than 90% of the study group of interest
   - Adequate (+): if the outcome was assessed at the end date of the study for 60-90% or more than 90% but with an unknown end date of the study

4. *Detection bias (evaluated for each outcome separately)*
   Blinding of outcome assessor to prognostic factors
   - Adequate (+): if the outcome assessors were blinded with regard to important prognostic factors (cumulative anthracycline dose, mediastinal radiotherapy)

External validity

1. *Study group*
   Patient characteristics
   - Well-defined (+): if mean, median or range of the cumulative anthracycline dose were mentioned and if 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

   Start of follow-up
   - Well-defined (+): if follow-up started at the start of liposomal anthracycline treatment or a fixed point thereafter

2. *Duration of follow-up*
   Follow-up characteristics
   - Well-defined (+): if the mean, median or range of follow-up is mentioned

3. *Outcome*
   Survival
   - Well-defined (+): if the definition of survival used in the study was provided

   Tumour response
   - Well-defined (+): if the definition of tumour response used in the study was provided

   Cardiotoxicity
   - Well-defined (+): if 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.

   Other toxicities grade $\geqslant$III
   - Well-defined (+): if the definition of other toxicities used in the study was provided (for each described toxicity separately)

[a] Items only relevant for studies with a control group.

could be included. Scanning the ongoing trials registers retrieved three ongoing trials. One additional ongoing trial was provided by an expert in the field (Table 3). Thus, 15 studies were included (inter-observer agreement 95.2%) (Fig. 1).[16–30] The other 413 articles were excluded since they were a laboratory or animal study, did not describe liposomal anthracyclines, did not include childhood cancer patients, were not published in English, Dutch, French or German or lacked separate data on children.

3.2. Description of included studies

Study characteristics and results of included studies are presented in Table 4 (Available online).

3.2.1. General

Two of the 15 studies were only available as an abstract.[16,28] There were nine prospective cohort studies,[16–18,21–24,26,27] two retrospective cohort studies,[25,29] three case-reports,[19,20,30]

Table 3 – Ongoing trials on liposomal anthracyclines in children.

Registration name	Title	Study design	Intervention and control treatment	Preliminary results
ISRCTN94206677	Relapsed AML 2001/01: a randomised phase III study on the treatment of children and adolescents with refractory or relapsed acute myeloid leukaemia	RCT	Intervention: Liposomal daunorubicin and FLAG Control treatment: FLAG	2006: 2nd interim analysis with blinded efficacy data Patients: 322 eligible and evaluable patients with first relapsed AML (250 (78%) randomised) *Toxicities*: 'significant grade III/IV toxicity, but no unexpected toxicity, and no clinically relevant differences between the arms with and without liposomal daunorubicin, especially not in cardiotoxicity' No further information provided[32]
ISRCTN29644734	Phase I escalation study of clofarabine (Clolar®) and liposomal daunorubicin (DaunoXome®) in childhood and adolescent acute myeloid leukaemia	Phase I clinical trial	Intervention: Clofarabine and liposomal daunorubicin	
NCT00111345	Multicentre Therapy-Optimising Trial AML-BFM 2004 for the Treatment of Acute Myeloid Leukaemias in Children and Adolescents	RCT	Intervention: Standard risk: liposomal daunorubicin High risk: liposomal daunorubicin and 2-CDA Control treatment: Standard risk: idarubicin High risk: idarubicin	
NTR1880	ITCC020 I-BFM 2009/02: A phase II study of clofarabine in combination with cytarabine and liposomal daunorubicin in children with relapsed/refractory paediatric AML	Phase II clinical trial	Intervention: Clofarabine, liposomal daunorubicin and cytarabine	

RCT: randomised controlled trial; FLAG: fludarabine, cytarabine and granulocyte colony stimulating factor; 2-CDA: 2-chloro-2-deoxyadenosine; AML: acute myeloid leukaemia.

and one study with an unclear design.[28] We did not identify any RCT or CCT. None of the studies included a formal control group, but one study retrospectively reported on 3 patients treated with conventional anthracyclines and 1 patient with a liposomal anthracycline due to previous cardiotoxicity.[25]

In total, 214 childhood cancer patients treated with liposomal anthracyclines were included (range 1 to 69 per study). Included patients had several types of childhood cancer, the majority of which were relapsed or refractory to previous treatment. Six studies included patients diagnosed with leukaemia (i.e. acute lymphoblastic leukaemia and/or acute myeloid leukaemia).[16,17,25–28] Three studies included patients with various types of central nervous system tumours.[18,21,29] In the remaining six studies patients with various types of solid tumours were included.[19,20,22–24,30]

Different liposomal anthracyclines were studied, i.e. liposomal daunorubicin, pegylated liposomal doxorubicin and liposomal doxorubicin. In five studies it was given as a single agent.[16,21–24] In the other studies patients received $\geqslant 1$ other chemotherapeutic agents,[17–20,25–30] including a conventional anthracycline in three studies.[19,27,30] In one case report a child was treated with liposomal doxorubicin for the primary disease and with loco-regional conventional doxorubicin for refractory disease.[19] Radiotherapy was not given. Nine studies reported the range, mean and/or median cumulative liposomal anthracycline dose,[18,19,21,24,27–29] or the dose patients should have received according to protocol.[25,26]

Eleven studies provided information on previous anthracycline treatment.[16–24,26,30] In three studies no previous anthracycline therapy was given.[19,20,30] In eight studies 14% to 100%

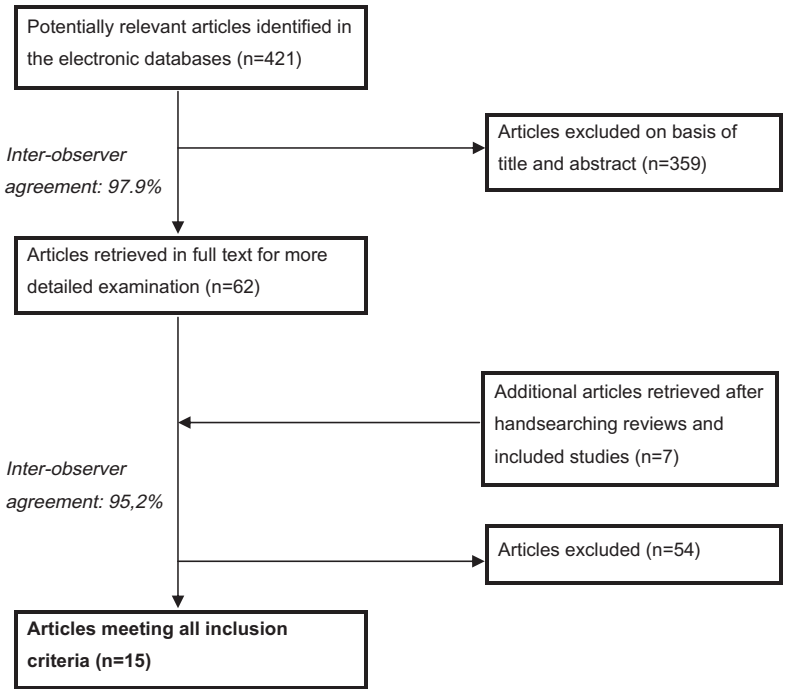

Fig. 1 – Selection of articles.

of patients were previously treated with anthracyclines.[16–18,21–24,26] Four studies provided the previous cumulative dose: range 60 to 450 mg/m^2.[21–24] Eight studies reported on previous mediastinal radiotherapy.[18–23,25,30] In four studies no previous mediastinal radiotherapy was given.[18–20,30] In four studies previous mediastinal radiotherapy was given to at least 9% to 100% of patients (doses not provided).[21–23,25]

Eight studies mentioned previous cardiac dysfunction,[17–19,22–25,29] based on echocardiographic definitions (six studies),[18,22–25,29] or on signs of clinical heart failure (two studies).[17,19] One patient had echocardiographic cardiac dysfunction prior to the current study.[25]

Duration of follow-up was reported in ten studies and ranged from 1 to 58+ months.[16–22,25,27,30] In all ten studies the follow-up started at the beginning of the described treatment.[16–22,25,27,30]

3.2.2. *Survival and tumour response*

Since no RCTs or CCTs were identified, we could not summarise the effect of liposomal anthracyclines on survival or tumour response.

3.2.3. *Cardiotoxicity*

Eleven studies evaluated the cumulative incidence of clinical and/or asymptomatic cardiotoxicity during or after liposomal or conventional anthracycline treatment.[16–19,21–24,27–29] It ranged from 0% to 67%. In 6 studies (1 to 22 patients), none of the children developed cardiotoxicity (median follow-up time 12–56 months in 3 studies, in 3 studies not mentioned).[17–19,23,24,29] In the remaining 5 studies the cumulative incidence of asymptomatic or grade I or II cardiotoxicity ranged from 5% to 67% (9 to 69 patients; median follow-up time in 3 studies 4–27.6 months, ⩾30 days in one study and not mentioned in one study).[16,21,22,27,28] Clinical cardiotoxicity was diagnosed during treatment in 2 patients (1 study; 48 patients). Both died as a result of cardiotoxicity.[22] One of these two patients developed cardiotoxicity following a second 'off study' course of liposomal daunorubicin.[22]

For three of the patients that developed cardiotoxicity (all asymptomatic) it is certain that they did not receive prior cardiotoxic treatment. They all received single-agent treatment with liposomal daunorubicin and developed cardiotoxicity during treatment.[21,22] Definitions of cardiotoxicity were given in ten studies and varied amongst these studies.[16–19,21–24,27,29]

3.2.4. *Other toxicities*

Eleven studies reported on the occurrence of at least one other toxicity ⩾grade III.[16,18,19,21–25,27–29] Nine of these stated a definition of toxicities, which varied amongst studies.[16,18,21–25,27,29]

Two studies (8 and 22 patients) provided data on HFS grade III or IV.[23,29] In both studies it did not occur.[23,29]

Five studies (8 to 48 patients) reported allergy grade III or IV during treatment, ranging from 4% to 12.5%.[22–24,28,29] In three studies (with allergy reported in 0%, 4%, and 9%) the allergy was assessed after single-agent treatment with liposomal anthracyclines.[22–24]

Eight studies (1 to 69 patients) provided data on treatment-related death, which occurred in 0% to 44% of patients.[19,21,22,24,25,27–29] Patients in the study with 44% treatment-related deaths (out of 9 patients) all died because of transplant-related causes.[28] Of the remaining seven studies, five reported no deaths,[19,21,24,25,29] and two studies reported 4% of deaths in 48 and 69 patients.[22,27] In one of these studies the deaths occurred after single-agent treatment, both deaths due to cardiotoxicity.[22]

For more information on other toxicities we refer to Table 4 (Available online). In patients treated with single-agent

Table 5 – Quality assessment of included studies (with the exception of case reports).

Author, year [reference]	Internal validity							External validity				
	Selection bias[a]	*Performance bias*		*Attrition bias*[b]		*Detection bias*[b]		*Study group well-defined*		*Duration of follow-up well-defined*	*Outcome well-defined*[b]	
	Representative sample	Blinding of health care provider	Blinding of patient	Assessment of follow-up complete		Blinding of outcome assessor						
				Cardiotoxicity	Other toxicities	Cardiotoxicity	Other toxicities	Patient characteristics	Start of follow-up		Cardiotoxicity	Other toxicities
Lippens, 1999 [21]	+	n.a.	n.a.	++	++	uc	n.a.	–	+	+	+	n.a.
Pea, 2003 [26]	+	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	–	+	–	n.a.	n.a.
Lowis, 2006 [22]	+	n.a.	n.a.	+	+	uc	uc	–	+	–	+	+
Fiorillo, 2004 [18]	+	n.a.	n.a.	+	+	uc	n.a.	–	+	+	+	n.a.
Munoz, 2004 [24]	+	n.a.	n.a.	+	+	uc	uc	–	+	–	+	+
Reinhardt, 2002 [27]	+	n.a.	n.a.	uc	uc	uc	uc	–	+	+	–	+
Marina, 2002 [23]	uc	n.a.	n.a.	–	+[c]	uc	uc	–	+	–	+	+
Clavio, 2004 [17]	uc	n.a.	n.a.	+	n.a.	uc	uc	–	+	+	–	–
Wagner, 2007 [29]	+	n.a.	n.a.	–	–	uc	uc	–	+	–	+	+
Pawson, 2001 [25]	+	n.a.	n.a.	n.a.	+	uc	uc	–	+	+	n.a.	+[d]
Baruchel, 1998 [16]	+	n.a.	n.a.	uc	uc	uc	uc	–	+	+	+	+
Sedky, 2007 [28]	+	n.a.	n.a.	uc	uc	uc	uc	–	+	–	–	–

uc: Unclear; n.a.: not applicable (because the item was not evaluated in the study, not applicable because the study did not have a control group, or if, in case of survival, the study reported only overall survival and no other forms of survival (like disease-free survival)).

[a] None of the included studies was a randomised controlled trial.

[b] Here only results for toxicities are reported and not for anti-tumour efficacy (i.e. survival and tumour response), since those outcomes were not included in the review due to a lack of RCTs/CCTs.

[c] With the exception of hematotoxicity, which was –.

[d] With the exception of treatment-related death, which was –.

liposomal anthracyclines some patients developed ⩾grade III hematotoxicity, mucositis, infections and/or hepatotoxicity.

3.2.5. *Quality assessment*

We assessed the quality of all study designs with the exception of case reports, i.e. in twelve studies.[16–18,21–29] All studies had methodological limitations (Table 5).

3.3. *Internal validity*

The risk of selection bias was low in most studies. In ten studies the study cohort was representative (i.e. >90% of the original cohort).[16,18,21,22,24–29] In the two remaining studies this was unclear.[17,23] Since the included studies were no controlled trials, assessment of blinding of patients and care providers (performance bias) was not applicable. In six studies there was no or a low risk of attrition bias, since follow-up was complete for all reported outcomes at the end date of the study (one study),[21] or with outcome assessments in more than 90% of the cohort but with an unknown end date of the study (five studies).[17,18,22,24,25] In the remaining five studies attrition bias could not be ruled out for some of the reported outcomes.[16,23,27–29] Detection bias could not be ruled out in 11 of the studies, since it was unclear if blinding of outcome assessors with regard to prognostic factors was performed.[16–18,21–25,27–29] In one study toxicities were not reported and, therefore, attrition and detection bias were not applicable.[26]

3.4. *External validity*

The external validity varied amongst included studies. The study group was not well-defined in all studies: none of the studies described the mean, median or range of the cumulative anthracycline dose and what other (prior) cardiotoxic treatment was given to the study group. From all studies it could be extracted what the starting point of follow-up was,[16–18,21–29] but in only six studies the mean, median or range of follow-up was mentioned.[16–18,21,25,27] In seven studies the reported toxicities were well-defined.[16,18,21–24,29] In four studies one or more of the reported outcomes were not well-defined.[17,25,27,28] In the remaining study toxicities were not reported.[26]

3.4.1. *Meta-analyses*

Many studies did not report all data needed to adequately evaluate the comparability of the various study groups. Furthermore, all included studies had methodological problems. Due to the associated high risk of bias, we did not perform meta-analyses.

4. Discussion

In this systematic review we evaluated all available evidence on the benefits and risks of liposomal anthracyclines in childhood cancer patients. There is no evidence available from RCTs or CCTs. It is, therefore, impossible to know whether there are differences in outcomes between conventional and liposomal anthracyclines or between different liposomal anthracycline derivates. Thus far, only observational studies in cohorts of children with cancer have been reported. For the evidence on the adverse effects of liposomal anthracyclines observational studies can be useful.[12,13] We found that children are still at risk for developing cardiotoxicity and also for grade ⩾III allergies, hematotoxicities, mucositis, infections and/or hepatotoxicity, since these toxicities occurred in children treated with single-agent treatment with a liposomal anthracycline. However, the exact cumulative incidence of these toxicities is difficult to estimate due to the generally low quality of the included studies and the lack of comparison groups. With regard to the risk of HFS and treatment-related death associated with liposomal anthracyclines, no definitive conclusions can be made. None of the studies in this review showed patients with grade ⩾III HFS after single-agent treatment with liposomal anthracyclines, but due to the low numbers of patients HFS can not be excluded. Two treatment-related deaths occurred after single-agent treatment (due to cardiotoxicity) in two patients, but both had previously been treated with cardiotoxic treatment and we, therefore, can not conclude that it was exclusively caused by the liposomal anthracycline treatment.

All studies had some methodological problems. Especially detection bias could not be ruled out and in approximately half of the studies there was a risk of attrition bias. In none of the studies the study group was well-defined, which makes it difficult to extrapolate the results to future childhood cancer patients. In all studies at least part of the patients were treated with previous potentially cardiotoxic treatment, but necessary details were not provided. Therefore, it is difficult to comment on the degree of cardiotoxicity attributable to liposomal anthracyclines alone. Also, it is difficult to distinguish between early and late cardiotoxicity; early cardiotoxicity occurs during anthracycline therapy or in the first year after its completion, late cardiotoxicity refers to heart damage that only shows itself at least one year after the completion of anthracycline therapy.[31] In patients who developed cardiotoxicity after the current liposomal anthracycline treatment, but who were previously treated with cardiotoxic treatment it is impossible to state if they developed early or late cardiotoxicity. Only for 3 patients that developed cardiotoxicity after treatment with liposomal anthracyclines it is completely clear that they did not receive prior or concomitant cardiotoxic treatment; they all developed early cardiotoxicity. In all studies, patients were followed from the start of liposomal anthracycline treatment onwards, thus representing the true cumulative incidence of reported outcomes. However, in only half of the studies the duration of follow-up was well-defined. Also, the duration of follow-up was very heterogeneous, ranging from 1 to 58+ months. It is, therefore, difficult to extrapolate the results found in these studies to children with longer follow-up. Finally, only 7 of 11 studies used an objective outcome definition for the reported toxicities. When an objective outcome definition is lacking, it is impossible to relate a study finding to individual patients treated with liposomal anthracyclines. Other items that are important for the extrapolation of study results to individual patients, although not included in our quality assessment, are tumour diagnosis, stage of disease and concomitant cancer treatment. Patients included in this review were very heterogeneous with regard to these

items. Most patients were diagnosed with refractory or relapsed disease. In general, these patients have a short life expectancy and it is difficult to extrapolate results found in these studies to children with a better life expectancy, who might, for example, be at risk for late cardiotoxicity.

Before any definitive conclusions can be made about the use of liposomal anthracyclines in children, high quality studies need to be undertaken. These studies should preferably be RCTs, since it is widely recognised that that is the only study design which can be used to obtain unbiased evidence on the efficacy of treatment, provided that design and execution are adequate. We are currently awaiting the results of two ongoing RCTs. For the long-term risk of adverse effects of liposomal anthracyclines, such as cardiotoxicity, adequate studies with long follow-up and within well-defined study populations should be done. When efficacy and safety of liposomal anthracyclines is proven, new RCTs are needed to identify the most effective and safest liposomal anthracycline derivate in children.

In conclusion, there is currently no adequate evidence on the effect of liposomal anthracycline treatment in children on survival and tumour response. Observational studies showed that children treated with liposomal anthracyclines are at risk for developing cardiotoxicity and other serious toxicities. However, it is unclear what the exact cumulative incidence of adverse effects is and if the risk of cardiotoxicity is lower than that associated with conventional anthracyclines. It is, therefore, too early to conclude that liposomal anthracyclines are a better treatment option than conventional anthracyclines in children.

As more high quality evidence becomes available clinicians can make well-informed decisions about the treatment of childhood cancer patients with liposomal anthracyclines and adequate follow-up protocols. Until then, we recommend monitoring of cardiac function in children treated with a liposomal anthracycline and awareness of serious toxicities.

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Role of the sponsor

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Conflict of interest statement

None declared.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejca.2011.03.024.

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