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Beneficial and harmful effects of anthracyclines in the treatment of childhood acute lymphoblastic leukaemia: a systematic review and meta-analysis

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Summary

Anthracyclines are used to treat childhood acute lymphoblastic leukaemia (ALL) but non-randomized studies suggest that cardiotoxicity may be a problem. Individual patient data from trials in childhood ALL that randomized anthracyclines or methods of reducing cardiotoxicity were analysed by standard meta-analysis methods. Results were grouped and combined according to: addition of an anthracycline to standard therapy, type of anthracycline, mode of administration, and the use of a cardioprotectant. Data from 958 patients in 4 trials, recruiting between 1972 and 1984, showed that addition of an anthracycline reduced bone marrow relapse and, non-significantly, non-bone marrow relapse, resulting in an increased relapse-free interval. However there was a non-significant increase in induction failures, and in deaths in first remission. Event-free survival at 5 years was 56·7% with anthracycline *versus* 52·8% without (Odds Ratio = 0·91; 95% Confidence Interval = 0·76–1·10; $P = 0·3$). There were no significant differences found in other treatment comparisons. The limited data from trials did not demonstrate differences in clinically evident cardiotoxicity. Anthracyclines are effective against bone marrow relapse but have not been shown to significantly increase event free survival in childhood ALL. The evidence on type of anthracycline, method of administration or use of cardioprotectant was insufficient to be able to rule out important differences.

Keywords: anthracycline, leukaemia, childhood ALL, meta-analysis, randomized.

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There has been steady improvement in the outcome for children with acute lymphoblastic leukaemia (ALL), due to the gradual development of chemotherapy treatment protocols. One class of drug believed to play an important part in this is the anthracyclines, which were first introduced into randomized trials in the 1960s. Now that the great majority of children are cured it is important to make every effort to minimize any adverse long term effects of treatment. The most serious known adverse effect of anthracyclines is their cardiotoxicity (Elliott, 2006; Lipshultz, 2006). The emergence of this problem has led to the development of strategies aimed at reducing cardiac adverse effects while maintaining efficacy against the disease: including the use of cardioprotective therapies during anthracycline treatment, use of different derivatives of anthracyclines, and use of different infusion schedules during administration. A further concern long term with chemotherapy is the possible risk of second malignancies.

Despite the prominence of anthracycline treatment in childhood ALL there have been few studies of anthracycline safety specific to ALL in children. Also, only published data have been available for meta-analysis (van Dalen *et al*, 2005, 2006a,b; Bryant *et al*, 2007). This review uses data on each individual patient to look at the total evidence available on the effectiveness of anthracyclines, and of the different methods aimed at reducing the long term cardiotoxicity, in treating childhood ALL. As useful data on cardiotoxicity were not available from the trials, a literature review was performed to identify evidence on cardiotoxicity from randomized controlled trials. As cardiotoxicity was not anticipated to be specific to ALL, evidence from all diseases was considered to be relevant. Cochrane systematic reviews were found (van Dalen *et al*, 2005, 2006a,b) and, as this is the most reliable source when only published data are available, relevant results from this were included in the results section.

Materials and methods

Trials included

Individual patient data were sought from all properly randomized trials that commenced before 2000 and involved unconfounded treatment comparisons of anthracycline therapy for newly diagnosed childhood acute lymphoblastic leukaemia. Trials were included if at least 50% of patients were up to 21 years of age. The types of anthracycline therapy considered were: addition or not of an anthracycline to standard therapy; type of anthracycline; mode of administration of anthracycline; and the presence or not of a cardioprotectant.

Trials were identified following detailed searching of electronic clinical trial databases including MEDLINE and EMBASE. Additional hand searching was undertaken of content lists of major cancer and general medical journals, of review articles, of meeting abstracts and of reference lists of published trials. Members of the Childhood ALL Collaborative Group (CALLCG) and other experts were consulted to ensure the completeness of the resulting list of trials.

Trial protocol details collected included period of recruitment, eligibility criteria, randomized treatment doses and timing, and any anthracycline treatment given in addition to that randomized.

Data checking

For all trials the following information was sought on each patient aged 21 years or younger at random assignment to treatment: sex, white blood cell count (WBC) at diagnosis, immunophenotype, treatment allocation and site of first relapse; dates of birth, diagnosis, random assignment to treatment, first remission, relapse, and death or last contact; and the date and type of any secondary tumour.

Data were checked for internal consistency, balance between treatment groups by initial features, randomization dates, and length of follow-up, and consistency with publications on the trials. Data were amended only through correspondence with the principal trial investigators, who, additionally, received relevant summary tables for verification.

Events analysed

Primary outcome measures were event-free survival and overall survival (from date of randomization) with an event defined as any relapse or death. As these trials did not reliably record non-fatal secondary tumours, only fatal ones were included. Secondary outcome measures were no remission (defined as death without remission achievement), bone marrow (BM) relapse (including combined relapses with BM involvement), non-BM relapse, death in remission (including death due to secondary tumour), and relapse-free interval, which was defined as time to any relapse. In analyses of relapse, patients who died without achieving remission were excluded and deaths in remission were censored. Data were obtained only for first relapse, so analyses of a particular type of relapse were censored at relapse of any other type.

Grouping of trials and subgroup analyses

Trials were grouped and the results combined according to the type of treatment they compared. Trials addressing the addition of anthracycline treatment were subgrouped by the type of anthracycline and whether it was given in induction or maintenance. Comparisons by type of anthracycline were only combined if more than one trial addressed the same two types. Anthracycline administration trials comparing long duration infusion *versus* shorter administration were subgrouped by length of infusion time. Pre-specified subgroup analyses were by gender, age group (<10, ≥10 years), WBC (<10, 10–19,

20–49, 50–99, ≥100 × 10^9/l) and immunophenotype (B-lineage, T-lineage).

Statistics

Within-trial analyses were of time from randomization to event, with the observed minus expected (o−e) number of events and its variance (v) obtained by the log-rank method. These o–e values were then added over all trials to produce a total (T), with variance (V) equal to the sum of the separate variances. These were used to calculate an overall odds ratio (OR), or ratio of event rates, and its 95% confidence interval (CI) equal to exp(T/V ± 1·96/√V). Results are presented as forest plots with a square representing the point estimate of the OR and horizontal line showing the 99% CI for each trial. The size of the square is proportional to the amount of information available, with larger squares representing trials or subgroups with a larger number of events. Overall estimates are shown by a diamond with the width representing the 95% CI. All *P*-values given are two-sided and were considered significant when <0·05. Heterogeneity between the effects in different trials or subgroups was tested with X^2_{n-1} equal to $S-T^2/V$, where S is the sum of $(o-e)^2/v$ from each of *n* trials or *n* subgroups (EBCTCG, 1990).

T and V, obtained by summing o-e and v from log rank analyses restricted to each one year time period, were used to estimate the log OR, b, for each year. The estimated overall event rate in each time period, r, equals the number of events divided by the number of person years, and the probability of surviving event-free during that year is exp(−*r*). Descriptive survival curves were drawn from the separate probability estimates $P + 0{\cdot}5\,P(P-1)b$ for one treatment group, and $P-0{\cdot}5\,P(P-1)b$ for the other treatment group [Early Breast Cancer Trialists' Collaborative Group (EBCTCG), 1990].

Results

The only trials for which data were not available were two older trials (1968–1973) looking at the addition of an anthracycline or not to standard therapy [SWOG (Southwest Oncology Group) 690/691, and ALGB (Acute Leukemia Group B) 6801].

Addition of an anthracycline

Eight trials were found, but two were excluded {one only included patients aged over 20 years [Cancer and Leukemia Group B (CALGB) 7612] and one was in relapsed disease [Pediatric Oncology Group (POG) 869]}. Details of the included trials are shown in Table I. One trial [Dana Farber Cancer Institute (DFCI) 73001] randomized children between the addition of daunorubicin, doxorubicin, or neither to induction treatment. Doxorubicin was included in consolidation for all patients, whereas the other trials only included anthracyclines in treatment if randomized to them. Five trials randomized daunorubicin, one (ALGB 6801) for use during both induction and maintenance, two during induction [Dutch Childhood Leukemia Study Group (DCLSG) - European Organization for Research and Treatment of Cancer (ALL-V/EORTC) 99801 and United Kingdom Medical Research Council (MRC) UKALL VIII] and two during maintenance therapy (DCSLG-ALL-1 and SWOG 690/691). Cumulative doses in these trials were all below 100 mg/m^2 daunorubicin, 80 mg/m^2 doxorubicin, or 60 mg/m^2 daunorubicin plus 35 mg/m^2 doxorubicin. In the DFCI 73001, DCLSG-ALL-V/EORTC 99801 and MRC UKALL VIII trial protocols all patients received cranial irradiation. It was randomized in SWOG 690/691, and not given in DCSLG-ALL-1 and ALGB 6801.

Individual patient data were available for four of the six eligible trials, involving a total of 455 events in 958 patients. Median follow-up for these 4 trials was long, at 13·6, 16·1, 22·5 and 24·1 years (Table II). There was a reduction in bone marrow relapse (OR = 0·77; 95% CI = 0·60–1·00; $P = 0{\cdot}05$) with anthracycline, and a non-significant reduction in non-bone marrow relapse (OR = 0·88; 95% CI = 0·63–1·25; $P = 0{\cdot}5$). This resulted in improved relapse-free interval (OR = 0·81; 95% CI = 0·66–1·00; $P = 0{\cdot}05$). However, there was a non-significant increase in induction failures (21 vs. 14; OR = 1·44; 95% CI = 0·73–2·82; $P = 0{\cdot}3$), and in deaths in first remission (32 vs. 21; OR = 1·45; 95% CI = 0·84–2·48; $P = 0{\cdot}2$) (Table III). In these trials, only one patient who failed to achieve remission survived to the end of the follow-up period. Thus the addition of an anthracycline did not significantly affect event-free interval, either overall (OR = 0·91; 95% CI = 0·76–1·10) (Fig 1), or if the comparison was restricted to induction trials (OR = 0·88; 95% CI = 0·72–1·06). Within the induction failures, there was a non-significant increase in the number of early deaths in the anthracycline group (14 vs. 6 within 40 d; $P = 0{\cdot}08$) but similar numbers of later deaths, likely to be due to resistant disease, in the two groups (7 vs. 8). Event-free survival at 5 years was 56·7% with anthracycline *versus* 52·8% without (Fig 2), with a long-term difference of 3·7% (95% CI = −3·2% to 10·6%).

There was no significant heterogeneity between trials, and no evidence of a different effect in any age, sex, WBC or immunophenotype subgroup. However immunophenotype data were very limited in these trials, which all began in or before 1981 (Table II). Additionally, National Cancer Institute risk subgroups were examined (High risk: WBC ≥ 50 × 10^9/l or age ≥ 10 years; Standard risk: all other) but did not reveal any heterogeneity. The only trial which used doxorubicin (DFCI 73001) was too small to enable indirect comparisons of the effects of different types of anthracycline.

Type of anthracycline

Four trials comparing different anthracyclines were found, but one was excluded as it was for relapsed patients [Children's

Table I. Trial characteristics.

Trial name	Trial start year	Trial end year	References	Trial entry criteria	Treatment period of anthracycline randomization	Anthracycline randomization	Other anthracycline therapy	Cumulative anthracycline dose (mg/m^2)
Anthracycline *versus* not								
ALGB 6801 induction / maintenance	1968	1971	Halazun *et al*, 1974	Untreated, age < 20 years	Induction/ Maintenance	Dnr (total dose range 360–1260 mg/m^2 iv bolus, first dose given at half dosage) *versus* not	None (all anthracycline is randomized)	360–1260
SWOG 690/691/ ALinC 9	1971	1973	Komp *et al*, 1976	Age < 15 years	Dnr given monthly around time of CNS therapy	Dnr (monthly iv) *versus* not Dose unclear	None (all anthracycline is randomized)	Not reported
DCLSG-ALL-I	1972	1973	van der Does-van den Berg *et al*, 1975	Age < 15 years, no med mass	Maintenance	Rand if CR at day 42: Dnr (30 mg/m^2 iv x2) *versus* not	None (all anthracycline is randomized)	60
DFCI 73001	1973	1974	Sallan *et al*, 1977	Untreated, age < 20 years	Induction	Dnr (60 mg/m^2 iv, d1) *versus* not; Dox (45 mg/m^2 iv, d1) *versus* not	Dox (35 mg/m^2 iv consolidation d22)	80–95
DCLSG-ALL-V/ EORTC 99801	1979	1982	van der Does-van den Berg *et al*, 1989	SR only (age 0-15 years, WBC < 50 × 10^9/l, no med mass &/or cerebreomeningeal leukaemia at diagnosis)	Induction	Dnr (25 mg/m^2/week iv over 4 weeks) *versus* not	None (all anthracycline is randomized)	100
MRC UKALL VIII	1981	1984	Eden *et al*, 1991	Age < 15 years	Induction	Dnr (45 mg/m^2 iv d1,d2) *versus* not	None (all anthracycline is randomized)	90
Type of anthracycline								
DFCI 73001	1973	1974	Sallan *et al*, 1977	Untreated, age < 20 years	Induction	Dnr (60 mg/m^2 iv, d1) *versus* Dox (45 mg/m^2 iv, d1)	Dox (35 mg/m^2 iv consolidation d22)	80–95
New Delhi 1989	1989*	1998	Bhutani *et al*, 2002	Untreated, age 11–70 years	Induction	Dox (30 mg/m^2 iv d1,d8,d15,d22) *versus* Epi (45 mg/m^2 iv d1,d8,d15,d22)	Dox (30 mg/m^2 iv early intensification d1,d8,d15,d22)	240–300
FRALLE 93 IR, ind	1993	1999	Leblanc *et al*, 1996	IR**	Induction	Dnr (40 mg/m^2 iv d8,d15, ±d22†) *versus* Ida (8 mg/m^2 iv d8,d15, ±d22†)	Dox (25 mg/m^2 iv d1,d8,d15)	91–195

Table I. (Continued).

Trial name	Trial start year	Trial end year	References	Trial entry criteria	Treatment period of anthracycline randomization	Anthracycline randomization	Other anthracycline therapy	Cumulative anthracycline dose (mg/m^2)
Anthracycline administration								
MSK-NY-II	1986	1991	Steinherz *et al*, 1993	SR or HR (exclude if age 2–10 with WBC < 10)	Induction and maintenance	Dnr push (60 mg/m^2 iv bolus (d1, d2 or d3, d4) x2, 20 mg/m^2 iv bolus daily ×18 over 2 years) *versus* Dnr infusion (120 mg/m^2 iv infusion (d1–d2 or d3–d4) ×1, 40 mg/m^2 iv 48 h infusion ×9 over 2 years)	None (all anthracycline is randomized)	600
DFCI ALL 91-001, high risk (Dox)	1991	1995	Silverman *et al*, 2001	HR (at least one of: WBC ≥ 20 × 10^9/l, 1 ≤ age < 2 years or age ≥ 9 years, leukaemic blasts in CSF, med mass, T-cell)	Intensification	Dox (30 mg/m^2 iv bolus, every 3w ×10) *versus* Dox (30 mg/m^2 iv 48 h infusion, every 3w ×10)	Dox (30 mg/m^2 induction d1, d2)	360
COALL-05-92	1992	1994	Escherich *et al*, 2007	LR (age 1–9 years, WBC < 25 × 10^9/l, C or pre-B ALL) or HR (WBC > 25 × 10^9/l or age ≥ 10 years or T-cell or pre-pre-B ALL)	Pre-phase	Dnr (36 mg/m^2 iv 1 h infusion d7) *versus* Dnr (36 mg/m^2 iv 24 h infusion d7)	Dnr (36 mg/m^2 iv induction d1,d8,d15). Dox (30 mg/m^2 iv reinduction d1,d8, (& d22, d29 (HR only))	204–264
Cardioprotectant								
DFCI ALL 95-001	1996	2000	Barry *et al*, 2008	Age 1–18 years & HR (one of: WBC ≥ 50 × 10^9/l, age > 10 years, T-cell, med mass, CNS disease) or age < 1 year	Induction (?)	Dzr (30 mg/m^2 ×10) pre-Dox *versus* not	Dox (30 mg/m ×10)	300
POG-9404	1996	2001	Unpublished observations	Age 1–21 years, T-cell	Induction and consolidation	Dzr (300 mg/m^2 iv ×12) pre-Dox *versus* not	Dox (30 mg/m^2 iv induction ×3 over 6w). Dox (30 mg/m^2 iv consolidation ×9 over 27 weeks)	360

SR, standard risk; IR**, intermediate risk; HR, high risk; Dnr, daunorubicin; Dox, doxorubicin; Dzr, dexrazoxane; Epi, epirubicin; Ida, idarubicin; Med mass, medullary mass; CSF, cerebrospinal fluid; CNS, central nervous system.

*Published report states 1990 but first patient in dataset randomized in 1989.

†3rd dose given if marrow not blast free at day 21.

**Non B ALL: age 7–15 years, or if 1 year < age < 15 years, tumour syndrome, or, 10 × 10^9/l < WBC < 100 × 10^9/l, or Hb > 100 g/l, or one myeloid marker, or testicular or CNS localization, or abnormal karotype [exclude t(9;22) or t(4;11)].

Table II. Patient characteristics.

Trial name	Total patients	Median follow up (years)	Gender		Age group (years)			WBC ($\times 10^9$/l)			Immunophenotype		
			Male	Female	0–1	2–9	≥10	<20	20–49	≥50	B-lineage	T	Other/ unknown
Anthracycline *versus* not													
DCLSG-ALL-I	43	13·6	22	21	4	32	7	29	9	5	0	0	43
			51%	49%	9%	74%	16%	67%	21%	12%	0%	0%	100%
DCLSG-ALL-V / EORTC 99801	240	16·1	119	121	28	170	42	208*	28	0	132	2	106
			50%	50%	12%	71%	18%	86%	12%	0%	55%	1%	44%
MRC UKALL VIII	630	22·5	337	293	61*	471	97	443	91	96	394	46	190
			53%	47%	10%	75%	15%	70%	14%	15%	63%	7%	30%
Type of anthracycline													
DFCI 73001 (also addressed anthracycline *versus* not)	45	24·1	28	17	2	36	7	34	7	4	0	0	45
			62%	38%	4%	80%	16%	76%	16%	9%	0%	0%	100%
New Delhi 1989	42	6·0	36	6	0	0	42	23	9	10	0	0	42
			86%	14%	0%	0%	100%	55%	21%	24%	0%	0%	100%
FRALLE 93 IR, ind	532	3·2	287	245	33	445	54	368	126	38	530	0	2
			54%	46%	6%	84%	10%	69%	24%	7%	100%	0%	0%
Anthracycline administration													
MSK-NY-II	44	15·4	30	14	5	20	19	27	4	13	35	8	1
			68%	32%	11%	45%	43%	61%	9%	30%	80%	18%	2%
DFCI ALL 91-001, high risk (Dox)	204	8·9	116	88	34	111	59	95	49	60	178	21	5
			57%	43%	17%	54%	29%	47%	24%	29%	87%	10%	2%
COALL-05-92	178	10·0	104	74	14	129	35	103	40	35	159	19	0
			58%	42%	8%	72%	20%	58%	22%	20%	89%	11%	0%
Cardioprotectant													
DFCI ALL 95-001	205	5·7	120	85	31	90	84	88	26	91	155	49	1
			59%	41%	15%	44%	41%	43%	13%	44%	76%	24%	0%
POG-9404	363	6·2	267	96	11	187	165	89	66	208	0	363	0
			74%	26%	3%	52%	45%	25%	18%	57%	0%	100%	0%

*1, 4 missing values for age, WBC, respectively.

Cancer Group (CCG) 1884]. One small trial (DFCI 73001) compared daunorubicin with doxorubicin on day 1 of induction, with all patients receiving one dose of doxorubicin in consolidation. Another small trial (New Delhi 1989) compared four doses of epirubicin with four doses of doxorubicin in induction, with all patients receiving four doses of doxorubicin in intensification. The numbers of patients involved are too small to draw conclusions on clinical outcomes, but, for completeness, numbers of events are given in Table III.

One trial (FRALLE [French Acute Lymphoblastic Leukaemia study group] 93) randomized 532 children between two doses of daunorubicin or two doses of idarubicin in induction. Patients received a further dose of randomized anthracycline if their marrow was not blast free at day 21. All patients received three doses of doxorubicin in intensification.

Cumulative doses in these trials were: 60 mg/m^2 daunorubicin plus 35 mg/m^2 doxorubicin or 80 mg/m^2 doxorubicin (DFCI 73001); 80 (or 120) mg/m^2 daunorubicin plus 75 mg/m^2 doxorubicin or 16 (or 24) mg/m^2 idarubicin plus 75 mg/m^2 doxorubicin (FRALLE 93); and 240 mg/m^2 doxorubicin or 120 mg/m^2 doxorubicin plus 180 mg/m^2 epirubicin (New Delhi 1989).

No significant differences in any outcome measure were found (Table III), but median follow-up available for FRALLE 93 is only just over 3 years at present.

There were insufficient data to make subgroup analyses meaningful.

A Cochrane systematic review suggested that for adults the rate of clinical heart failure (CHF) might be lower with epirubicin compared with doxorubicin (van Dalen *et al*, 2006a). In adult patients with solid tumours there were three cases of CHF among 521 patients randomized to epirubicin, and 12 cases among 515 patients randomized to doxorubicin. However the difference was not statistically significant even when over 1000 patients were randomized, as the number of events was small [relative risk (RR) = 0·35, 95% CI 0·12–1·11; P = 0·07]. Two trials (Batist *et al*, 2001; Harris *et al*, 2002) comparing liposomal-encapsulated *versus* conventional doxorubicin appeared to indicate that the former reduced CHF in

Table III. Effects of treatment on different endpoints.

	Numbers with outcome by randomized treatment allocation		Log rank odds ratio	95% lower confidence interval	95% upper confidence interval	2p
Anthracycline *versus* not						
	Anthra *n* = 491	Control *n* = 467				
No remission	21	14	1·44	0·73	2·82	0·3
Any BM relapse	106	130	0·77	0·60	1·00	0·05
Non BM relapse	62	69	0·88	0·63	1·25	0·5
Death in first remission	32	21	1·45	0·84	2·48	0·2
Any event	221	234	0·91	0·76	1·10	0·3
Any death	182	182	1·00	0·81	1·23	0·9
Type of anthracycline						
Dnr *versus* Ida (FRALLE 93)						
	Dnr *n* = 262	Ida *n* = 270				
Any BM relapse	18	22	0·83	0·45	1·55	0·6
Non BM relapse	6	6	1·00	0·32	3·11	1·0
Death in first remission	3	2	1·58	0·27	9·11	0·6
Any event	27	30	0·92	0·55	1·54	0·7
Any death	14	13	1·11	0·52	2·36	0·8
Dnr *versus* Dox (DFCI 73001)						
	Dnr *n* = 16	Dox *n* = 14				
Any BM relapse	5	5	0·88	0·25	3·06	0·8
Non BM relapse	0	0	–	–	–	–
Death in first remission	1	0	–	–	–	–
Any event	6	5	1·05	0·32	3·45	0·9
Any death	5	4	1·13	0·31	4·20	0·9
Epi *versus* Dox (New Delhi 1989)						
	Epi *n* = 20	Dox *n* = 22				
No remission	1	3	–	–	–	–
Any BM relapse	8	8	1·03	0·38	2·74	1·0
Non BM relapse	0	1	–	–	–	–
Death in first remission	1	0	–	–	–	–
Any event	10	12	0·86	0·37	1·98	0·7
Any death	10	12	0·85	0·37	1·98	0·7
Anthracycline administration						
48 h infusion *versus* bolus						
	48 h inf *n* = 102	Bolus *n* = 102				
Any BM relapse	15	13	1·08	0·51	2·27	0·8
Non BM relapse	0	3	0·13	0·01	1·22	0·07
Death in first remission	2	6	0·36	0·09	1·43	0·1
Any event	17	22	0·73	0·39	1·37	0·3
Any death	14	18	0·75	0·37	1·49	0·4
24 h infusion *versus* 1 h infusion						
	24 h inf *n* = 93	1 h inf *n* = 84				
Any BM relapse	15	14	0·96	0·46	1·98	0·9
Non BM relapse	3	3	0·87	0·18	4·36	0·9

Table III. (Continued).

	Numbers with outcome by randomized treatment allocation		Log rank odds ratio	95% lower confidence interval	95% upper confidence interval	2p
Death in first remission	5	4	1·14	0·31	4·20	0·8
Any event	23	21	0·98	0·54	1·77	0·9
Any death	21	15	1·27	0·66	2·45	0·5
Infusion *versus* push						
	Infusion $n = 23$	Push $n = 21$				
Any BM relapse	4	1	3·10	0·52	18·43	0·2
Non BM relapse	1	0	10·75	0·20	587·47	0·2
Death in first remission	1	1	1·20	0·07	19·14	0·9
Any event	7	4	1·90	0·57	6·29	0·3
Any death	5	4	1·38	0·37	5·15	0·6
Cardioprotectant						
	Yes $n = 292$	No $n = 276$				
Any BM relapse	33	27	1·15	0·69	1·90	0·6
Non BM relapse	13	16	0·76	0·36	1·57	0·5
Death in first remission	9	4	2·01	0·68	5·97	0·2
Any event	67	63	1·02	0·72	1·44	0·9
Any death	54	47	1·11	0·75	1·63	0·6

Dnr, daunorubicin; Dox, doxorubicin; Dzr, dexrazoxane; Epi, epirubicin; Ida, idarubicin; BM, bone marrow.

adult patients with breast cancer. There were two cases of CHF in 250 patients randomized to liposomal-encapsulated and 14 cases in 271 patients randomized to conventional doxorubicin (RR = 0·20; 95% CI 0·05–0·75; $P = 0·02$). This Cochrane review found no published results for children or for leukaemia, and data on cardiotoxicity was not collected for the trials in our review.

Methods of administration

Three trials including 437 children compared slow infusion, over 24 or 48 h, with short infusion over 1 h or bolus injection. In the two trials giving anthracycline by 48 h infusions, either no [Memorial Sloan–Kettering-New York II Protocol (MSK-NY-II)], or just 2 doses (DFCI ALL 91-001), of anthracycline were given apart from the randomized treatment. However, in the third trial [COALL (Co-operative study group for childhood acute lymphoblastic leukaemia) -05-92] the randomized comparison only applied to one dose in the pre-phase period and all patients had further anthracycline doses by 1 h infusion (three in induction, and two in reinduction, plus two more if high risk). Cumulative doses were 600 mg/m^2 daunorubicin, 330 mg/m^2 doxorubicin, and 60 or 120 mg/m^2 doxorubicin plus 144 mg/m^2 daunorubicin, respectively. Median follow-up was over 8 years for all these trials.

No significant differences in outcome were found (Fig 3, Table III), nor evidence of any different effect in any subgroup. All those who failed to achieve remission died.

A Cochrane systematic review showed that there is evidence that giving anthracyclines to adult cancer patients by an infusion of 6 or more hours reduces cardiotoxicity (van Dalen *et al*, 2006b). Outcomes examined in the review were CHF and subclinical heart failure (SHF), defined as ≥10% decrease in left ventricular ejection fraction (LVEF). Two trials were for childhood ALL, but relevant data were not available from the publications so these could not be included in the analyses. One trial, DFCI ALL91-001, reported echocardiogram measurements for 121 children and concluded that both regimens used were associated with progressive subclinical cardiotoxicity (Lipshultz *et al*, 2002). The other, MSK-NY-II, reported on 36 patients monitored with serial echocardiograms (Steinherz *et al*, 1993). Four children, all on the bolus arm, had a clinically significant decrease in cardiac function, but this difference was not statistically significant ($P = 0·10$). The small numbers randomized mean that there is a lack of information with respect to longer duration infusions in children for both cardiotoxicity and disease recurrence.

Cardioprotectant

Two trials involving 568 children compared anthracycline with the addition of cardioprotectant to the same anthracycline treatment. Median follow-up was 6 years. The cumulative anthracycline doses given in these trials, which both used doxorubicin, were 300 mg/m^2 and 360 mg/m^2. Median follow-up is over 5 years.

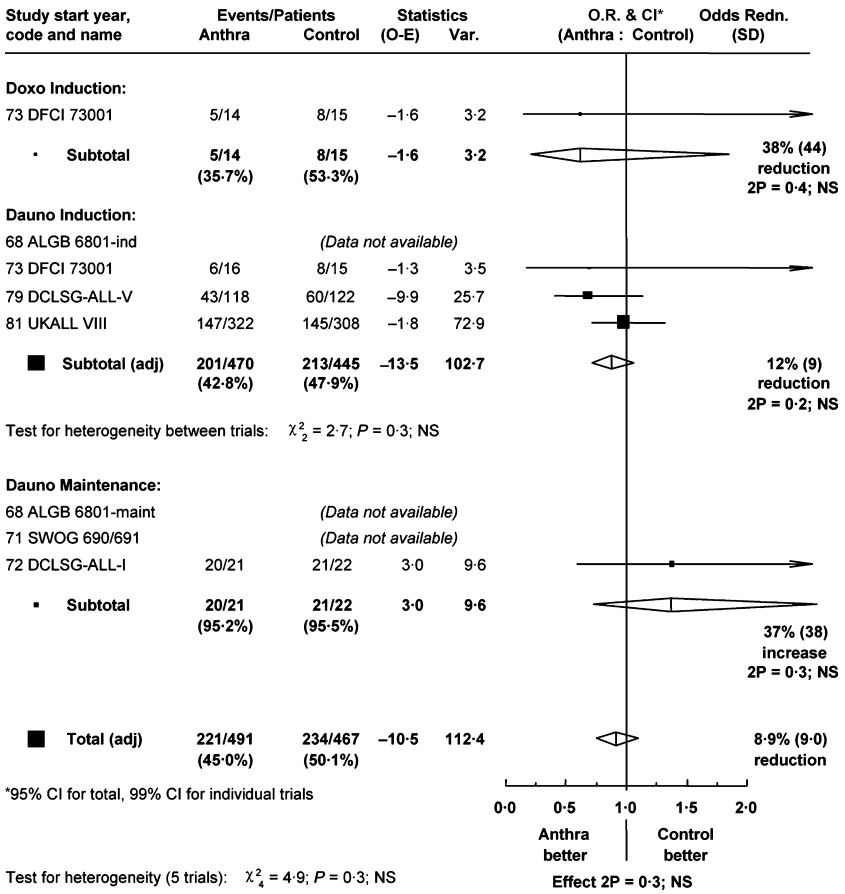

Fig 1. Effect of the addition of an anthracycline on overall event rate. O.R. = Odds ratio. CI = confidence interval. The result for each trial and its 99% confidence interval is represented by a black square, whose size is proportional to the amount of information available, and a horizontal line. Overall results for each subgroup and overall are represented by diamonds whose widths indicate 95% confidence intervals. Total numbers of events and patients are adjusted for trials contributing more than one comparison so that patients are only counted once. Anthra, anthracyline; Doxo, doxorubicin; Dauno, daunorubicin; NS, not significant.

There were no significant differences seen for any endpoint (Table III). For event free survival the OR = 1·02 (95% CI = 0·72–1·44) (Fig 4). Event free survival at 5 years was 77·0% with, and 77·5% without, cardioprotectant, a difference of −0·5% (95% CI = −7·7% to 6·8%). There was no evidence of any different effect within subgroups.

A Cochrane systematic review of cardioprotectants showed that there were insufficient data for any conclusions on any drug except for dexrazoxane (van Dalen *et al*, 2005). In meta-analysis of five trials of dexrazoxane which included mainly adults, but also some children, with solid tumours, a reduction in the rate of CHF was demonstrated (RR = 0·18; 95% CI 0·10–0·35; $P < 0·00001$), with 10 cases of CHF in 472 patients randomized to dexrazoxane and 59 in 503 control patients.

The randomized trials in the current meta-analysis have not reported on CHF and surrogate measures of heart failure have yielded little information. In DFCI ALL 95-001, there were no significant differences between treatments in echocardiogram measurements performed in a subgroup of children (Lipshultz *et al*, 2004). A recent review of clinical and cost-effectiveness of cardioprotection in children with cancer, which included one additional (non-randomized) study more than the current review, also reported that conclusions could not be drawn given the limited quality and quantity of the evidence (Bryant *et al*, 2007).

Discussion

It is likely that anthracyclines are effective against ALL in childhood. Relapses were prevented with their use, but the increased incidence of treatment-related deaths resulted in no significant effect on event-free survival. However, the event-free survival with modern protocols is generally about 20% higher than in the trials included in the review, so the average absolute benefit obtained by adding an anthracycline is likely to be smaller. Randomized evidence on cardiotoxicity comes from trials that mostly used higher cumulative doses of anthracyclines than are generally used for childhood ALL.

There are insufficient data comparing different types of anthracyclines to draw firm conclusions on differences in event rates, with only the daunorubicin *versus* idarubicin comparison including a significant number of patients. Even here there was

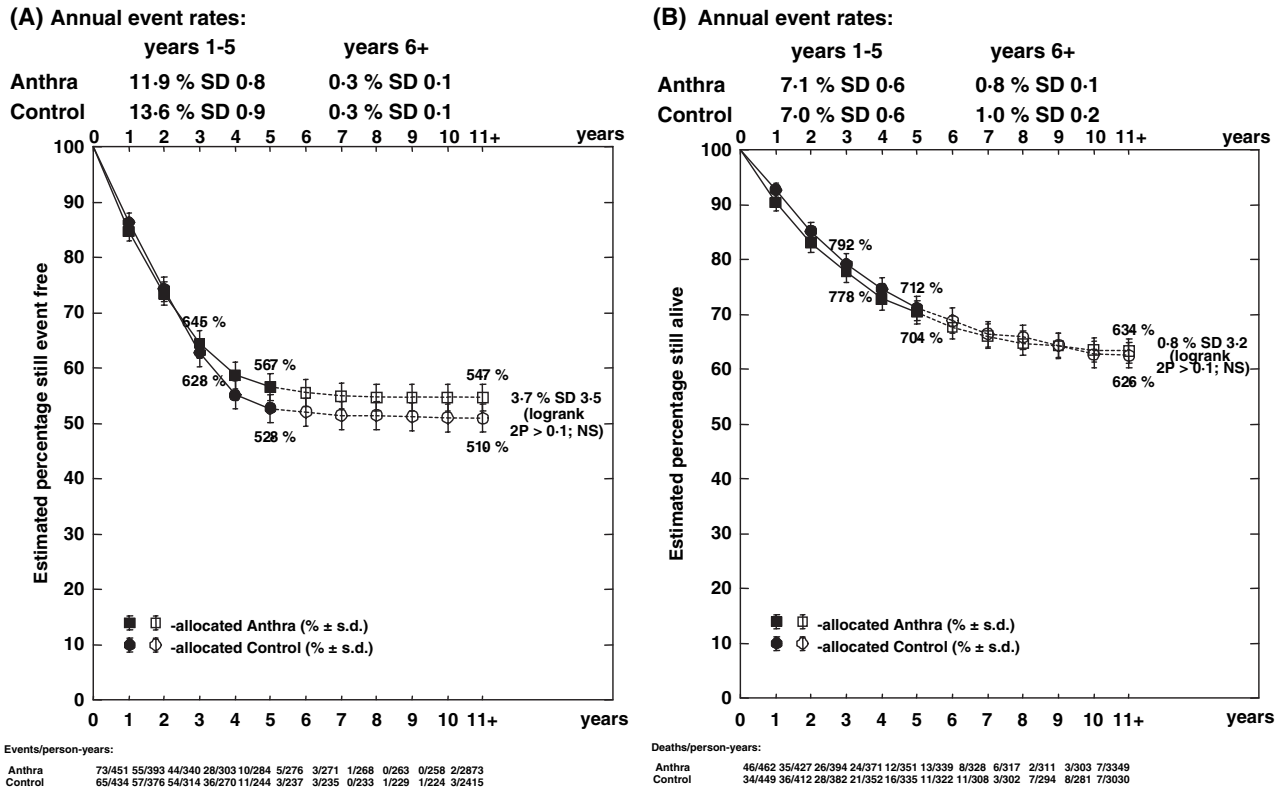

Fig 2. Descriptive curve showing the effect of the addition of an anthracycline on (A) event-free survival and (B) overall survival. Anthra, anthracyline.

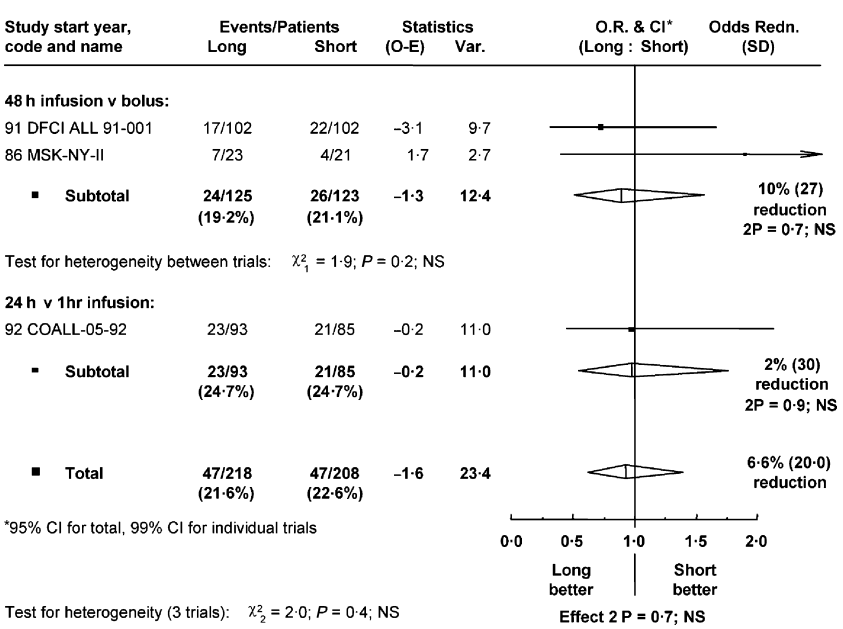

Fig 3. Effect of the method of anthracycline administration on overall event rate. Abbreviations and symbols as in Fig 1.

only one trial (FRALLE 93), and an absolute difference in events of as much as 10% cannot be ruled out. Treatment with different anthracycline derivatives or formulations may affect cardiac adverse events. A Cochrane systematic review in adults with various cancers demonstrated significantly reduced rates of subclinical and CHF with liposomal encapsulated doxorubicin

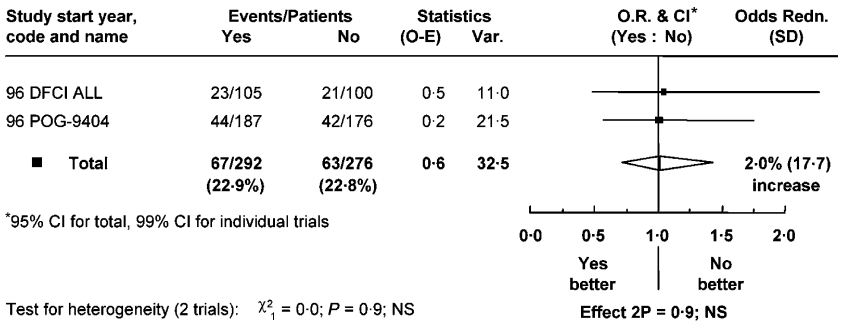

Fig 4. Effect of cardioprotectant on overall event rate. Abbreviations and symbols as in Fig 1.

compared with standard doxorubicin (van Dalen *et al*, 2006a), with no evidence to suggest any differences in anti-tumour response rate or survival. The review also suggested a lower rate of CHF with epirubicin compared with doxorubicin treatment, although the difference was not significant.

The limited evidence on giving anthracycline as a continuous infusion over 24 or 48 h did not suggest a difference in effectiveness, although in two of these trials all patients also received some standard administration of i.v. anthracycline during induction, which may have weakened the comparison.

Previous cardiac studies have shown impairment in both adults and children with long-infusion, suggesting that it may not in any case be a way of preventing clinical cardiotoxicity. However, in some reports, different dosage schedules of anthracycline have been found to affect the incidence of cardiac damage. The meta-analysis of trials in adults showed a statistically significant lower rate of heart failure with an infusion duration of 6 or more hours compared with a duration of 1 h or less, but data were not available for children. A lower incidence of subclinical cardiac damage was also observed with longer infusions, although this effect was not statistically significant (van Dalen *et al*, 2006b).

The use of dexrazone as a cardioprotectant seems more promising, with evidence that it has a beneficial effect on surrogate measures of cardiac damage. However, although the totality of the evidence does not show that it affects the activity of anthracycline against the disease, the small number of patients randomized means that an absolute difference in event-free survival of as much as 7% cannot be ruled out. Event-free survival in these trials was 77% at 5 years. Even if newer treatments were to increase this to 85%, applying the relative event rate estimates from the trial evidence would include a possible 5% detriment with cardioprotectant.

A recent systematic review of published data looking at the clinical and cost-effectiveness of cardioprotection found some limited evidence of protection against toxicity (Bryant *et al*, 2007). In the only two studies in children, dexrazoxane (Lipshultz *et al*, 2004) and coenzyme Q_{10} (Iarussi *et al*, 1994) were reported to protect cardiac function during anthracycline therapy. In another review in adult cancer patients a meta-analysis of six studies found that dexrazoxane showed a statistically significant protective benefit against development of heart failure (van Dalen *et al*, 2005).

No different treatment effects were found in age, sex, WBC or immunophenotype subgroups for any of the review questions. However, although this review used all available data in childhood ALL, the meta-analysis did not include sufficient numbers of patients in subgroups to rule out differences that may exist, particularly in immunophenotype, for which data were very limited in the early trials.

Primary outcome measures in the meta-analysis were event-free survival and overall survival. Cardiotoxicity data were not generally collected in the trials, but in any case, the follow up times may have been too short to demonstrate any differences in cardiac damage. It is questionable whether a surrogate endpoint, such as SHF, should be used rather than death.

Anthracycline therapy has been used in childhood ALL since the 1960s, since when it may have contributed to the increase in the 5-year survival rate from 30% to its current level of over 70% (Gatta *et al*, 2002). However due to the risk of cardiac damage and heart failure there has been a tendency in some countries to drop the use of anthracyclines in their treatment protocols or to use them only for selected high risk cases.

Numerous retrospective studies have assessed the cardiac risk of anthracyclines in children. Prevalence of subclinical cardiac damage of up to 56% has been reported in children 6·4 years following anthracycline treatment for various cancers (Kremer *et al*, 2002a), with a risk of developing CHF of 2% at 2 years and 5% at 15 years following treatment (Kremer *et al*, 2001). Reported incidence of heart failure varies from 0% to 16% at 0·9–4·6 years following anthracycline treatment (Kremer *et al*, 2002b). The only independent risk factor yet identified is a cumulative anthracycline dose of 300 mg/m^2. In a long term follow up study of 830 children this dosage increased the risk of heart failure to 9·8% at 20 years compared with 0·5% for patients receiving <300 mg/m^2 (van Dalen *et al*, 2006c).

Conclusion

Anthracyclines significantly reduced bone marrow relapse when added to standard therapy but did not significantly

increase event-free survival. There were no significant differences in any relapse, event or death between any anthracycline derivatives, between 48 or 24 and 1 h anthracycline infusions or between treatment with or without the cardioprotectant dexrazoxane. Keeping cumulative doses below 300 mg/m^2 appears to reduce cardiotoxicity but there is no clear evidence that other strategies have an effect. Future studies need to be larger, longer term, and to look at clinically important outcomes. With the high survival rates on current protocols and the possibility of long term cardioxicity even at lower doses, whether anthracyclines are necessary for at least some patients remains an important issue. This meta-analysis suggests that, as they appear to have a valuable anti-leukaemic effect but involve increased toxicity, especially cardiac, they should perhaps be reserved for higher risk patients.

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