Childhood cancer survivors: Evidence and care

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Chapter 5

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

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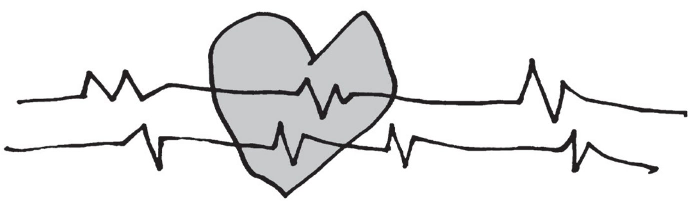

Abstract

In an effort to prevent or reduce anthracycline-induced cardiotoxicity, liposomal anthracyclines have been developed. The objective of this systematic review was to summarize 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 randomized 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 suggests 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.

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 ≥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 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 randomized 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 summarized. 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 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 summarize all available evidence on the benefits and risks of liposomal anthracyclines in childhood cancer patients regarding survival, tumour response, cardiotoxicity and other adverse effects.

Methods

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. 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 ≤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 ≤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

Table 1 Search strategy for MEDLINE/PubMed

#	Search
1.	caelyx OR liposomal doxorubicin OR doxorubicin, liposomal OR doxil OR DOX-SL OR DOX SL OR PLDH OR PLD OR myocet OR NPLD
2.	(adriablastin* OR adriamycin OR doxorubicin OR adriamyc* OR doxorubic* OR doxorubicin hydrochloride OR hydrochloride, doxorubicin) AND (pegylated OR pegyl* OR encapsulated OR encapsul* OR liposomal OR liposom* OR non-pegylated OR non-pegyl*)
3.	daunoxome OR daunosom* OR daunoxom*
4.	(dauno-rubidomycine OR dauno rubidomycine OR rubidomycin OR rubomycin OR daunomycin* OR cerubidine OR daunoblastin* OR daunorubicin hydrochloride OR hydrochloride, daunorubicin OR daunorubic* OR rubidomyc*) AND (pegylated OR pegyl* OR encapsulated OR encapsul* OR liposomal OR liposom* OR non-pegylated OR non-pegyl*)
5.	#1 OR #2 OR #3 OR #4
6.	infant OR infan* OR newborn OR newborn* OR new-born* OR baby OR baby* OR babies OR neonat* OR child OR child* OR schoolchild* OR schoolchild OR school child OR school child* OR kid OR kids OR toddler* OR adolescent OR adoles* OR teen* OR boy* OR girl* OR minors OR minors* OR underag* OR under ag* OR juvenil* OR youth* OR kindergar* OR puberty OR puber* OR pubescen* OR prepubescen* OR prepuberty* OR pediatrics OR pediatric* OR paediatric* OR peadiatric* OR schools OR nursery school* OR preschool* OR pre school* OR primary school* OR secondary school* OR elementary school* OR elementary school OR high school* OR highschool* OR school age OR schoolage OR school age* OR schoolage* OR infancy OR schools, nursery OR infant, newborn
7.	#5 AND #6

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.

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).

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.

Table 2 Quality assessment criteria

Internal validity	
1.	*Selection bias* Study design: • Adequate (+): if study was a randomized 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

Table 2 Quality assessment criteria (*continued*)

Internal validity	
	• 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
	Tumor response
	• Well-defined (+): if the definition of tumor 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 ≥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

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 summarized 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.

Results

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 7 potentially relevant studies, which we retrieved in full text. Two more studies 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%) (Figure 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.

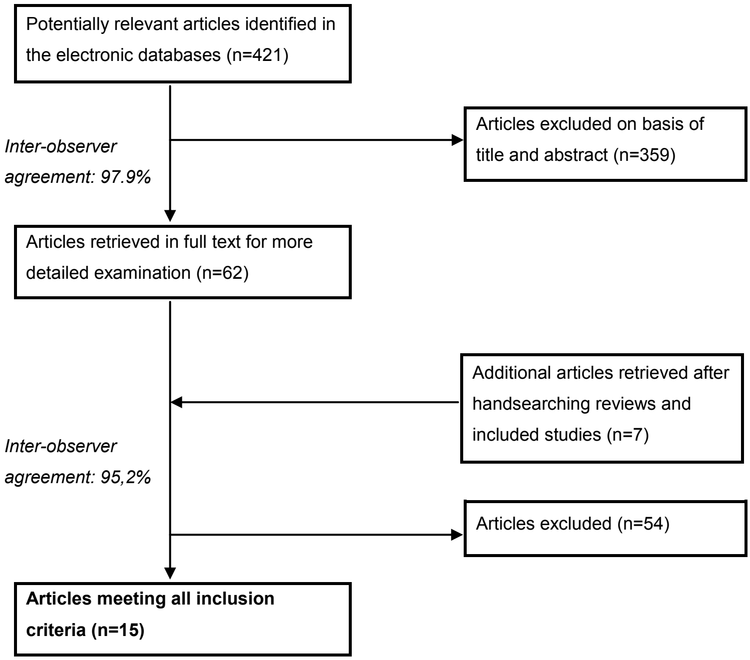

Figure 1 Selection of articles

Description of included studies

Study characteristics and results of included studies are presented in Table 4.

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%) randomized). *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	Multicenter Therapy-Optimizing Trial AML-BFM 2004 for the Treatment of Acute Myeloid Leukemias 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 pediatric AML	Phase II clinical trial	Intervention: Clofarabine, liposomal daunorubicin and cytarabine	

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

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] 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 was 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 ≥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 locoregional 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% 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]

Survival and tumour response

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

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 among these studies.[16-19, 21-24, 27, 29]

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 among 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 occurred 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. In patients treated with single-agent liposomal anthracyclines some patients developed ≥grade III hematotoxicity, mucositis, infections and/or hepatotoxicity.

Table 4 Study characteristics and results of all included studies

Study characteristics					
Author	**Lippens**	**Pea**	**Lowis**	**Fiorillo**	**Munoz**
Year of publication [reference]	1999 [21]	2003 [26]	2006 [22]	2004 [18]	2004 [24]
Original study					
Study design	Prospective cohort	Prospective cohort	Prospective cohort	Prospective cohort	Prospective cohort
Patients in original study	14	23	48	7	8
Patients					
Patients eligible for review	14	1	48	7	8
Patient characteristics					
Type(s) of childhood cancer	Various types of CNS tumors	ALL	Various types of solid tumors	Various types of CNS tumors	Various types of sarcomas
Age at treatment (years)	Median: 11.25 Range: 1.9 – 18.5	15	Mean: 9.6 Range: 1.3 – 18.5	Median: 9 Range: 3 – 13	Median: 14 Range: 5 – 17
Prior cardiotoxic treatment					
Anthracyclines	Yes: 2 (14%)	Yes: 1 (100%)	Yes: 31 (65%)	Yes: 2 (29%)	Yes: 8 (100%)
Mediastinal radiotherapy	Yes: 5 craniospinal (36%)	n.m.	Yes: 9 (19%)	No	n.m.
Prior cardiac dysfunction (definition)	n.m.	n.m.	No (echocardiogram FS ≥ 29%)	No (normal systolic and diastolic performance on echocardiogram)	No (EF >50%)
Interventions					
Anthracyclines					
Type	Liposomal daunorubicin	Liposomal daunorubicin	Liposomal daunorubicin	Liposomal daunorubicin	Pegylated liposomal doxorubicin
Brand name	DaunoXome	DaunoXome	DaunoXome	n.m.	Caelyx / Doxil

Table 4 Study characteristics and results of all included studies (*continued*)

Cumulative dose	Median: 330 mg Range: 95 – 1000 mg	n.m. (According to protocol 1300 mg/m^2)	n.m.	Median: 400 mg/m^2 Range: 100 – 600 mg/m^2	Mean: 181 mg/m^2 Range: 50 – 300 mg/m^2 [a]
Other treatment					
Other chemotherapy used in protocol	None	Cytarabine	None	Carboplatin, etoposide	None
Follow-up					
Duration of follow-up (months)	Median: 13.5 Range: 1 – 36	n.m.	At least 30 days after final cycle	Median: 21 Range: 2 – 29	n.m.
Outcome					
Toxicities					
Cardiotoxicity					
Definition	WHO and NCIC-CTG (version n.m.)	n.m.	NCI-CTC version 1 or if not possible, according to severity. Cardiotoxicity was additionally defined as FS<29% or decrease of EF > 20%	drop FS ≥10 % or FS < 29%	WHO
Cardiotoxicity (all grades)	Asymptomatic cardiac dysfunction: 3/14 (21%), grade n.m.	n.m.	Grade I: 6/45 (13%) Grade II: 5/45 (11%) Grade IV: 2/45 (4%) [b]	0 (0%)	0 (0%)
Other toxicities					
Definition	WHO and NCIC-CTG (version n.m.)	n.m.	NCI-CTC version 1 or according to severity	WHO	WHO

Table 4 Study characteristics and results of all included studies (*continued*)

Toxicities grade ≥III	Hematotoxicity: Granulocytopenia: grade IV: 1/14 (7%) Thrombocytopenia: grade III: 2/14 (14%), grade IV: 1/14 (7%) Hepatotoxicity: grade III: 1/14 (7%) Deaths: 0/14 (0%)	n.m.	Allergy: 2/48 (4%), grade III/IV Hematotoxicity:[c] grade III/IV: Neutropenia: 39/43 (91%) Leukocytopenia: 35/43 (81%) Thrombocytopenia: 21/43 (49%) Anemia: 14/43 (33%) Deaths: 2/43 (4%), by cardiotoxicity	Hematotoxicity: grade III/IV: 0/7 (0%) Ototoxicity: grade III/IV: 0/7 (0%)	Allergy: grade III/IV: 0 (0%) Hematotoxicity: grade IV: 0 (0%) Mucositis: grade III/IV: 0 (0%) Other skin reactions: grade III/IV: 0 (0%) Deaths: 0 (0%)
Study characteristics					
Author	**Reinhardt**	**Marina**	**Clavio**	**Wagner**	**Pawson**
Year of publication reference	2002 [27]	2002 [23]	2004 [17]	2008 [29]	2001 [25]
Original study					
Study design	Prospective cohort	Prospective cohort	Prospective cohort	Retrospective cohort	Retrospective cohort
Patients in original study	69	22	62	8	14
Patients					
Patients eligible for review	69	22	3	8	*Liposomal anthracycline*: 1 *Conventional anthracycline*: 3
Patient characteristics					
Type(s) of childhood cancer	AML	Various types of solid tumors	1 AML, 2 ALL	Various types of CNS tumors	ALL
Age at treatment (years)	Median: 8.2 Range: 0.4 – 16.6	Median: 9.3 Range: 4 – 21	Median: 19 Range: 13 – 21	Median 11.7 Range: 5.7 – 15	*Liposomal:* 15 *Conventional:* Range: 9 – 19 Median: 18

Table 4 Study characteristics and results of all included studies (*continued*)

Prior cardiotoxic treatment					
Anthracyclines	n.m	Yes: 12 (55%)	Yes: at least 2 (67%)	n.m.	n.m.
Mediastinal radiotherapy	n.m.	Yes: at least 2 TBI (9%)	n.m.	n.m.	Yes *Liposomal:* TBI: 1 (100%) *Conventional:* TBI: 3 (100%)
Prior cardiac dysfunction (definition)	n.m.	No (FS ≥ 27% or EF > 50% on echocardiogram)	No prior congestive heart failure (definition n.m.)	No (Normal echocardiogram or ECG before start of treatment)	*Liposomal:* Yes: 1 (100%) (EF between 45 – 50% on echocardiogram) *Conventional:* No (EF>50% on echocardiogram)
Interventions					
Anthracyclines					
Type	Liposomal daunorubicin: 69, conventional idarubicin: unclear, max 11	Pegylated liposomal doxorubicin	Liposomal daunorubicin	Pegylated liposomal doxorubicin	Liposomal daunorubicin: 1, conventional idarubicin: 3
Brand name	n.m.	Doxil	DaunoXome	n.m.	DaunoXome
Cumulative dose	Median: 240 mg/m^2 Range: 120 – 360 mg/m^2	n.m.	n.m.	Mean: 122 mg/m^2 Range: 40 – 210 mg/m^2	n.m. (According to protocol 240 mg/m^2)
Other treatment					
Other chemotherapy used in protocol	Cytarabine, thioguanin, busulfan, cyclophosphamide, melphalan, FLAG	None	Fludarabine and cytosine arabinoside, "high dose therapy with stem cell support"	Topotecan	Fludarabine, high dose cytosine arabinoside

Table 4 Study characteristics and results of all included studies (*continued*)

Follow-up					
Duration of follow-up (months)	Median: 27.6 Range: 2.4 – 55.2	n.m.	Median: 12 Range: 4 – 15	n.m.	*Liposomal:* 7 *Conventional:* Median: 20. Range: 3 – 58
Outcome					
Toxicities					
Cardiotoxicity					
Definition	NCI (version n.m.) Clinical cardiotoxicity: clinical symptoms of cardiac insufficiency, a contractility disorder or cardiomyopathy. Asymptomatic cardiac dysfunction: asymptomatic reduction of EF compared to baseline Abnormal FS: FS ≤ 30%	NCI-CTC version 1	Cardiac toxicity clearly related to therapy	NCI-CTC version 2	n.m.
Cardiotoxicity (all grades)	Clinical cardiotoxicity: 0/43 (0%) Asymptomatic cardiac dysfunction: Grade I/II: 29/43 (67%) Abnormal FS: Grade I/II: 23/43 (53%)	0/5 (0%)	0/3 (0%)	0/8 (0%)	n.m.
Other toxicities					
Definition	NCI (version n.m.)	NCI-CTC version 1	n.m.	NCI-CTC version 2[d, e]	GvHD: Acute: WHO Chronic: extensive versus limited Other toxicities: n.m.

Table 4 Study characteristics and results of all included studies (*continued*)

Toxicities grade ≥III	Mucositis: grade III/IV: 8/43 (19%) Infection: grade III/IV: 25/43 (58%) Fever: grade III/IV: 26/43 (60%) Neurotoxicity: grade III/IV: 0/43 (0%) Deaths: 3/69 (4%), by infection (2) and bleeding (1)	Allergy: grade III: 2/21 (10%) Hematotoxicity:[c] grade III/IV: Neutropenia:[e] 10/17 (56%) Thrombopenia: 6/17 (35%) Mucositis: grade III: 4/21 (19%) HFS: grade III/IV: 0/21 (0%) Other skin reactions: grade III/IV: 0/21 (0%)	n.m.	Allergy: grade III: 1 (13%) Hematotoxicity: grade IV: 3/8 (38%), grade III: 2/8 (25%) Stomatitis: grade III: 1/8 (13%) Dermatitis: grade ≥III: 0/7 (0%) HFS: grade ≥III: 0 (0%) Infection: grade III: 2/7 (29%) Diarrhoea: grade III: 1/8 (13%) Vomiting: grade ≥III: 0/8 (0%) Deaths: 0/8 (0%)	*Liposomal:*[f] Acute GvHD: grade III/IV: 0 (0%) Chronic GvHD: extensive: 1 (100%) Deaths: 0 (0%) *Conventional:*[f] Acute GvHD: grade III/IV: 0/3 (0%) Chronic GvHD: extensive: 0/2 (0%) Deaths: 0/3(0%)
Study characteristics					
Author	**Katzenstein**	**Woesman**	**Fiorillo**	**Baruchelg**	**Sedkyg**
Year of publication (reference)	2002 [20]	2003 [30]	2009 [19]	1998 [16]	2007 [28]
Original study					
Study design	Case report	Case report	Case report	Prospective cohort	n.m.
Patients in original study	1	1	1	21	9
Patients					
Patients eligible for review	1	1	1	21	9
Patient characteristics					
Type(s) of childhood cancer	Hepatoblastoma	Melanotic neuroectodermal tumor of infancy	Endovascular papillary angioendothelioma	ALL	ALL
Age at treatment (years)	4.2	0.17 (2 months)	4	Median: 9 Range: 5 – 18	n.m.

Table 4 Study characteristics and results of all included studies (*continued*)

Prior cardiotoxic treatment					
Anthracyclines	No	No	No	Yes, 21 (100%)	n.m.
Mediastinal radiotherapy	No	No	No	n.m.	n.m.
Prior cardiac dysfunction (definition)	n.m.	n.m.	No (no abnormal clinical findings and a normal chest X-ray)	n.m.	n.m.
Interventions					
Anthracyclines					
Type	Liposomal doxorubicin	Liposomal daunorubicin and conventional doxorubicin	*Primary disease*: pegylated liposomal doxorubicin *Refractory disease:* conventional doxorubicin	Liposomal daunorubicin	Liposomal daunorubicin
Brand name	Doxil	n.m.	n.m.	DaunoXome	DaunoXome
Cumulative dose	n.m.	n.m.	*Primary disease:* 160 mg/m^2 *Refractory disease:* 120 mg/m^2	n.m.	300 mg/m^2
Other treatment					
Other chemotherapy used in protocol	Irinotecan	Vincristine, dactinomycin, ifosfamide, etoposide, vinblastine, cyclophosphamide,, vinblastine	Dacarbazine, vincristine, dactinomycin, etoposide, carboplatin	None	PEG-asparaginase, corticosteroids, vinca alkaloids
Follow-up					
Duration of follow-up (months)	6	22	*Primary disease:* 12 (until diagnosis refractory disease) *Refractory disease:* 44+ *Total: 56+*	Median: 4 Range: 1 – 18	n.m.

Table 4 Study characteristics and results of all included studies (*continued*)

Outcome					
Toxicities					
Cardiotoxicity		*Not evaluated*			
Definition	n.m.		CCSG	WHO	n.m.
Cardiotoxicity (all grades)	n.m.		0 (0%)	Moderate and reversible decrease in FS: 1 (5%), grade n.m	Grade II: 1 (11%)
Other toxicities		*Not evaluated*			
Definition	n.m.		n.m.	WHO	n.m.
Toxicities grade ≥III	n.m.		Death: 0 (0%)	Sepsis: grade III/IV: 3 (14%) Aspergillosis: grade III/IV: 2 (10%) Pneumonia: grade III/IV: 2 (10%) Mucositis: grade III/IV: 0 (0%)	Allergy: grade III: 1 (11%) Neutropenia: grade IV: 4 (11%) Hemostasis (thrombosis): grade III: 1 (11%) Infection: grade III: 6 (67%) Deaths: 4 (44%), from transplant related causes

[a] Cumulative anthracycline dose according to table in the article
[b] One patient developed cardiotoxicity following a second "off study" course of DaunoXome
[c] After first treatment cycle only
[d] After three treatment cycles
[e] According to text of the article, in the table different numbers were stated
[f] All patients in the study had undergone a second stem cell transplantation
[g] Based on conference proceeding

Abbreviations: CNS: central nervous system; ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia; n.m: not mentioned; TBI: total body irradiation; FS; fractional shortening; EF: ejection fraction; FLAG: fludarabine, cytarabine and granulocyte colony stimulating factor; WHO: World Health Organization; NCIC-CTG: National Cancer Institute of Canada Clinical Trials Group; NCI-CTC: National Cancer Institute, Common Toxicity Criteria; HFS: hand-foot syndrome; ECG: electrocardiogram; GvHD: graft-versus-host disease; CCSG: Childhood Cancer Survivor Group.

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).

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]

External validity

The external validity varied among 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]

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.

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

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]						
				Assessment of follow-up complete		*Blinding of outcome assessor*		*Study group well-defined*			*Outcome well-defined*[b]	
	Representative sample	*Blinding of health care provider*	*Blinding of patient*	Cardiotoxicity	Other toxicities	Cardiotoxicity	Other toxicities	Patient charac-teristics	Start of follow-up	*Duration of follow-up well-defined*	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	-	+	-	-	-

[a] None of the included studies was a randomized 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 exeption of hematotoxicity, which was -

[d] With the exeption of treatment-related death, which was -

Abbreviations: 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)).

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 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 recognized 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 2 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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References

1. van Dalen EC, Raphael MF, Caron HN, Kremer LC. Treatment including anthracyclines versus treatment not including anthracyclines for childhood cancer. Cochrane Database Syst Rev 2009;(1):CD006647.
2. van Dalen EC, van der Pal HJ, Kok WE, Caron HN, Kremer LC. Clinical heart failure in a cohort of children treated with anthracyclines: a long-term follow-up study. Eur J Cancer 2006;42(18): 3191-3198.
3. Kremer LC, van der Pal HJ, Offringa M, van Dalen EC, Voute PA. Frequency and risk factors of subclinical cardiotoxicity after anthracycline therapy in children: a systematic review. Ann Oncol 2002;13(6):819-829.
4. Lipshultz SE, Lipsitz SR, Sallan SE et al. Chronic progressive cardiac dysfunction years after doxorubicin therapy for childhood acute lymphoblastic leukemia. J Clin Oncol 2005;23(12): 2629-2636.
5. van Dalen EC, Michiels EM, Caron HN, Kremer LC. Different anthracycline derivates for reducing cardiotoxicity in cancer patients. Cochrane Database Syst Rev 2006;(4):CD005006.
6. Tardi PG, Boman NL, Cullis PR. Liposomal doxorubicin. J Drug Target 1996;4(3):129-140.
7. Forssen EA, Coulter DM, Proffitt RT. Selective in vivo localization of daunorubicin small unilamellar vesicles in solid tumors. Cancer Res 1992;52(12):3255-3261.
8. Working PK, Newman MS, Sullivan T, Yarrington J. Reduction of the cardiotoxicity of doxorubicin in rabbits and dogs by encapsulation in long-circulating, pegylated liposomes. J Pharmacol Exp Ther 1999;289(2):1128-1133.
9. Chanan-Khan A, Szebeni J, Savay S et al. Complement activation following first exposure to pegylated liposomal doxorubicin (Doxil): possible role in hypersensitivity reactions. Ann Oncol 2003;14(9):1430-1437.
10. Hackbarth M, Haas N, Fotopoulou C, Lichtenegger W, Sehouli J. Chemotherapy-induced dermatological toxicity: frequencies and impact on quality of life in women's cancers. Results of a prospective study. Support Care Cancer 2008;16(3):267-273.
11. Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE. Developmental pharmacology--drug disposition, action, and therapy in infants and children. N Engl J Med 2003;349(12):1157-1167.
12. Miettinen OS. The need for randomization in the study of intended effects. Stat Med 1983; 2(2):267-271.
13. Vandenbroucke JP. When are observational studies as credible as randomised trials? Lancet 2004;363(9422):1728-1731.
14. Grimes DA, Schulz KF. Cohort studies: marching towards outcomes. Lancet 2002;359(9303): 341-345.
15. Laupacis A, Wells G, Richardson WS, Tugwell P. Users' guides to the medical literature. V. How to use an article about prognosis. Evidence-Based Medicine Working Group. JAMA 1994; 272(3):234-237.
16. Baruchel A, Auvrignon A, Perel Y et al. Liposomal daunorubicin (Daunoxome (R)) for childhood acute lymphoblastic leukemia: A phase I-II study. Blood 1998;92(10):234A.
17. Clavio M, Venturino C, Pierri I et al. Combination of liposomal daunorubicin (DaunoXome), fludarabine, and cytarabine (FLAD) in patients with poor-risk acute leukemia. Ann Hematol 2004;83(11):696-703.

18. Fiorillo A, Maggi G, Greco N et al. Second-line chemotherapy with the association of liposomal daunorubicin, carboplatin and etoposide in children with recurrent malignant brain tumors. J Neurooncol 2004;66(1-2):179-185.
19. Fiorillo A, DeRosa G, Giugliano F, DeLillo ML, Sabbatino MS, Veneziano A. Efficacy of pegylated lyposomal anthracyclines and of intra-arterial carboplatin and doxorubicin combined with local hyperthermia in a case of malignant endovascular papillary angioendothelioma. Curr Drug Deliv 2009;6(1):58-61.
20. Katzenstein HM, Rigsby C, Shaw PH, Mitchell TL, Haut PR, Kletzel M. Novel therapeutic approaches in the treatment of children with hepatoblastoma. J Pediatr Hematol Oncol 2002; 24(9):751-755.
21. Lippens RJ. Liposomal daunorubicin (DaunoXome) in children with recurrent or progressive brain tumors. Pediatr Hematol Oncol 1999;16(2):131-139.
22. Lowis S, Lewis I, Elsworth A et al. A phase I study of intravenous liposomal daunorubicin (DaunoXome) in paediatric patients with relapsed or resistant solid tumours. Br J Cancer 2006; 95(5):571-580.
23. Marina NM, Cochrane D, Harney E et al. Dose escalation and pharmacokinetics of pegylated liposomal doxorubicin (Doxil) in children with solid tumors: a pediatric oncology group study. Clin Cancer Res 2002;8(2):413-418.
24. Munoz A, Maldonado M, Pardo N, Fernandez JM, Vela E, Cubells J. Pegylated liposomal doxorubicin hydrochloride (PLD) for advanced sarcomas in children: preliminary results. Pediatr Blood Cancer 2004;43(2):152-155.
25. Pawson R, Potter MN, Theocharous P et al. Treatment of relapse after allogeneic bone marrow transplantation with reduced intensity conditioning (FLAG +/- Ida) and second allogeneic stem cell transplant. Br J Haematol 2001;115(3):622-629.
26. Pea F, Russo D, Michieli M et al. Disposition of liposomal daunorubicin during cotreatment with cytarabine in patients with leukaemia. Clin Pharmacokinet 2003;42(9):851-862.
27. Reinhardt D, Hempel G, Fleischhack G, Schulz A, Boos J, Creutzig U. Effektive Rezidivtherapie der akuten myeloischen Leukamie im Kindesalter mit liposomalem Daunorubicin und Cytarabin. Klin Padiatr 2002;214(4):188-194.
28. Sedky MS, Vannier JP, Leverger G et al. Liposomal daunorubicin and polyethylated glycol conjugated asparaginase (PEG-ASPA) in children with relapsed and refractory acute lymphoblastic leukemia treated on compassionate basis. Haematologica 2007;92:405.
29. Wagner S, Peters O, Fels C et al. Pegylated-liposomal doxorubicin and oral topotecan in eight children with relapsed high-grade malignant brain tumors. J Neurooncol 2008;86(2):175-181.
30. Woessmann W, Neugebauer M, Gossen R, Blutters-Sawatzki R, Reiter A. Successful chemotherapy for melanotic neuroectodermal tumor of infancy in a baby. Med Pediatr Oncol 2003; 40(3):198-199.
31. Shan K, Lincoff AM, Young JB. Anthracycline-induced cardiotoxicity. Ann Intern Med 1996; 125(1):47-58.
32. Kaspers G. TRIAL Relapsed AML 2001/01: a randomised phase III study on the treatment of children and adolescents with refractory or relapsed acute myeloid leukaemia (AML). ISRCTN94206677. Available from: http://www.controlled-trials.com/ISRCTN94206677