Articles

Duration and intensity of maintenance chemotherapy in acute lymphoblastic leukaemia: overview of 42 trials involving 12 000 randomised children

*Childhood ALL Collaborative Group**

Summary

Background The effects on long-term outcome in childhood acute lymphoblastic leukaemia (ALL) of the duration and the intensity of maintenance chemotherapy need to be assessed reliably. With this objective the Childhood ALL Collaborative Group coordinated a worldwide overview of all randomised trials that began before 1987.

Methods Individual patient data were sought for about 3900 children in trials of longer *vs* shorter maintenance (eg, 3 *vs* 2 years), 3700 in trials of intensive "reinduction" chemotherapy during maintenance, and 4400 in trials of various other questions, including 1300 in trials of pulses of vincristine and prednisone (VP) during maintenance. Analyses were of survival in first remission, overall survival, and cause-specific mortality.

Findings Deaths during remission were increased by longer maintenance (2·7% *vs* 1·2%), VP pulses (4·0 *vs* 3·2%), and intensive reinduction (4·8% *vs* 3·3%), but these increases were counterbalanced by reductions in relapses. Total events (relapse or death) were significantly reduced by longer maintenance (23·3% *vs* 27·6%), VP pulses (31·2% *vs* 40·4%) and intensive reinduction (27·8% *vs* 35·8%) (each $2p<0·001$). Many of those who relapsed were successfully re-treated, however, and only for intensive reinduction was overall survival significantly improved (18·5% *vs* 22·3%; $2p=0·01$).

Interpretation Intensive reinduction chemotherapy in these trials produced an absolute improvement of about 4% in long-term survival; if the extra deaths in remission had been avoided, this would have been a 5% benefit. Further improvements in survival seem more likely to be obtained with intensive treatment than with longer low-level maintenance.

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Introduction

Three out of four children with acute lymphoblastic leukaemia (ALL) can now expect to be cured in what was, only a few decades ago, an invariably fatal disease. Better survival has involved successively better drugs, better scheduling of those drugs and better supportive care, allowing substantially greater intensity of antileukaemic treatment. However, such treatments still involve serious risks. To determine which types of patient are, on balance, likely to benefit from the addition or removal of particular components of the primary treatment of their disease, both risks and benefits must be assessed reliably. A worldwide collaborative overview (or meta-analysis) of the randomised evidence has therefore been organised. Randomisation avoids any systematic differences between patients allocated different treatments, increasing the total number of patients reduces chance fluctuation, and reviewing all trials avoids unduly data-dependent emphasis on particular studies.[1–3]

This report is only of those trials that compared maintenance treatment strategies of different durations or intensities. By definition, "maintenance" therapy in a trial began when at least one randomised arm started on a protracted course of low-intensity treatment, and any randomised comparisons of intensity or duration thereafter are included. The three most widely studied types of comparison were between different durations of maintenance; between maintenance with and without additional periodic pulses of vincristine and prednisone (VP pulses); and between maintenance with and without the inclusion of one or two additional courses of multidrug intensive treatment ("reinduction").

Materials and methods

Trials included

Randomised trials of any aspect of the primary treatment of ALL that began before 1987 were identified by computer-aided searching of MEDLINE and of clinical trial databases, by hand searching meeting abstracts, by scrutiny of reference lists of trials and review articles, and by correspondence with colleagues and with pharmaceutical companies. Trials were to be excluded only if they were not properly randomised (eg, if the method of treatment allocation allowed foreknowledge, when deciding whether to enter a particular patient, of the treatment that that patient would be allocated).

For each patient aged 21 or under, information was sought on gender, white cell count at diagnosis (WBC), treatment allocation and the dates of birth, diagnosis, randomisation, complete remission, relapse, death, or last contact. The data were checked centrally for various inconsistencies, for balance between treatments within different patient groups, and for evidence that any randomised patients had been excluded. (All randomised patients were to be evaluated according to the treatment

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randomly assigned to them.) Errors and omissions were rectified by correspondence with the principal investigators, summary tables of their own results were returned to the trialists for checking, and the draft of this report was circulated to them for comment and revision.

Events analysed

The main analyses are of survival and of survival in first remission from the date of randomisation, with an "event" defined as relapse, death in remission or (rare in these maintenance studies) death without remission. Some analyses of relapse were subdivided by site: bone marrow (including combined bone marrow and any other site), central nervous system (CNS, excluding those with simultaneous bone marrow relapse), and isolated testicular. The few isolated relapses at other sites or at an unknown site have been included with those in the bone marrow rather than being analysed separately. Their number is too small to have any material effect on the analyses of bone marrow relapse. In the analyses of non-CNS relapse, deaths in remission and CNS relapses without bone marrow involvement are "censored".[4] In some analyses mortality is subdivided into death in first remision and death after relapse.

For the few trials from which individual patient data were not available, tabular data on the numbers of events and deaths in each arm have been sought from publications and used in the overall analyses. These trials are not included in survival curves, in stratified analyses or in analyses of subsidiary outcomes.

Statistics

The statistical methods[4,5] involve comparison of the observed number of patients in one treatment group (O) who have suffered some particular type of event with the log rank expected number (E), which is based on the average experience of both treatment groups. Exact event dates are used when calculating these expected numbers. From this log-rank (O-E) and its variance can be calculated the "odds ratio" for that trial and its 99% confidence interval.[4,5] Information from different trials is then combined by summing the separate O-E values, one per trial. The variance of this grand total is simply the sum of the separate variances. Use of this grand total ensures that patients within one trial are directly compared only with other patients in that same trial, and not with those in other trials. Finally, the grand total and its variance are used to calculate not only a significance test but also an overall odds ratio (OR) and its 95% confidence interval (CI)[4,5] and to help calculate descriptive survival curves.[4]

Results

Completeness of coverage

Table 1 describes the 42 trials of maintenance therapy from which information is currently available.† Information is not yet available from seven studies, and it is possible that a few more studies have been overlooked completely. However, the unavailable studies are likely to be small. Thus, about 80% of the studies and over 90% of the children from all the randomised trials that began before 1987 are thought to be included in table 1. Centrally reviewed data on individual patients were available for 90% of patients in table 1, and published data were used for the remainder.

Duration of maintenance

17 trials compared maintenance of different durations, the commonest comparison being of 3 versus 2 years. Data were not available from the first of these trials. In the other 16 trials, 3861 children were randomised and individual patient data are available from all except the 746 children in the German (BFM) trials. In all trials except St Jude V (USA) the stop/continue randomisation was scheduled to take place when the shorter treatment ended. Hence, most patients on the "shorter" arm were not to receive any maintenance treatment for the first year after randomisation, whereas those on the "longer" arm were to continue for an average of about 13 extra months. The trials started between 1970 and

†An appendix giving brief details of the regimens in the trials is available from *The Lancet* or the Childhood ALL Secretariat

Treatment comparison	Trials	Patients	Relapse or death
Longer *vs* shorter maintenance	16	3861	984
Addition of pulses of vincristine and prednisone during maintenance	5	1251	447
Addition of intensive reinduction treatment during maintenance	6	3696	1246
Other drug additions during maintenance			
Higher *vs* lower dose	2	476	276
Cytarabine+cyclophosphamide+doxorubicin	1	711	263
Cytarabine+cyclophosphamide	2	365	284
Cyclophosphamide	4	990	446
L-asparaginase+cytarabine	1	191	131
Cytarabine	2	296	182
Prednisolone	1	33	29
Vincristine	1	31	26
6-mercaptopurine	1	40	22
All studies with data available	42	11 941	4336

Table 1: **Randomised comparisons with outcome data available that began before 1987 of the duration or intensity of maintenance chemotherapy in childhood ALL**

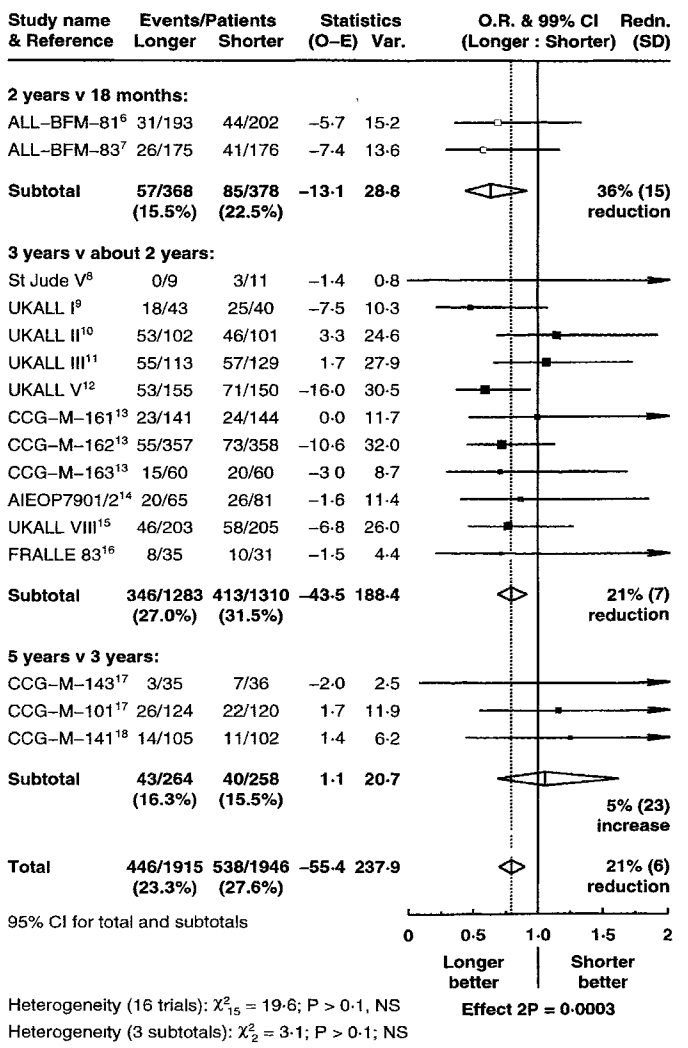


Figure 1: **Duration of maintenance chemotherapy in childhood ALL: effects on survival in first remission**

Larger squares indicate more informative trials, and hence shorter CIs. If square is to left of solid line survival in first remission is better in group allocated longer maintenance treatment but if CI crosses this line this result is not of extreme statistical significance (2p>0·01). Empty squares are used for studies where individual patient data were not available. Subtotals and overall total are represented as diamonds centred on OR estimate, with 95% CI shown by width of diamond and with odds reduction also given as percentage along with its SD. Because only a minority have suffered an event, the overall odds reduction in these trials (21%) is about five times as big as the absolute risk reduction (27·6%–23·3%=4·3%).

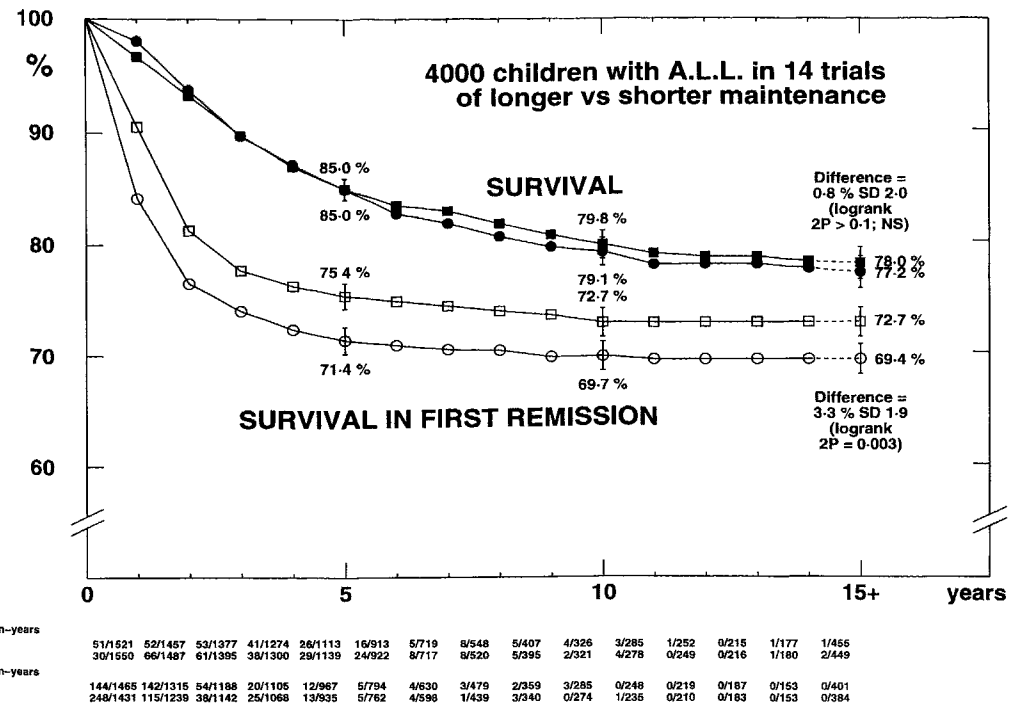


Figure 2: **Duration of maintenance chemotherapy in childhood ALL: effects on survival, and on survival in first remission**

Upper pair of lines describe survival, and lower pair (open symbols) survival in first remission from time of randomisation: both pairs derive from stratified analyses.[4] Squares and circles denote active and control, respectively.

1983 with the last patients randomised in 1990, and for all but one a median follow-up of over 5 years is available.

Figure 1 displays the results from each separate trial for survival in first remission. The overall odds reduction is 21% with standard deviation (SD 6) (2p=0·0003). This corresponds to an absolute reduction in the risk of relapse or death of 4·3%, from 27·6% (538/1946) with shorter to 23·3% (446/1915) with longer maintenance. CIs for all 16 trials overlap the average 21% odds reduction (dotted vertical line) in the failure rate. Thus, no trial yielded a difference significantly better or significantly worse than the average result, and a statistical test likewise shows no significant hererogeneity between the 16 trials or between the three subtotals, although extra maintenance did not appear to reduce the risk of an event in the few studies of 5 versus 3 years of maintenance treatment.

Figure 2 illustrates the effects of longer treatment not only on survival in first remission, but also on survival. The two trials without individual patient data are not included, so the p value for survival in first remission is less extreme than in figure 1.

Longer maintenance approximately halved the relapse rate during the first year, during which one group was still receiving maintenance therapy and most of the other was not, but had no significant effect on long-term survival. There were three reasons why the definite difference in early relapse did not translate into better long-term survival. First, those given longer maintenance therapy were more likely to die in remission (upper part of table 2), so during the first year longer maintenance was associated with some additional deaths (figure 2). Second, those early relapses that could be prevented by longer maintenance therapy may be particularly likely to be responsive to salvage chemotherapy. Third, when maintenance therapy finally ended in those who had been allocated longer treatment, there was then a slight excess risk of relapse in the second and third years after randomisation that reduced the early advantage.

Analyses within sex, age, and WBC groups did not demonstrate any different effect of treatment within any subgroup of patients either in survival in first remission (figure 3) or in survival (data not shown).

Addition of pulses of VP during maintenance

Seven trials compared maintenance treatment with and without pulses of VP. Data were not available from two.[23] In the other five trials 1251 children were randomised, and individual patient data are available from all except

Outcome	Numbers with specified outcome, by random treatment allocation		Odds ratio (and SD)	2p
Duration of maintenance chemotherapy (14 trials)				
	Longer (1547)	Shorter (1568)		
Any failure	389	453	0·82 (0·06)	0·003
Bone marrow relapse	232	296	0·74 (0·08)	0·00005
CNS relapse	58	53	1·03 (0·19)	NS
Testes relapse/males	57/776	85/789	0·64 (0·14)	0·009
Death in first remission	42	19	2·11 (0·38)	0·004
Death after relapse	225	259	0·87 (0·09)	NS
Any death	267	278	0·96 (0·08)	NS
Addition of VP pulses during maintenance (4 trials)				
	VP pulses (526)	Control (526)		
Any failure	168	223	0·69 (0·08)	0 0003
Bone marrow relapse	91	131	0·64 (0·11)	0·0008
CNS relapse	37	30	1·15 (0·26)	NS
Testes relapse/males	19/281	45/300	0·41 (0·17)	0·0003
Death in first remission	21	17	1·18 (0·35)	NS
Death after relapse	102	127	0·79 (0·12)	0·08
Any death	123	144	0·84 (0·11)	NS
Addition of intensive reinduction during maintenance (5 trials)*				
	Re-induction (1383)	Control (1382)		
Any failure	400	507	0·74 (0·05)	0·00001
Bone marrow relapse	212	279	0·71 (0·08)	0·0001
CNS relapse	70	115	0·59 (0·11)	0·0003
Testes relapse/males	46/875	60/862	0·69 (0·16)	0·06
Death without remission	5	7	0·67 (0·52)	NS
Death in first remission	67	46	1·40 (0·22)	0·08
Death after relapse	184	255	0·71 (0·08)	0·0003
Any death	256	308	0·81 (0·08)	0·01

Statistical analyses (unless they include deaths after relapse) are censored at time of first failure NS denotes 2p>0·1.

*Includes only 2 versus 0 blocks from UKALLX/XA: see figure 4.

Table 2: **Results from trials with data on sites of first relapse and deaths in first remission**

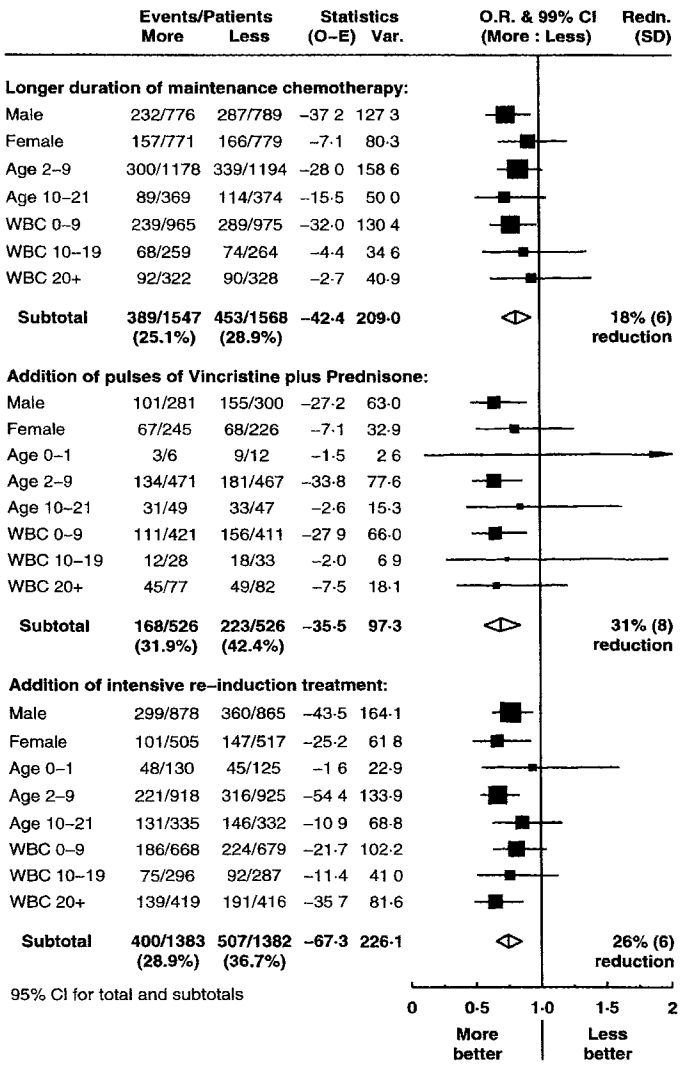


Figure 3: **Duration and intensity of maintenance chemotherapy in childhood ALL: subdivision by sex, age and initial white blood count of the effects on survival in first remission**
Format as figure 1. Results from trials with individual patient data. Two patients had unknown WBC. "Addition of intensive reinduction" analyses include only two versus 0 blocks from UKALLX/XA: see figure 4. In each of these analyses there is no significant heterogeneity with respect to age, sex, or WBC.

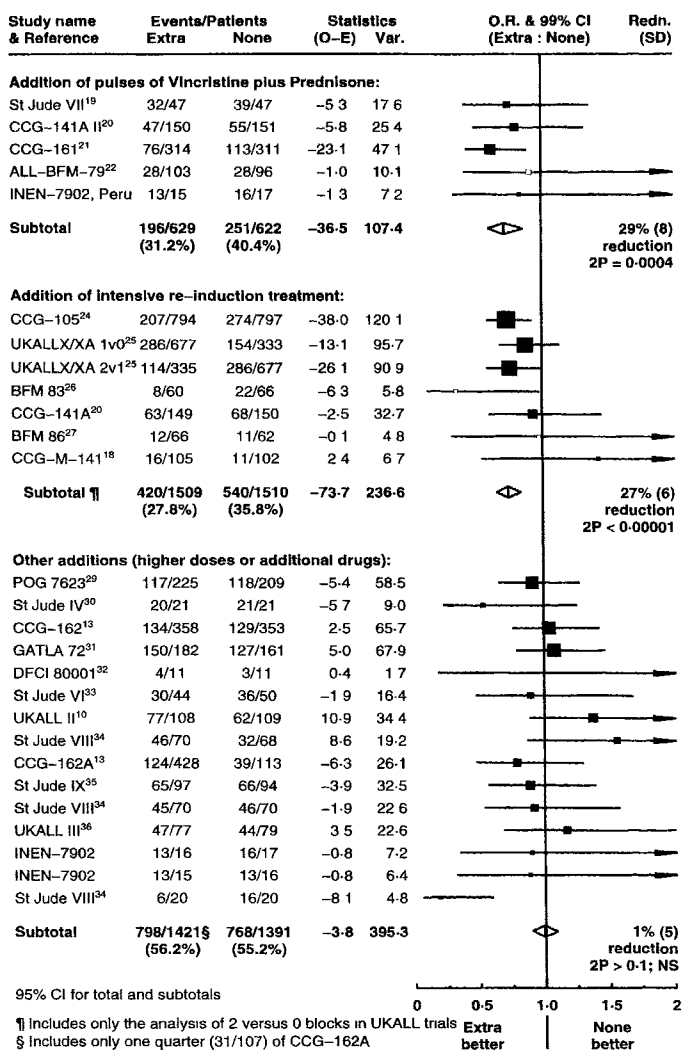


Figure 4: **Various additional treatments during maintenance chemotherapy in childhood ALL: effects on survival in first remission**
Format as figure 1.

remission among those allocated VP (table 2) and partly by fewer responses of relapsed patients to salvage treatment.

Again, analyses within sex, age and WBC groups did not demonstrate any markedly different effect of treatment within any subgroup of patients either in survival in first remission (figure 3) or in survival (data not shown).

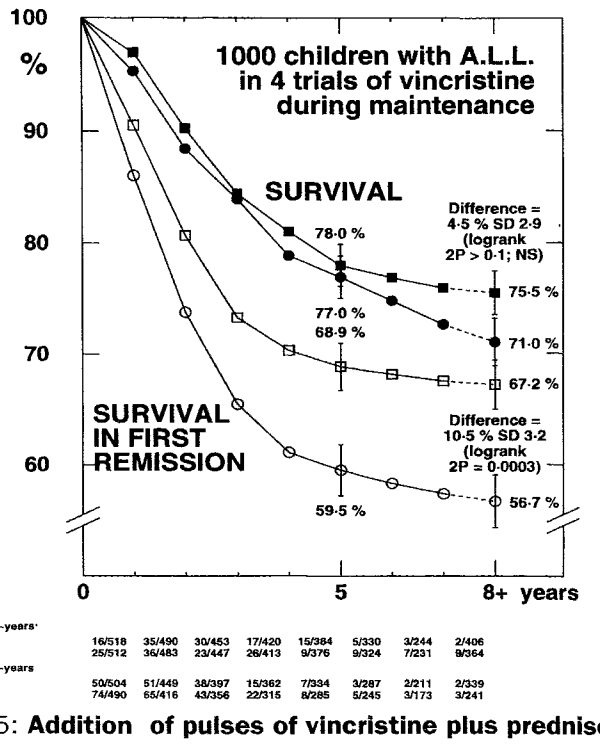
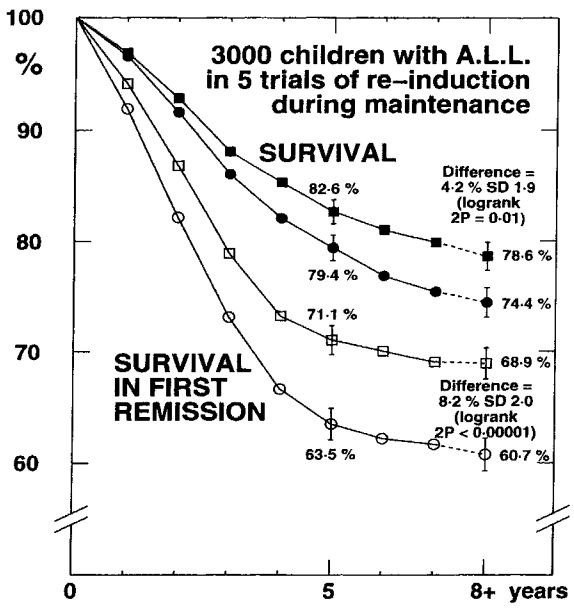


Figure 5: **Addition of pulses of vincristine plus prednisolone during maintenance chemotherapy in childhood ALL: effects on survival, and on survival in first remission**
Format as figure 2.



Deaths/person–years								
Re–induction	43/1354	55/1298	65/1226	35/1101	29/915	14/693	7/491	8/498
None	47/1350	68/1287	75/1198	52/1085	29/894	22/666	9/462	6/473
Events/person–years								
Re–induction	80/1334	99/1233	108/1120	73/971	24/787	9/599	6/423	1/430
None	112/1323	135/1191	121/1049	84/900	35/720	11/526	3/370	6/397

Figure 6: **Addition of intensive reinduction treatment during maintenance chemotherapy in childhood ALL: effects on survival, and on survival in first remission**
Format as figure 2.

Addition of intensive "reinduction" during maintenance

Seven randomised trials assessed the addition during maintenance of one or two blocks of intensive "re-induction" treatment—ie, a course of treatment that is so intensive that it might well have been able to induce remission in a newly diagnosed patient. Information is not available from the last of these trials.[28] In the first six trials 3696 children were randomised, and individual patient data are available for all except 254 children in two trials. For trials where individual patient data were available, the median follow-up was at least 5 years.

The randomised treatments consisted of one block of chemotherapy at about 5 months after diagnosis in CCG-105 and BFM-83, one block at 1 year in BFM-86, one block at about 3 years in CCG -M-141 and CLB 761R and two blocks at 6 and 12 months in CCG-141A. The MRC UKALLX and UKALLXA trials randomised two such blocks, so that patients were allocated one block at 4 weeks, one block at 20 weeks, both blocks or neither. For these MRC trials three comparisons are presented: one block versus none, two blocks versus one and (in the total) two blocks versus none. Randomisation occurred soon after diagnosis (except in CCG-M-141, where it was at 3 years). From the UKALL XA trial for adults, only those aged 21 or under are included in the present overview.

Analysis of survival in first remission again shows a highly significant 27% SD 6 reduction in the odds of an event ($2p<0{\cdot}00001$; figure 4. As with the addition of VP pulses, the difference in relapse rates that is produced by additional intensification persists for several years (figure 6), so that by the fifth year the ab solute difference in survival in first remision is 7·6% (63·5% *vs* 71·1%). There is also a significant, although smaller, 19% SD 8 reduction in the odds of death ($2p=0{\cdot}01$), which corresponds to an absolute difference in survival of about 3% at 5 years and of 4% at 8 years.

The final section of table 2 shows the different types of event separately. There is a significant decrease in relapses at all sites—including the CNS—and a non-significant increase in the number of deaths in remission among those allocated an additional intensification block. In contrast with the analyses of longer treatment and of VP pulses, the analyses of additional intensification found a highly significant reduction in post relapse deaths ($2p=0{\cdot}0003$) which results in a significant reduction in the overall number of deaths (18·5% *vs* 22·3%; $2p=0{\cdot}01$). Most of these deaths were in the CCG-105 trial C128/794 with one additional block of treatment vs 156/797 without) and the UKALLX/XA trials (70/335 with two additional blocks of treatment vs 98/333 with none).

Again, subdivision by sex, age and initial WBC did not demonstrate any clearly significant heterogeneity in the effects of treatment on survival in first remission (figure 3) or on survival (data not shown).

Other maintenance treatment comparisons

Other studies compared different ways of giving the same drugs, or randomised the addition of extra drugs, but the total numbers randomised were not large, and no clear conclusions emerged. The final part of figure 4 gives the results for survival in first remission.

Discussion

This collaboration has brought together substantial amounts of randomised evidence on two main aspects of the treatment of childhood ALL—namely, the duration and the intensity of maintenance chemotherapy. Most of the evidence on duration comes from trials of 3 years versus 2 years of continuous low-dose maintenance, and most of the evidence on intensity comes either from the trials of adding pulses of vincristine and prednisone or from the trials of adding intensive reinduction chemotherapy during maintenance. In all of these comparisons there have been significantly fewer relapses plus fewer (but, in the case of duration and VP pulses, non-significantly fewer) leukaemic deaths. Only for intensive reinduction, however, has the decrease in leukaemic deaths significantly outweighed the small but definite increases in non-leukaemic deaths.

The trials of more versus less prolonged maintenance treatment provide no evidence that five years was better than three years of maintenance, although they do show that the addition of a third year of maintenance significantly reduced the likelihood of haematological and testicular relapse during that third year. However, there was no apparent effect on overall survival because any small reduction in the risk of death from leukaemia was counterbalanced by the small but definite increase in the risk of death in remission. Although some of these remission deaths might nowadays be avoidable it is unlikely that all would be. In addition, patients who relapsed following shorter maintenance treatment were more likely to respond to reinduction therapy, and nowadays reinduction treatment should be even more effective. This suggests that the third year of continuous low-dose maintenance chemotherapy was chiefly preventing (or delaying) salvageable relapses and hence, even without any deaths in remission, such treatment would produce little improvement in survival.

In contrast, the results for intensive reinduction blocks during maintenance show a reduction in both CNS and haematological relapses, and also a reduction in the number of deaths from leukaemia. This resulted in an improvement in overall survival as well as survival in first remission, with an absolute improvement of about 4% in

long-term survival. The results from the trials of adding VP pulses during maintenance were intermediate between those for duration and those for intensive re-induction, with relapse prevented or delayed but (perhaps because of the smaller numbers randomised) with the improvements in survival not clearly significant.

Taken together, these three sets of findings indicate that, as long as adequate supportive care is available, further improvements in survival are more likely to be obtained with one or more courses of really intensive treatment than with an extra year or two of low-dose maintenance.

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