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A systematic collaborative overview of randomized trials comparing idarubicin with daunorubicin (or other anthracyclines) as induction therapy for acute myeloid leukaemia

THE AML COLLABORATIVE GROUP*

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Summary. A collaborative overview, using individual patient data, has been performed to compare idarubicin versus daunorubicin or other anthracyclines, when used with cytosine arabinoside as induction chemotherapy for newly diagnosed acute myeloid leukaemia. There were 1052 patients in five trials versus daunorubicin, 100 in one trial versus doxorubicin, and 745 in one trial versus zorubicin. In the trials of idarubicin versus daunorubicin, early induction failures were similar with the two treatments (20% idarubicin *v* 18% daunorubicin; $P = 0{\cdot}4$), but after day 40 the later induction failures were fewer with idarubicin (17% *v* 29%; $P < 0{\cdot}0001$). Therefore complete remission rates were higher with idarubicin (62% *v* 53%; $P = 0{\cdot}002$). Among remitters, fewer of the patients allocated to idarubicin relapsed ($P = 0{\cdot}008$) but slightly more died in remission, leading to a non-significant benefit ($P = 0{\cdot}07$) in disease-free survival. Overall survival in these five trials was significantly better with idarubicin than with daunorubicin (13% *v* 9% alive at 5 years; $P = 0{\cdot}03$). There was a trend ($P = 0{\cdot}006$ for remission rate) for the benefit of idarubicin over daunorubicin to decrease with increasing age. There were no significant differences in outcome in the small trial comparing idarubicin versus doxorubicin, or in the large trial comparing idarubicin versus zorubicin. The induction regimens based on idarubicin achieved, in the particular circumstances of the trials reviewed here, better remission rates and better overall survival than those based on daunorubicin.

Keywords: AML, overview, anthracycline, idarubicin, induction.

Daunorubicin was for many years the only anthracycline that was commonly used during induction chemotherapy for acute myeloid leukaemia (AML). In the 1980s various alternatives were introduced, such as idarubicin. Several randomized trials have compared induction regimens based on idarubicin with those based on daunorubicin, or on other anthracyclines. The results from all these trials need to be reviewed together to obtain the most reliable evidence possible on the relative effects of these treatments. Reviews that are restricted to published trials (Carella *et al*, 1990) have various potential limitations (Stewart & Parmar, 1993). In particular, the results of those trials that were published may differ systematically from those that were not, and the published reports may not provide sufficient detail. A systematic collaborative overview of the data on each individual patient in all the relevant randomized trials can overcome such problems (Peto, 1987; Peto *et al*, 1996; Clarke & Stewart, 1994), and the Acute Myeloid Leukaemia Collaborative Group (AMLCG) has been established for this purpose. The present report is of the randomized trials that compared an induction regimen based on idarubicin versus one based on another anthracycline. For brevity these are referred to as trials of idarubicin versus other anthracyclines, although the trials actually compared different AML induction regimens (each with its own strategies for the management of toxicities) rather than different drugs.

METHODS

Trial identification. Relevant studies were identified by computer-aided search of databases such as MEDLINE and Physician Data Query (PDQ), by systematic hand-searching

* The members of the AML Collaborative Group who supplied data for the overview are listed in the Acknowledgments.

Correspondence: Dr K. Wheatley, AML Collaborative Group Secretariat, CTSU, Radcliffe Infirmary, Oxford OX2 6HE.

or computer-aided searching of publications, meeting abstracts and lists of protocols, and by communication with trialists and pharmaceutical companies.

Data checking. The coordinators of studies that began before 1993 were invited to participate. The data items to be collected for each patient were agreed in consultation with the trialists, and included age, sex, FAB (French–American–British cytology) type, white blood count, performance status, allocated treatment, and the dates of diagnosis, randomization, complete remission, first relapse and death (or date last seen). Data were not available for this report on antecedent haematological disorder, cytogenetics or multidrug resistance.

All data sets were checked centrally for internal consistency, for consistency with any previous publications, for balance between treatment groups, and for the exclusion of any randomized, or the inclusion of any non-randomized, patients. Any apparent problems were referred to the trialist responsible so that errors and omissions could be rectified where possible. Summary tables of the information for each trial were also sent to trialists for checking, and the present report was circulated to each trial group both for their comments and to ensure that the results presented for their trial are correct.

Definitions. Complete remission was defined by the criteria of each trial (see Appendix). The deaths of those who failed to achieve complete remission were divided into 'early induction failures' (those within 40 d of randomization, most of which were likely to have been primarily due to hypoplastic causes) and 'later induction failures' (those >40 d from randomization, most of which were likely to be related to failure of the induction therapy to control the disease). Disease-free survival (from complete remission until first relapse or death without relapse) was calculated only for those patients who achieved remission. Overall survival ran from the time of randomization and was calculated for all patients.

Statistical methods. These have been described in detail elsewhere (Early Breast Cancer Trialists' Collaborative Group, 1990; Antiplatelet Trialists' Collaboration, 1988). All trials were analysed according to the original treatment allocation, with no post-randomization exclusions (i.e. according to the 'intention-to-treat' principle). The observed minus expected (O − E) number of events and its variance were calculated for the idarubicin-allocated group within each trial either by means of simple contingency tables or, for analyses of time to failure, by the logrank test (using the exact dates of relevant events). Having calculated O − E and its variance for each trial, these quantities were then summated to give two grand totals. This process ensured that patients within any one trial were directly compared only with other patients in that same trial, and not with those in other trials. The two grand totals were then used to calculate overall odds ratios and odds reductions. (An odds ratio of 0·90 would, for example, correspond to an odds reduction of 10%.) All *P* values were two-tailed. Standard tests of heterogeneity or trend were used to compare the treatment effects in different trials or in different subgroups of patients.

Table I. Idarubicin versus other anthracyclines: induction failures and complete remissions.

	Early induction failure (<40 d) (%)		Later induction failure (day 40+) (%)		Complete remission (%)	
	Idarubicin	Other	Idarubicin	Other	Idarubicin	Other
Idarubicin *v* daunorubicin						
GIMEMA	36·3	24·8	23·4	35·2	40·3 (50/124)	40·0 (50/125)
MSKCC	5·8	7·5	14·5	32·8	79·7 (55/69)	59·7 (40/67)
SECSG	13·5	21·0	18·0	25·2	68·5 (76/111)	53·8 (64/119)
A. Einstein	16·5	17·1	17·5	26·1	66·0 (68/103)	56·8 (63/111)
BGMT	21·1	14·5	12·3	25·5	66·7 (76/114)	60·0 66/110)
Subtotal	20·2	18·0	17·5	28·8	62·4 (325/521)	53·2 (283/532)
Idarubicin *v* doxorubicin						
Witwatersrand	11·5	18·7	23·1	22·9	65·4 (34/52)	58·3 (28/48))
Idarubicin *v* zorubicin						
GOELAM	7·5	10·2	23·9	20·4	68·6 (256/373)	69·4 (258/372)
Statistical tests						
Idarubicin *v* daunorubicin						
(O − E) for idarubicin	5·6		−29·7		−24·1	
Variance of O − E	39·4		46·7		61·8	
	NS		$P<0·0001$		$P=0·002$	
Tests for heterogeneity of treatment effect						
Between daunorubicin trials (χ^2_4)	7·1		2·0		5·2	
	NS		NS		NS	
Between daunorubicin, doxorubicin and zorubicin trials (χ^2_2)	3·2		13·1		4·3	
	NS		$P=0·001$		$P=$NS	

Trials and patients. Seven trials were identified that compared idarubicin with daunorubicin. Two further trials compared idarubicin with either doxorubicin or zorubicin, both of which are anthracyclines and similar in structure to daunorubicin. In each trial all patients were also to receive cytosine arabinoside (Ara-C). Individual patient data were supplied from seven of these nine trials (Mandelli *et al*, 1991 (GIMEMA); Berman *et al*, 1991 (MSKCC); Vogler *et al*, 1992 (SECSG); Wiernik *et al*, 1992 (A. Einstein); Rieffers *et al*, 1996 (BGMT); Bezwoda & Dansey, 1990 (Witwatersrand); Harousseau *et al*, 1996 (GOELAM)), which together included 1898 patients (96% of the total). In all of these trials the treatment allocation was relatively well balanced, both overall and by presentation features. Details of these seven trials are given in the Appendix. Data were not supplied for the two remaining trials (Gonzalez-Llaven *et al*, 1991; Eridani *et al*, 1989), both of which were small, with only 62 and 24 patients respectively.

In addition to these nine trials, there are currently two three-arm trials comparing idarubicin, mitozantrone and daunorubicin (an Eastern Co-operative Oncology Group trial evaluating them in conjunction with Ara-C, and a European Organization for Research on the Treatment of Cancer trial assessing them in combination with Ara-C and etoposide), and also a paediatric Berlin–Frankfurt–Munich trial comparing idarubicin with daunorubicin in conjunction with Ara-C and etoposide. These three trials all began after the cut-off date for the overview of 1 January 1993 and their results are not currently available. One additional trial that compared idarubicin versus daunorubicin in intensive 'timed-sequential' therapy was abandoned early because of the gastrointestinal toxicity of the idarubicin schedule (H. G. Prentice, personal communication, September 1996), and was not available. Irrespective of whether or not its results would be considered relevant, its small size (only eight patients were randomized) meant that its inclusion or exclusion could make no material difference to the results of the overview.

Table II. Idarubicin versus daunorubicin: complete remission rates in various types of patient.

		Complete remission (%)	
Type of patient	No. randomized	Idarubicin	Daunorubicin
Sex			
Male	562	60	50
Female	491	65	57
Age			
<40	171	86	62
40–59	313	71	61
60+	569	51	46
White blood count ($\times 10^9$/l)			
0–9	531	65	57
10–49	279	59	52
50–99	139	67	50
100+	104	54	44
FAB type			
M1	196	52	39
M2	340	66	57
M3	74	74	67
M4	219	66	55
M5	140	61	55
M6	45	50	43
Other or unknown	39	61	52
Performance status			
0	218	71	57
1	362	67	56
2	378	57	54
3/4	95	47	29
All patients	1053	62	53

Note: Except for age (see Table III), there was no significant heterogeneity (or, where relevant, trend) between different types of patient in the effects of the treatment allocations.

RESULTS

Remission

The numbers of induction failures and of complete remissions for each trial are shown in Table I. In absolute terms, the proportions of deaths within the first 40 d, many of which would have been deaths due to hypoplasia, varied greatly from one trial to another. But this was chiefly due to differences in eligibility criteria, in particular with respect to age. In trials where the early risk was high it tended to be high in both treatment groups, and where it was low it tended to be low in both groups. Considering only the five trials of idarubicin versus daunorubicin, there was little difference between the two treatments in the numbers who died within 40 d (20% [105/521] early induction failures with idarubicin versus 18% [96/532] with daunorubicin; $P = 0{\cdot}4$). However, there was a highly significant difference between the two treatments in the numbers of later induction failures (17% [91/521] with idarubicin versus 29% [153/532] with daunorubicin; $P < 0{\cdot}0001$). Most of these later deaths would have been due to resistant disease. Overall, therefore, there is a highly significantly better rate of complete remission with idarubicin than with daunorubicin (62% [325/521] *v* 53% [283/532]; $P = 0{\cdot}002$). Moreover, of those who achieved remission, the proportions doing so after only one course of induction chemotherapy were 81% [263/325] with idarubicin as against 73% [207/283] with daunorubicin ($P = 0{\cdot}02$). In the one small trial of idarubicin versus doxorubicin there were no significant differences in early induction failures, in later induction failures or in complete remission rates (62% [32/52] idarubicin versus 56% [27/48] doxorubicin; $P = 0{\cdot}5$) between the two regimens. The one trial of idarubicin versus zorubicin was a much larger study, and again found no significant differences in early induction failures, later induction failures or in complete remission rates (69% [256/373] idarubicin versus 69% [258/372] zorubicin; $P = 0{\cdot}8$) between the two regimens.

Outcome after complete remission

There was a small 4% excess of deaths during first remission in patients who had been allocated idarubicin compared to

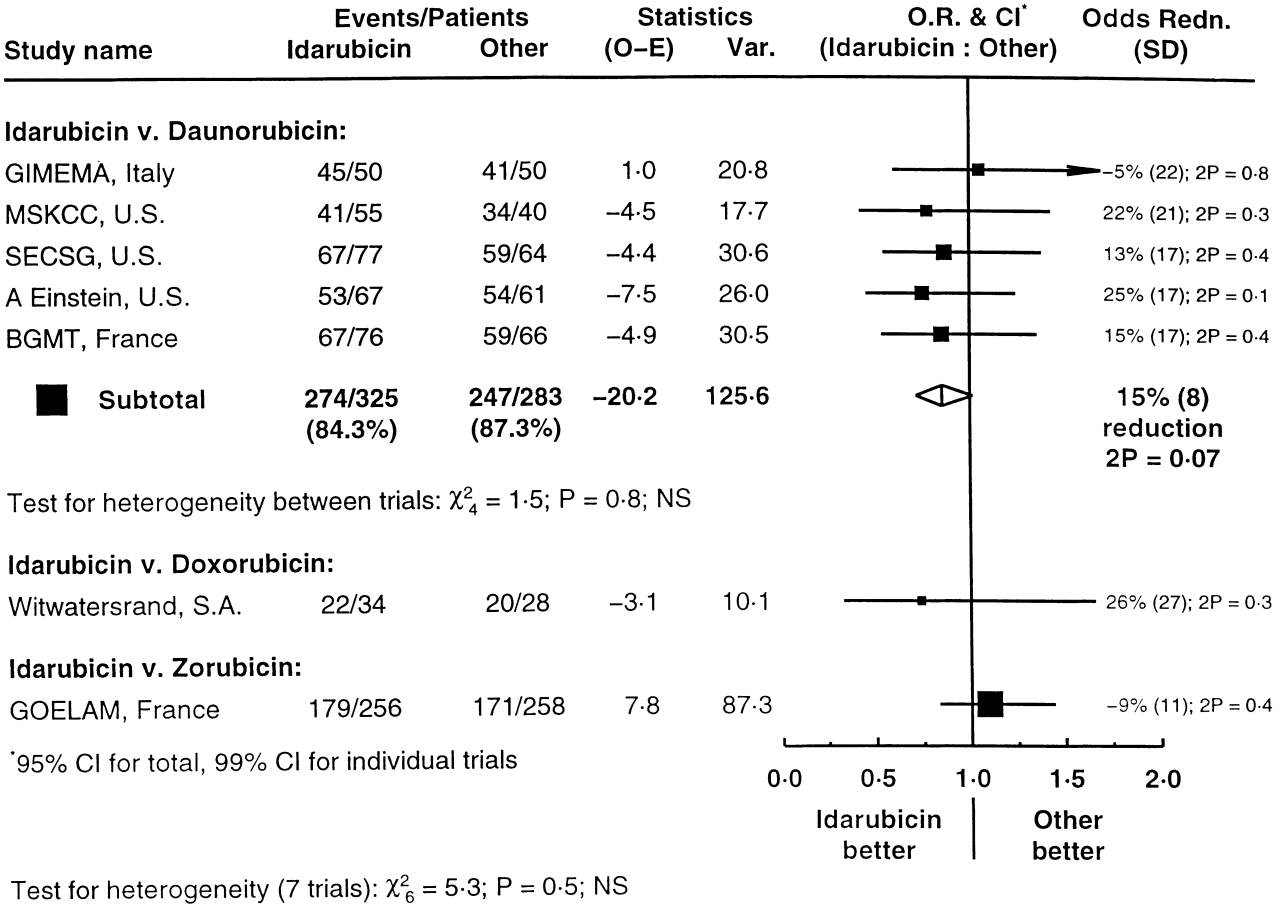

Fig 1. Disease-free survival in trials of idarubicin versus other anthracyclines. Large squares indicate larger trials which provide more information, and hence have narrower 99% confidence intervals (CI). If the square is to the left of the solid line then disease-free survival is better in the group allocated idarubicin, but if the CI crosses this line this result is not statistically significant at $2P < 0{\cdot}01$. The subtotal is represented as a diamond centred on the odds ratio (OR) estimate, with 95% CIs shown by the width of the diamond. For each trial and for the subtotal, the odds reduction is given as a percentage along with its standard deviation (SD).

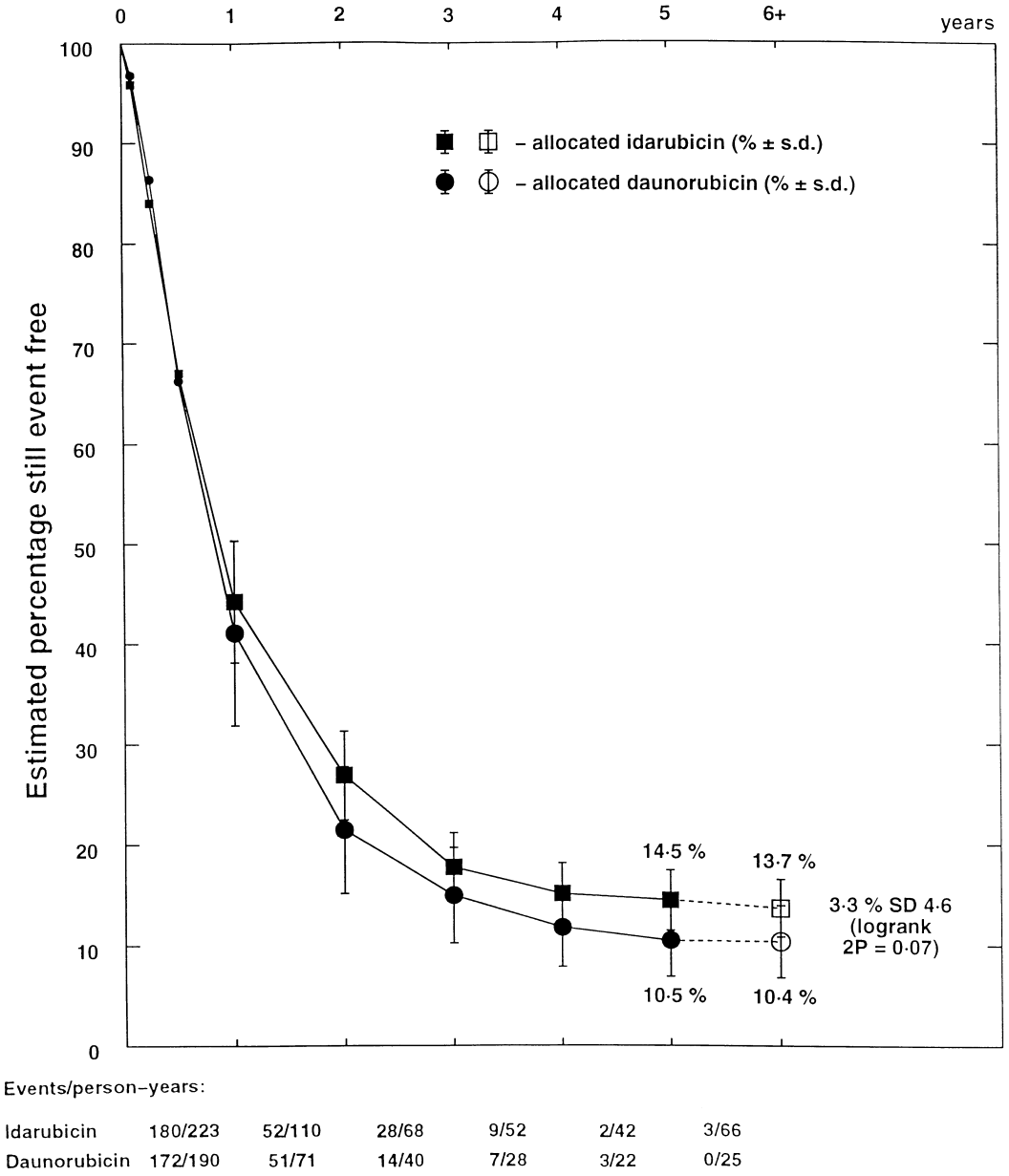

Fig 2. Disease-free survival in trials of idarubicin versus daunorubicin. Because of the small number of patients at risk, events beyond year 5 are combined. Note that 'day 0' is date of first complete remission.

those allocated daunorubicin ($P = 0{\cdot}2$), but this was counterbalanced by a significant reduction in their relapse rates ($P = 0{\cdot}008$). Overall the proportions of remitters who died in their first remission or relapsed were 84·3% with idarubicin and 87·3% with daunorubicin (logrank $P = 0{\cdot}07$; Fig 1). The pattern of disease-free survival among those who had achieved remission is illustrated in Fig 2, and indicates that the proportions of remitters who would, 5 years later, still be in their first remission were 14·5% with idarubicin and 10·5% with daunorubicin. In the trial of idarubicin versus doxorubicin, disease-free survival was non-significantly better with idarubicin, whereas the reverse was the case in the trial of idarubicin versus zorubicin (Fig 1). Survival after relapse was poor in all treatment groups, although a few of those who relapsed were rescued.

Survival

As idarubicin was associated with significantly better remission rates and a non-significantly better outcome after remission, overall survival (among all patients ever randomized) was significantly better with idarubicin than with daunorubicin (13% *v* 9% survival at 5 years, which corresponds to an 'odds ratio' of 0·86; $P = 0{\cdot}03$: Figs 3 and 4). In the trials that compared idarubicin with doxorubicin or with zorubicin there were no significant differences in survival. Specific causes of death were often

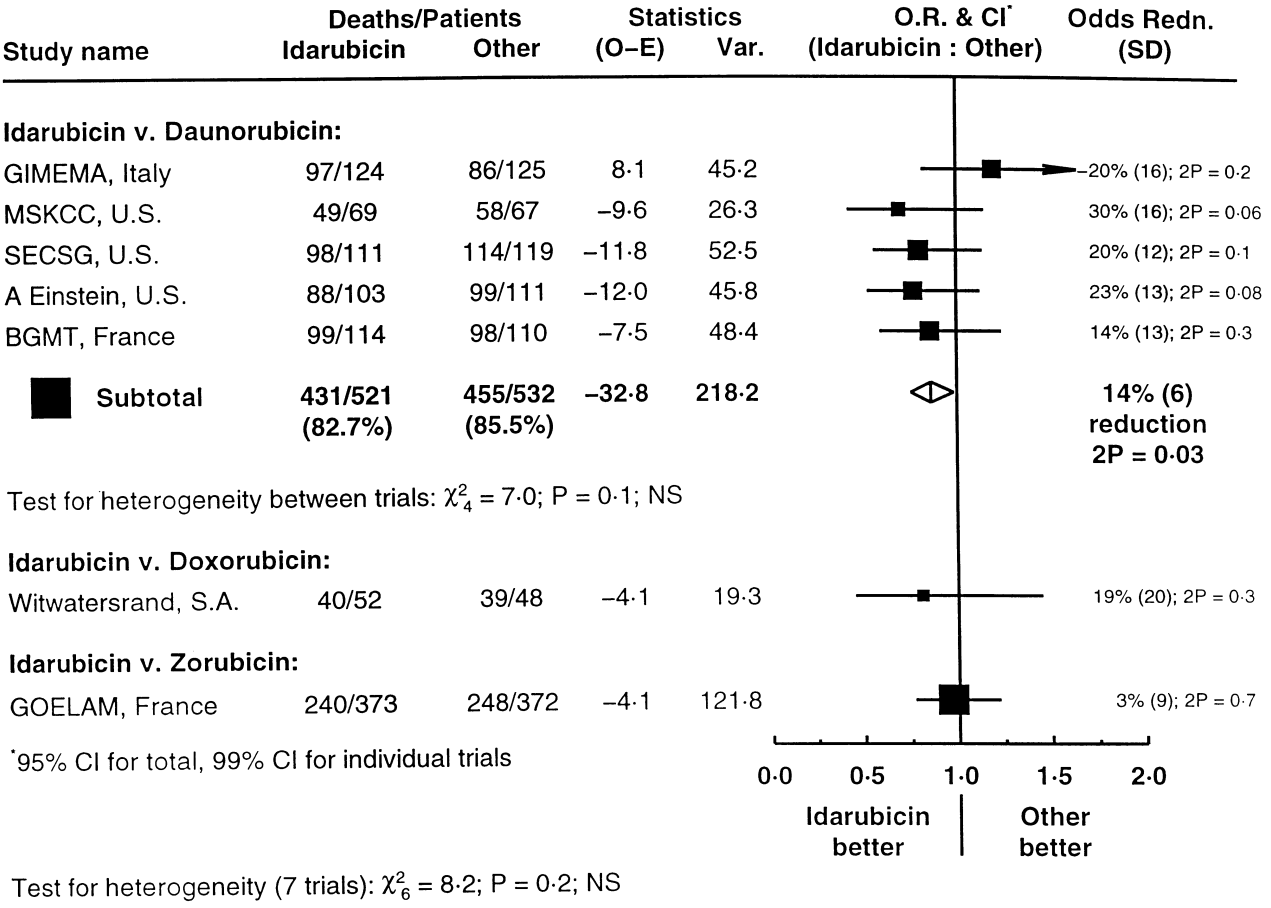

Fig 3. Overall survival in trials of idarubicin versus other anthracyclines. Format as Fig 1.

not provided, so cause-specific mortality cannot be reviewed reliably.

Outcome in different patient groups

Table II subdivides the complete remission rates by the baseline variables age, sex, white blood count, FAB type and performance status. Within each subgroup examined the remission rate was higher with idarubicin than with daunorubicin. There was, however, a tendency for these differences in remission rate to be greater in younger than in older patients, which is explored further in Table III. The mortality during the first 40 d was much greater in those aged > 60 than in those aged < 40. At older ages such deaths appeared to be slightly more numerous with idarubicin than with daunorubicin, but at younger ages the opposite appeared to be the case, though this trend was not quite significant ($P = 0{\cdot}06$). After 40 d there were fewer deaths with idarubicin at all ages, though the difference appeared slightly smaller in the older patients than in the younger (trend: $P = 0{\cdot}2$). The cumulative effect of these two trends

Table III. Idarubicin versus daunorubicin: induction failures and complete remissions by age.

	Early induction failure (%)		Late induction failure (%)		Complete remission (%)	
Age (years)	Idarubicin	Daunorubicin	Idarubicin	Daunorubicin	Idarubicin	Daunorubicin
<40	2·2 (2/93)	7·6 (6/78)	11·8 (11/93)	30·7 (24/78)	86·0 (80/93)	61·5 (48/78)
40–59	14·0 (20/143)	12·9 (22/170)	15·4 (22/143)	25·9 (44/170)	70·6 (101/143)	61·1 (104/170)
60+	29·1 (83/285)	23·9 (68/284)	20·3 (58/285)	29·9 (85/284)	50·5 (144/285)	46·1 (131/284)
All patients	20·2 (105/521)	18·0 (96/532)	17·5 (91/521)	28·8 (153/532)	62·4 (325/521)	53·2 (283/532)
	Effect: $P = 0{\cdot}4$ Trend: $P = 0{\cdot}06$		Effect: $P < 0{\cdot}0001$ Trend: $P = 0{\cdot}2$		Effect: $P = 0{\cdot}002$ Trend: $P = 0{\cdot}006$	

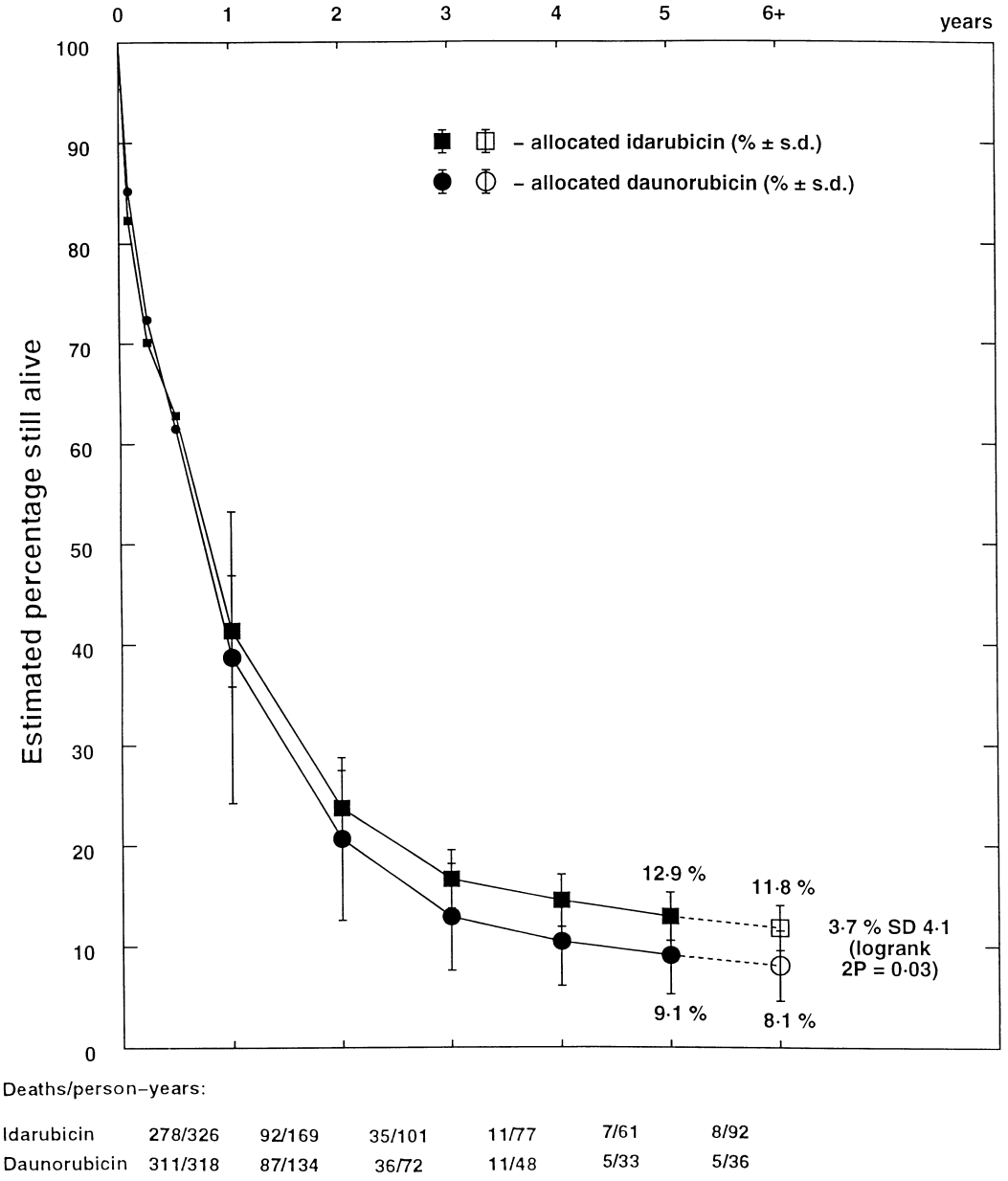

Fig 4. Overall survival in trials of idarubicin versus daunorubicin. Because of the small number of patients at risk, events beyond year 5 are combined. Note that 'day 0' is date of randomization.

was a highly significant trend ($P = 0{\cdot}006$) for the difference in complete remission rates between idarubicin and daunorubicin to be greater in younger than in older patients.

The number of patients in the two trials which compared idarubicin with either doxorubicin or zorubicin was too small for meaningful subgroup analysis.

Trials for which individual patient data were unavailable

The published complete remission rates in the two small idarubicin versus daunorubicin trials for which individual patient data were not supplied were statistically consistent with the results presented here. In the Mexican trial (Gonzales-Llaven *et al*, 1991) the remission rates were 56% (18/32) with idarubicin and 47% (14/30) with daunorubicin, and the corresponding figures for the British study (Eridani *et al*, 1989) were 8/13 (62%) and 2/11 (18%). These two studies were both small, so their inclusion or exclusion could not materially alter the results and their interpretation.

DISCUSSION

An overview of the results of several trials can be appropriate even if there are substantial differences between them in their designs or findings, and is even more appropriate when, as here, there are not. All five of the trials of idarubicin versus

daunorubicin had similar designs and tested similar dosages, and in all five cytosine arabinoside, at intermediate doses, was the only other drug used. In two further trials idarubicin was compared either with doxorubicin or with zorubicin. There is clear evidence of heterogeneity of effect between these two trials and the five daunorubicin trials with respect to late induction failures (Table I), so it would be inappropriate to combine all seven trials to give overall results for any endpoint. Therefore the doxorubicin and zorubicin trials have been presented separately.

The induction regimens based on idarubicin appeared, in the particular circumstances of these trials, to provide somewhat more effective anti-leukaemic therapy than did those based on daunorubicin, with less likelihood of primary resistant disease and a lower relapse risk, while not being substantially more toxic as measured by early induction failures or by deaths in complete remission. This led to superior complete remission rates and better overall survival with idarubicin. There was no evidence of any heterogeneity of treatment effect between the five idarubicin versus daunorubicin trials. The only subgroup effect that was of statistical significance was that the advantage of idarubicin seemed less definite in older patients, but even here there was no indication that the idarubicin-based regimens were inferior. For all analysed subgroups of patients, other than age, there was no good evidence that the benefit of idarubicin over daunorubicin was any greater or less. The numbers randomized were not large enough for the results in particular subgroups to be statistically stable, but in none of the subgroups that were analysed was there any indication that idarubicin was inferior. Indeed, in each of the subgroups in Table II the remission rates with the idarubicin-based regimens appear somewhat better than with the daunorubicin-based regimens, so the overall superiority of these idarubicin-based regimens appears to be of reasonably general validity.

The choice of day 40 as the cut off between early and late failure to achieve CR was to some extent arbitrary. However, the use of a different cut-off point would not alter the results or their interpretation in any major fashion. For example, the use of 30 or 50 d as the cut-off led to very similar differences: with 30 d, early failure was 17·5% with idarubicin and 14·1% with daunorubicin ($P = 0{\cdot}1$), and late failure was 20·2% and 32·8% respectively ($P < 0{\cdot}0001$); with 50 d, early failure was 22·1% *v* 20·1% ($P = 0{\cdot}4$), and late failure was 15·6% *v* 26·8% ($P < 0{\cdot}0001$).

Because more of the idarubicin patients achieved complete remission after just one course, the average number of courses of induction therapy was slightly smaller with idarubicin than with daunorubicin. But correction for any slight bias this might have introduced into the analysis of overall survival would, if anything, merely reinforce the overall findings.

Different drugs or different doses?

It is possible that these trials were not comparing therapeutically equivalent doses of idarubicin and daunorubicin. If equivalence were to be defined as equally toxic, then in terms of the major toxicity of early death there was no difference. In none of the five trials was the haematological toxicity of induction therapy, as measured by time to neutrophil/white cell and platelet recovery, significantly greater with idarubicin, though in two studies (Vogler *et al*, 1992; Wiernik *et al*, 1992) it was worse during the consolidation phase. No substantial differences in non-haematological toxicity were reported in any of the studies. Alternatively, equivalence could be defined as equally effective against the disease, in which case they were clearly not equivalent. It is, however, unclear whether increasing the dose of daunorubicin would have been effective, as it is possible that any reduction in resistant disease may have been counterbalanced by an increase in toxic deaths. Two randomized trials of different daunorubicin doses (Yates *et al*, 1982; Büchner *et al*, 1992) have been inconclusive, with both reporting slightly, but not significantly, better CR rates with the higher dose (though in both the lower dose was 30 mg/m^2/d). Thus, in the absence of trials comparing idarubicin with daunorubicin at doses of greater than 50 mg/m^2/d (new prospective trials of idarubicin at the doses reported here versus daunorubicin at 60–80 mg/m^2/d may be of interest), all this report can do is present the results of the comparison between these two agents in the context of the trials that have been performed. All five trials did, however, use daunorubicin at the generally accepted standard doses of 45–50 mg/m^2/d for 3 d. *In vitro* and preclinical studies have also suggested a possible clinical benefit of idarubicin over daunorubicin, with idarubicin showing faster cellular uptake, increased retention and lower susceptibility to multi-drug resistance (Carella *et al*, 1990; Berman & McBride, 1992).

It is not possible to determine reliably whether idarubicin is better or worse than doxorubicin or zorubicin in the circumstances of the trials reviewed here, since, even in the larger GOELAM study (Harousseau *et al*, 1996), the confidence intervals were wide and were compatible both with benefit for idarubicin or benefit for the other drug.

The results of any overview, like those of any individual trial, have to be based on patients who were first treated some years previously. The trials presented here were all carried out between 1984 and 1993, but this overview of their results is still of direct relevance to much current practice, as the two-drug regimens that were investigated continue to be used widely, especially for older patients (Mayer *et al*, 1994; Rowe *et al*, 1995). Some groups (e.g. EORTC and MRC) have recently begun to study intensified induction therapy by increasing the dose of Ara-C and by adding a third drug, particularly in younger patients, and the relative merits of idarubicin and daunorubicin (and also of mitozantrone) in the context of these more intensive treatment strategies are now being assessed in several trials. Until the results of these new trials are reported and included in future cycles of this overview (so as to avoid unduly data-dependent emphasis on particular trial results), this report provides the most reliable summary of the available evidence as to which anthracycline is the most appropriate for induction therapy in AML.

Appendix: Details of the Idarubicin versus Daunorubicin/Doxorubicin/Zorubicin Trials

Trial Name	Trial Group	Accrual period	Entry Criteria	Definition of complete remission
GIMEMA	GIMEMA, Italy	1984-87	Age 55-80; FAB M1-M6, include previous MDS, exclude blast transformation of CML; exclude if significant renal or hepatic pathology or ejection fraction <50%; no prior treatment for leukaemia	Normal cellular marrow with normal erythroid and myeloid elements and with myeloblasts, promyelocytes and other leukaemic cells totalling less than 5%, and with normal peripheral blood platelet and white blood cell counts
MSKCC L-19/L-22	Memorial & Sloan Kettering Cancer Center, New York, USA	1984-89	Age 18-60; exclude secondary AML; no prior malignancy treated with chemotherapy or radiotherapy; exclude if ejection fraction <50%; no prior treatment for AML	2 marrows ≤5% blasts with normal cytopoiesis, no evidence of disease, WBC <3 x 10^9/l, plts ≥100 x 10^9/l, HG ≥10 g/dl
SECSG AML 305	Southeastern Cancer Study Group, USA	1985-89	Age >14; FAB M1-M6, exclude secondary AML; no prior treatment for AML; normal cardiac ejection fraction	Marrow <5% blasts and normal erythropoiesis, granulopoiesis and adequate megakaryocytes
Albert Einstein 8509199	Albert Einstein College of Medicine, New York, USA	1985-89	Age ≥18; including previous MDS, preleukaemia or refractory anaemia; no prior radiotherapy nor chemotherapy	Normal cellular marrow with normal erythroid and myeloid elements and with myeloblasts, promyelocytes and other leukaemic cells totalling <5%, and with normal peripheral blood platelet and WBC counts
BGMT	BGMT Group, France	1987-91	Age 55-75; exclude secondary AML	Marrow <5% leukaemic cells, normal haematopoiesis, without clinical evidence of malignancy
Witwatersrand	Witwatersrand University, Johannesburg, South Africa	1985-86	Age >16	
GOELAM 1	GOELAM Group, France	1987-94	Age 15-65; exclude secondary AML	Normal cellular marrow with <5% leukaemic blasts, plts >100x10^9/l, granulocytes >1.0x10^9/l

Trial Name	No. of courses of therapy	Idarubicin arm			Daunorubicin/Doxorubicin/Zorubicin arm				Cytosine Arabinoside (common to both arms)		
		No. of patients	Dose[a]	Days	No. of patients	Drug[b]	Dose[a]	Days	Dose	Route	Days
GIMEMA	1-2 induction	124	12	1-3	125	Dnr	45	1-3	100	iv ci	1-7
	4 consolidation		12	1		Dnr	45	1	150	sc	1-5
MSKCC	1-2 induction	69	12	1-3	67	Dnr	50	1-3	200	iv ci	1-5
L-19/L-22	2 consolidation		12	1-2		Dnr	50	1-2	200	iv ci	1-4
SECSG AML	1 induction	111	12	1-3	119	Dnr	45	1-3	100	iv ci	1-7
305	3 consolidation		15	1		Dnr	50	1	200	iv ci	1-5
	4 maintenance		12	1-2		Dnr	45	1-2	100	iv ci	1-5
Albert Einstein	1-2 induction	103	13	1-3	111	Dnr	45	1-3	100	iv ci	1-7
8509199	1 consolidation		13	1-2		Dnr	45	1-2	100	iv ci	1-5
BGMT	1 induction	114	8	1-5	110	Dnr	50	1-3	100	iv ci	1-7
	1 consolidation										
Witwatersrand	2 induction	52	20	1-3	48	Dox	30	1-3	25	loading dose	
	1 consolidation								100	iv ci	1-7
GOELAM 1		373	8	1-5	372	Zorub	200	1-4	200	iv ci	1-7

Notes: [a] all drug doses are given in mg/m^2/day; [b] Dnr = Daunorubicin, Dox = Doxorubicin, Zorub = Zorubicin; all anthracyclines were administered intravenously except in the Witwatersrand trial, where idarubicin was given orally; iv = intravenous, sc = subcutaneous, ci = continuous infusion

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