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Treatment reduction for children and young adults with low-risk acute lymphoblastic leukaemia defined by minimal residual disease (UKALL 2003): a randomised controlled trial

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Summary

Background Minimal residual disease (MRD) is the most sensitive and specific predictor of relapse risk in children with acute lymphoblastic leukaemia (ALL) during remission. We assessed whether treatment intensity could be adjusted for children and young adults according to MRD risk stratification.

Methods Between Oct 1, 2003 and June 30, 2011, consecutive children and young adults (aged 1–24 years) with ALL from the UK and Ireland were recruited. Eligible patients were categorised into clinical standard, intermediate, and high risk groups on the basis of a combination of National Cancer Institute (NCI) criteria, cytogenetics, and early response to induction therapy, which was assessed by bone marrow blast counts taken at days 8 (NCI high-risk patients) and 15 (NCI standard-risk patients) after induction began. Clinical standard-risk and intermediate-risk patients were assessed for MRD. Those classified as MRD low risk (undetectable MRD at the end of induction [day 29] or detectable MRD [less than 0·01%] at day 29 that became undetectable by week 11) were randomly assigned to receive one or two delayed intensification courses. Patients had received induction, consolidation, and interim maintenance therapy before they began delayed intensification. Delayed intensification consisted of pegylated asparaginase on day 4; vincristine, dexamethasone (alternate weeks), and doxorubicin for 3 weeks; and 4 weeks of cyclophosphamide and cytarabine. Computer randomisation was done with stratification by MRD result and balancing for sex, age, and white blood cell count at diagnosis by method of minimisation. Patients, clinicians, and data analysts were not masked to treatment allocation. The primary outcome was event-free survival (EFS), which was defined as time to relapse, secondary tumour, or death. Our aim was to rule out a 7% reduction in EFS in the group given one delayed intensification course relative to that given two delayed intensification courses. Analyses were by intention to treat. This trial is registered, number ISRCTN07355119.

Findings Of 3207 patients registered in the trial overall, 521 MRD low-risk patients were randomly assigned to receive one (n=260) or two (n=261) delayed intensification courses. Median follow-up of these patients was 57 months (IQR 42–72). We recorded no significant difference in EFS between the group given one delayed intensification (94·4% at 5 years, 95% CI 91·1–97·7) and that given two delayed intensifications (95·5%, 92·8–98·2; unadjusted odds ratio 1·00, 95% CI 0·43–2·31; two-sided p=0·99). The difference in 5-year EFS between the two groups was 1·1% (95% CI –5·6 to 2·5). 11 patients (actuarial relapse at 5 years 5·6%, 95% CI 2·3–8·9) given one delayed intensification and six (2·4%, 0·2–4·6) given two delayed intensifications relapsed (p=0·23). Three patients (1·2%, 0–2·6) given two delayed intensifications died of treatment-related causes compared with none in the group given one delayed intensification (p=0·08). We recorded no significant difference between groups for serious adverse events and grade 3 or 4 toxic effects; however, the second delayed intensification course was associated with one (<1%) treatment-related death, and 74 episodes of grade 3 or 4 toxic effects in 45 patients (17%).

Interpretation Treatment reduction is feasible for children and young adults with ALL who are predicted to have a low risk of relapse on the basis of rapid clearance of MRD by the end of induction therapy.

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Introduction

Several step changes in outcomes for children with acute lymphoblastic leukaemia (ALL) were made in the last three decades of the 20th century; at the start of the 21st century, 80% of patients could expect to survive without relapse after first-line treatment.[1–4] The challenges for clinical trials at that time were to sustain that rate of improvement without new drugs and to address the problem of immediate and long-term toxic effects of treatment.

Historically, the intensity of treatment received by a patient with ALL was based on risk of relapse, which was predicted by a combination of clinical, cytogenetic, and morphological early response criteria.[1,3,4] However, risk groups identified by these variables are fairly non-specific, because most relapses arise in medium-risk and low-risk groups.[1,3,4] Monitoring of minimal residual disease (MRD) has been shown to be the most sensitive and specific predictor of relapse risk in several large studies.[5,6] These studies established that the positive and negative predictive

value of a specific MRD result depends on the sensitivity of the technique used to measure it, the point at which it is measured, and the treatment received by the patient before and after the point of assessment. Despite differences in these variables in published studies,[5,6] the significance of results relating to specific clinical endpoints is consistent. Patients who have undetectable MRD by the end of induction therapy have a negligible risk of relapse, whereas those who have more than 0·01% MRD at that timepoint have a relapse risk of more than 20%. Hence, MRD monitoring has been used in several clinical trials[1,7–9] to better predict the risk of relapse for an individual.

We tested whether adjustment of treatment intensity according to MRD risk stratification was feasible. We report the outcome for patients in the trial overall and the results of treatment reduction for MRD low-risk patients.

Methods

Study design and participants

From Oct 1, 2003, to June 30, 2011, we recruited consecutive children and young adults with ALL diagnosed at 45 centres in the UK and Ireland into the Medical Research Council UK ALL 2003 (MRC UKALL 2003) randomised controlled trial. ALL was diagnosed with standard morphological and flow cytometric criteria as previously described.[10] Patients aged younger than 1 year or with mature B-cell ALL were not eligible. Patients with Philadelphia-chromosome-positive ALL were transferred to other protocols such as the European Study for Philadelphia-chromosome-positive ALL (EsPhALL)[11] or UKALL XII[12] once their Philadelphia-chromosome status was known.

For **trial protocol** see http://www.ctsu.ox.ac.uk/research/mega-trials/leukaemia-trials/ukall-2003

The upper age limit of entry was 18 years at the start of the trial, but was increased to 20 years in February, 2006, and to 24 years from August, 2007, because retrospective studies showed that young adults obtained an improved outcome when treated with paediatric protocols. The overall treatment intensity for patients with Down's syndrome had to be reduced after June, 2008, because of excess treatment-related mortality; from that time, patients with Down's syndrome were registered on the trial but did not undergo randomisation and were treated as clinical standard-risk patients, with adjustment of postinduction treatment according to response to induction therapy.

Patients were stratified according to initial clinical risk of relapse, on the basis of three metrics: the National Cancer Institute (NCI) risk criteria (NCI standard risk: patients younger than 10 years with a white blood cell count of less than 50×10^9 per L; NCI high risk: patients aged 10 years or older and those with a white blood cell count of at least 50×10^9 per L), leukaemia cytogenetics (all patients with a cytogenetic abnormality involving rearrangement of the *MLL* gene, hypodiploidy [<45 chromosomes], or intrachromosomal amplification of chromosome 21 were classified as clinical high risk), and early response to induction therapy as assessed by bone-marrow morphology on day 8 and 15 of treatment in patients younger than 16 years. Patients who had more than 25% of the marrow made up of blast cells at day 8 (NCI high risk) or 15 (NCI standard risk) were reclassified to the clinical high risk group irrespective of initial classification and were not eligible for MRD stratification and randomisation. NCI standard-risk patients had to have an early response of less than 25% marrow blasts at the day 15 assessment (reclassified as clinical standard risk) and NCI high-risk patients who had less than 25% marrow blasts at day 8 were reclassified as clinical intermediate risk to be eligible for randomisation. All patients who were 16 years or older were treated as clinical intermediate risk irrespective of day 8 or 15 bone-marrow response and were eligible for MRD stratification and randomisation.

We stratified clinical standard and intermediate risk groups by bone-marrow MRD at the end of induction and recovery from consolidation (before start of interim maintenance). Clinical high-risk patients were not eligible for MRD stratification. MRD was measured by a standardised real-time quantitative PCR method for immunoglobulin and T-cell receptor antigen gene rearrangements. The quantitative range of the assay was 10^{-4}, which was done within four laboratories in the UK that participated in a European quality-assurance scheme.[13,14] All MRD results were centrally reviewed. Patients with undetectable MRD after induction (day 29) and before interim maintenance were classified as MRD low risk, as were those with detectable (less than 0·01%) MRD at the end of induction but undetectable MRD before the start of interim maintenance. Those with at least 0·01% MRD at the end of induction were classified as MRD high risk. Patients in whom MRD could not be measured because no or poor-quality samples were available and those with persistent disease which was less than 0·01% MRD before the start of interim maintenance were classified as MRD indeterminate.

The protocol was approved by the Scottish Multi-Centre Research Ethics Committee. Patients were enrolled at individual treatment centres by principal investigators after written informed consent from carers or patients was obtained. The trial was monitored by an independent data monitoring committee, which reviewed safety and efficacy data annually.

Randomisation and masking

MRD low-risk patients were randomly assigned (1:1) to receive one (reduced treatment) or two (standard treatment) delayed intensifications and MRD high-risk patients were randomly assigned (1:1) to standard treatment or an intensive schedule. Treatment allocation in both groups was obtained by telephone call to the central trials unit, where computer randomisation was done, with stratification by MRD result and balancing for sex, age (<10 years *vs* ≥10 years) and white blood cell count at diagnosis ($<50\times10^9$ per L *vs* $\geq50\times10^9$ per L) by method of minimisation. Patients, clinicians, and data analysts were not masked to treatment allocation.

Procedures

Patients received one of three escalating-intensity treatment regimens depending on their clinical risk grouping (figure 1; full regimen details are provided in the appendix). NCI standard-risk patients received a three-drug induction of vincristine, steroids, and asparaginase for 4 weeks. NCI high-risk patients also received daunorubicin during induction. All patients received two doses of intrathecal methotrexate in induction, and those who had blasts in their cerebrospinal fluid at diagnosis received an additional two doses at day 15 and 21.

During consolidation, clinical standard-risk patients received daily oral mercaptopurine and four doses of weekly intrathecal methotrexate. Clinical intermediate-risk patients also had 4 weeks of cyclophosphamide and cytarabine (Berlin–Frankfurt–Munster [BFM] consolidation). Clinical high-risk patients received an additional four doses of vincristine and two doses of pegylated asparaginase during the BFM consolidation course.

Clinical standard-risk and intermediate-risk patients received the same interim maintenance courses for 8 weeks: daily oral mercaptopurine and weekly methotrexate with monthly vincristine and steroid pulses. Clinical high-risk patients received escalating doses of intravenous methotrexate without folinic acid rescue, and vincristine and pegylated asparaginase as interim maintenance.

Clinical standard-risk and intermediate-risk patients assigned to standard treatment received two delayed intensification courses separated by interim maintenance courses (figure 1), and those assigned to reduced treatment received only one delayed intensification course followed by continuing therapy. Clinical standard-risk and intermediate-risk patients received the same delayed intensification courses: one dose of pegylated asparaginase on day 4; vincristine, dexamethasone (alternate weeks), and doxorubicin for 3 weeks; and then 4 weeks of cyclophosphamide and cytarabine as during the BFM consolidation course. Clinical high-risk patients received the same course but with the addition of two doses of vincristine and one dose of pegylated asparaginase.

See Online for appendix

For continuing therapy, all patients received oral mercaptopurine and methotrexate, monthly vincristine and steroid pulses, and intrathecal methotrexate every 3 months. Male patients received treatment for 3 years and female patients for 2 years from the start of interim maintenance.

All patients received 6 mg/m² oral dexamethasone daily during induction and maintenance courses, with a maximum dose of 10 mg. We could not establish the proportion of patients in whom the dose was capped, because data were not obtained centrally. In delayed intensification courses, all patients received 10 mg/m² daily dexamethasone (without a cap) for 2 weeks on alternate weeks.

All patients received pegylated asparaginase (Oncosopar; Gaithersburg, MD, USA; Medac GmBH; 1000 units/m² per dose given intramuscularly) throughout treatment. Clinical standard-risk and intermediate-risk patients received four doses (two in induction and one in each delayed intensification course). Clinical high-risk patients received 12 doses (two in induction, two in each interim

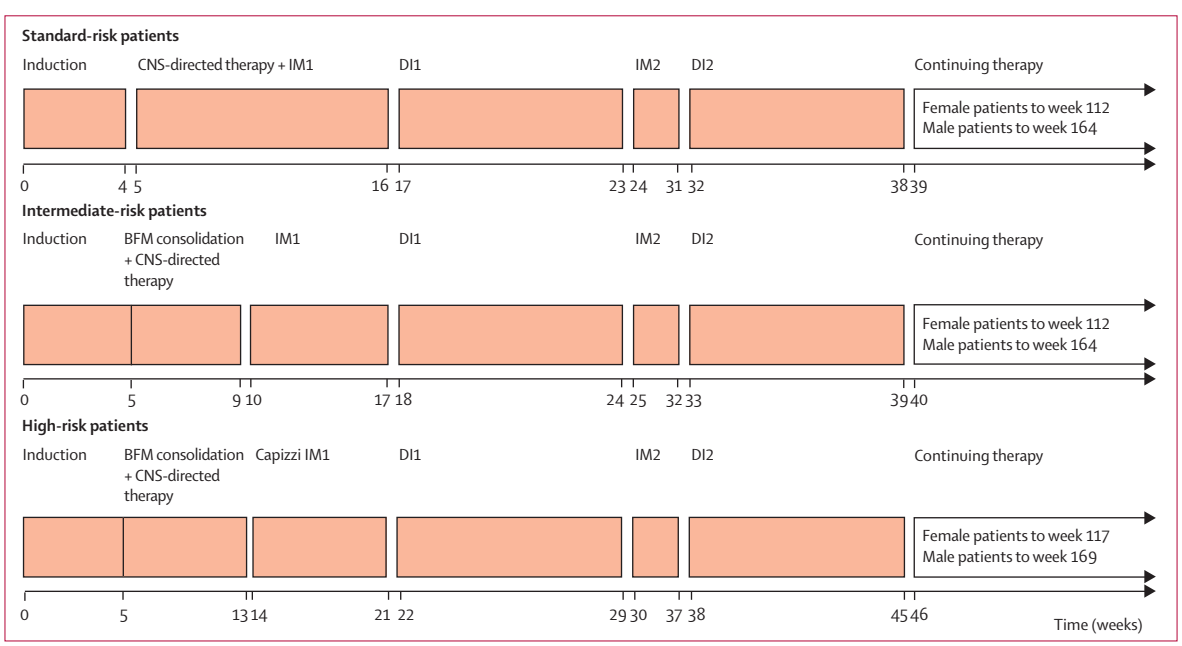

Figure 1: **Outline of treatment regimens for clinical risk groups defined by National Cancer Institute criteria, cytogenetics, and early response**
IM=interim maintenance. DI=delayed intensification. BFM=Berlin–Frankfurt–Munster. MRD=minimal residual disease. MRD low-risk patients assigned to one delayed intensification receive DI1 and then receive continuing therapy. MRD high-risk patients assigned to the intensive schedule transferred to clinical high-risk regimen after induction.

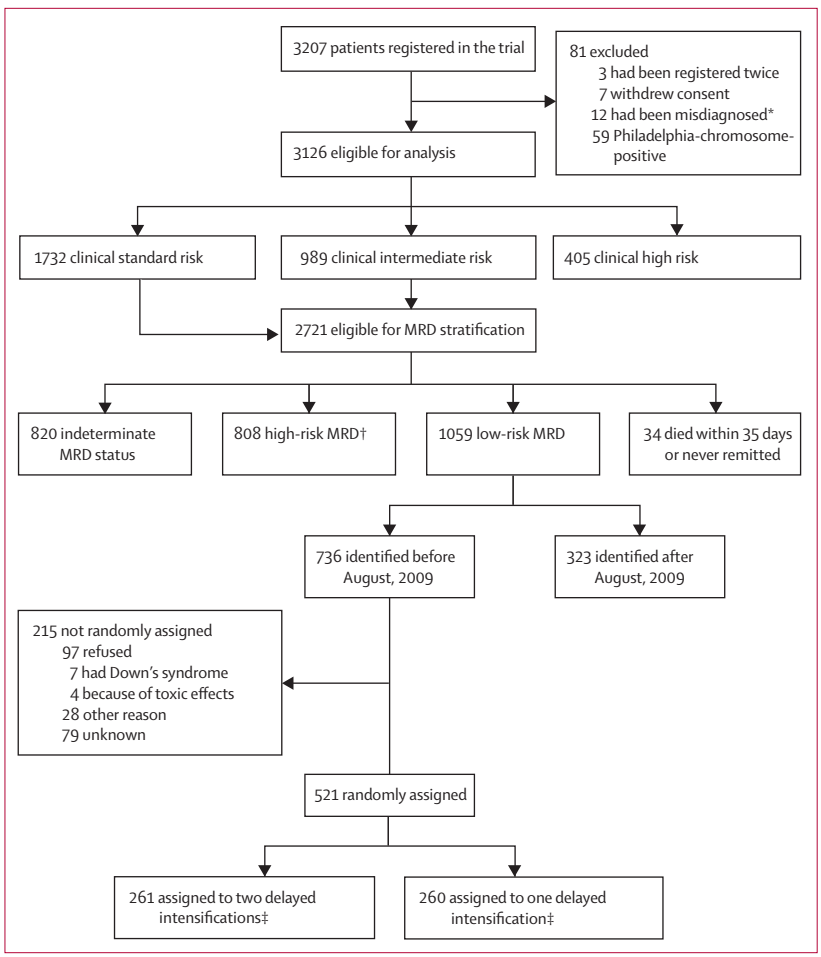

Figure 2: **Trial profile**
MRD=minimal residual disease. *One patient had Burkitt's lymphoma, one T-cell lymphoma, one T non-Hodgkin lymphoma, one mature B-cell acute lymphoblastic leukaemia, two acute myeloid leukaemia, five mixed-phenotype acute leukaemia, and one precursor B non-Hodgkin lymphoma. †Results not reported here; longer follow-up necessary. ‡No patients lost to follow-up before 1 year or excluded from analysis.

maintenance course, and three in each delayed intensification course).

Patients with five leucocytes per μL or more and blasts in a diagnostic sample of cerebrospinal fluid with fewer than ten red blood cells per μL received an extra two doses of intrathecal methotrexate in induction and 24 Gy cranial radiotherapy during consolidation until August, 2009, after which point they received only the additional doses of intrathecal methotrexate during induction. Patients with traumatic lumbar puncture and blasts in the cerebrospinal fluid, and those with fewer than five blasts per μL also received an extra two doses of intrathecal methotrexate during induction. Clinical high-risk patients received Capizzi intravenous methotrexate at doses of less than 500 mg/m² without folinic acid rescue during interim maintenance.

Patients whose bone marrow consisted of more than 25% blasts at day 29 of induction, or those with a high-risk karyotype whose bone marrow consisted of more than 5% blasts at that timepoint were eligible for allogeneic haemopoietic stem-cell transplantation in the first complete remission. Additionally, patients with an intrachromosomal amplification of chromosome 21 and a morphological slow early response at day 8 or 15, or MRD high-risk status at day 29 were eligible for allogeneic transplant in first complete remission.

Statistical analysis

We anticipated that total accrual to the trial in a 6-year period would be 2500 patients, of whom we expected about 400 to be eligible for the randomisation of the MRD low-risk group. The primary outcome measure was event-free survival (EFS). EFS was defined as time to relapse, secondary tumour, or death. The secondary outcome measures were cumulative risk of relapse, treatment-related toxic effects, and overall survival. In view of the few relapses expected in this group, and with a one-sided p value, we would have 80% power to detect a reduction in 5-year EFS in the group given one delayed intensification course from 95% to 88%. The chosen size of difference was pragmatic and was based on probable accrual to the trial and randomisation refusals.

However, the proportion of patients in the low-risk group was higher than had been originally anticipated and, because of a shortfall in recruitment to the high-risk group, the trial was kept open after its original closing date of Oct 31, 2009. Therefore, the data monitoring committee recommended an increase in sample size in the low-risk group to narrow the confidence intervals of the differences in outcome between groups. Randomisation of MRD low-risk patients ended on Aug 24, 2009, and randomisation of MRD high-risk patients on June 30, 2011, after the target number of patients had been recruited.

We compared categorical variables with standard χ^2 tests. We examined the relation between sex, age, white blood cell count, and immunophenotype, and between those variables and MRD risk group with logistic regression. For time-to-event outcomes, we produced Kaplan-Meier curves and compared them with the log-rank method. We counted only first events, censoring at competing events—eg, time to bone-marrow relapse included censoring at non-bone marrow relapse or death in remission for patients with these events as their first. Patients who died within 35 days of starting treatment or who never achieved remission, or both, were deemed to be induction failures. They were included in analyses of EFS and overall survival, but excluded from analyses of relapse or remission death.

We calculated hazard ratios and 95% CIs as $\exp[(O-E)/V +/- 1{\cdot}96/\sqrt{V}]$, in which O=observed events, E=expected events, and V=variance.[15] We calculated a CI for the difference in 5-year EFS for the MRD low-risk group on the basis of the fact that the odds ratio can be estimated by the logarithm of the survival in the reduced-treatment group divided by the logarithm of the survival in the standard group. We used Cox

regression multivariate analyses to test whether effects of prognostic factors were independent, with additional interaction tests and tests of proportional hazards using an interaction with time variable for significant factors. All analyses were by intention to treat and p values two-sided. We did statistical analyses in SAS (version 9.2) or in-house programs. We created all figures with R (version 2.15.1).

The chief investigator (AV) did a detailed review of individual treatment-related deaths to attribute causal association with phase of treatment. The analyses of treatment-related deaths are based on this detailed review, whereas numbers used for the survival analyses are not to allow comparison with previous trials.

This trial is registered, number ISRCTN07355119.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Of 3207 patients registered in the trial (figure 2), 59 were Philadelphia chromosome positive: 52 were transferred to EsPhALL and seven to UKALL XII. Initial stratification resulted in 1816 NCI standard-risk and 1310 NCI high-risk patients. On the basis of cytogenetics and early bone-marrow response, 1732 patients were reclassified as clinical standard risk, 989 clinical intermediate risk, and 405 clinical high risk (figure 2). All eligible trial patients, with the exception of those who died within 35 days or never achieved remission (n=34), were tested for MRD status after induction and before first interim maintenance, but clinical high-risk patients were not eligible for MRD stratification and randomisation. MRD status was low risk in 1090 (35%) of 3092 patients tested for MRD status, high risk in 1030 (33%), and indeterminate risk in 972 (31%). A further seven patients who failed induction treatment were also recorded as MRD high risk.

The proportion of patients who could not be classified on the basis of MRD (indeterminate group) decreased with time because of improvements in sample quality (599 [38%] of 1591 in 2003–07; 373 [25%] of 1501 in

	Trial overall (n=3126)	MRD low risk		Eligible but not randomised (n=215)	Underwent MRD low-risk randomisation			p value*
		Total (n=1059)	Eligible for randomisation (n=736)		One delayed intensification (n=260)	Two delayed intensifications (n=261)	Total (n=521)	
Sex								
Male	1776 (57%)	593 (56%)	415 (56%)	115 (53%)	142 (55%)	158 (61%)	300 (58%)	0·31
Female	1350 (43%)	466 (44%)	321 (44%)	100 (47%)	118 (45%)	103 (39%)	221 (42%)	..
Age (years)								
Median (IQR)	5 (3–10)	4 (3–8)	4 (3–8)	5 (3–9)	4 (3–8)	4 (3–8)	4 (3–8)	0·79
<2	210 (7%)	62 (6%)	42 (6%)	13 (6%)	13 (5%)	16 (6%)	29 (6%)	0·61†
2–9	2077 (66%)	764 (72%)	534 (73%)	153 (71%)	192 (74%)	189 (72%)	381 (73%)	..
10–15	610 (20%)	179 (17%)	127 (17%)	36 (17%)	46 (18%)	45 (17%)	91 (17%)	..
≥16	229 (7%)	54 (5%)	33 (4%)	13 (6%)	9 (3%)	11 (4%)	20 (4%)	..
Immunophenotype								
B lineage	2733 (87%)	978 (92%)	680 (92%)	194 (90%)	241 (93%)	245 (94%)	486 (93%)	0·16
T lineage	386 (12%)	81 (8%)	56 (8%)	21 (10%)	19 (7%)	16 (6%)	35 (7%)	..
Not known	7 (<1%)	0	0	0	0	0	0	..
National Cancer Institute risk group								
High‡	1310 (42%)	386 (37%)	263 (36%)	84 (39%)	85 (33%)	94 (36%)	179 (34%)	0·23
Standard§	1816 (58%)	673 (64%)	473 (64%)	131 (61%)	175 (67%)	167 (64%)	342 (66%)	..
White blood cell count (×10^9 per L)								
Median (IQR)	12 (5–40)	11 (5–34)	11 (5–31)	12 (5–36)	10 (4–30)	9 (5–28)	10 (5–28)	0·19
<10	1407 (45%)	494 (47%)	360 (49%)	99 (46%)	127 (49%)	134 (51%)	261 (50%)	0·56¶
10–19	502 (16%)	177 (17%)	128 (17%)	38 (18%)	44 (17%)	46 (18%)	90 (17%)	..
20–49	526 (17%)	184 (17%)	113 (15%)	32 (15%)	45 (17%)	36 (14%)	81 (16%)	..
50–99	315 (10%)	119 (11%)	75 (10%)	28 (13%)	24 (9%)	23 (9%)	47 (9%)	..
≥100	376 (12%)	85 (8%)	60 (8%)	18 (8%)	20 (8%)	22 (8%)	42 (8%)	..

Data are n (%), unless otherwise stated. *Comparing eligible MRD low risk who were and were not randomised. †p for trend (age groups as ordered categories)=0·51. ‡Patients in this group who were MRD low risk were clinical intermediate risk. §Patients in this group who were MRD low risk were clinical standard risk. ¶p for trend=0·13.

Table 1: **Baseline characteristics in the trial overall**

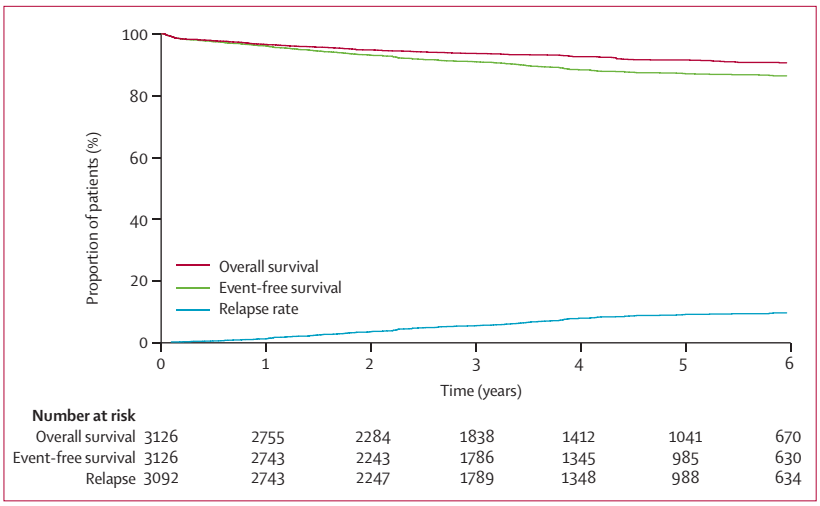

Figure 3: **Event-free survival, relapse, and overall survival in the trial overall**

	Number of events	Actuarial percentage at 5 years (95% CI)
Induction failure	34	1·1% (0·7–1·5)
Isolated CNS relapse	44	1·9% (1·3–2·5)
Any CNS relapse	69	3·0% (2·2–3·8)
Non-CNS relapse	123	5·9% (4·7–7·1)
Any bone marrow relapse	140	6·6% (5·4–7·8)
Non-bone marrow relapse	52	2·3% (1·7–2·9)
Relapse	192	8·8% (7·6–10·0)
Secondary tumour	15	0·6% (0·2–1·0)
Death in remission*	77	2·7% (2·1–3·3)
Any event	318	87·2% (85·8–88·6)†
Death	224	91·5% (90·3–92·7)†

With censoring at competing events. *Excludes patients who died after development of a secondary tumour. †Event-free percentage.

Table 2: **Kaplan-Meier estimates for specific events at 5 years**

2008–11). The proportion of patients with an informative MRD result who were MRD low risk or high risk varied by age, white blood cell count, and immunophenotype (data not shown).

Of 736 eligible MRD low-risk patients, 521 underwent randomisation (figure 2). We recorded no difference in the characteristics of MRD low-risk patients who did and did not undergo randomisation (table 1). Follow-up continued to Oct 31, 2011, with a median follow-up of 46 months (IQR 25–70) for the trial overall and 57 months (42–72) for patients who underwent low-risk randomisation, because this randomisation ceased 2 years before the high-risk randomisation. The results of the high-risk randomisation will be reported elsewhere once there has been sufficient time for follow-up.

Of the 3126 patients who were eligible for analyses in the trial overall, a small proportion experienced any event or died in the first 6 years of follow-up. 5-year EFS was 87·2% (95% CI 85·8–88·6) and 5-year overall survival was 91·5% (95% CI 90·3–92·7). The 5-year cumulative risk of relapse was 8·8% (95% CI 7·6–10·0; figure 3, table 2). The risk of bone-marrow relapse was higher than for non-bone-marrow relapse, any CNS relapse, and isolated CNS relapse (table 2). The risk of isolated CNS relapse was 1·8% (95% CI 1·2–2·4) for patients with B-lineage ALL and 3·2% (1·2–5·2) for those with T-lineage ALL. The only subgroup with a fairly high risk of isolated CNS relapse was patients with T-lineage ALL and a white blood cell count of greater than 200×10^9 per L (12·1%, 95% CI 0·5–23·7), but only four CNS events occurred in 55 such patients. Secondary tumours occurred in 16 patients (five had acute myeloid leukaemia [one post-relapse], one myelodysplasia, two second ALL, one T-cell lymphoma, one neuroblastoma, two histiocytic sarcoma, one Epstein–Barr virus lymphoma, one Ewing's sarcoma, one lymphoblastic lymphoma, and one low-grade glioma), of whom eight died. Of the 47 patients who received an allogeneic haemopoietic stem-cell transplantation, 30 (64%) were alive and relapse free as of Oct 31, 2011.

Analysis of outcome by leukaemia cytogenetics is in progress and will be reported separately. Of other prognostic factors, MRD risk status was the single most important determinant of outcome (appendix), with a 5-year cumulative relapse rate of 4·0% (95% CI 2·4–5.6) in MRD low-risk patients versus 15·0% (12·3–17·7) in high-risk patients (log-rank p<0·0001). Older age, high white blood cell count, and T-cell immunophenotype were significantly associated with MRD high-risk status (data not shown). With exclusion of MRD indeterminate patients, 106 (81%) of 131 relapses occurred within the MRD high-risk group. Multivariate Cox analyses showed that age, white blood cell count, and MRD risk group were independently associated with relapse-free survival (table 3, appendix). In Cox analyses, the effects of age ($p_{interaction}$=0·01) and white blood cell count ($p_{interaction}$=0·001), but not MRD ($p_{interaction}$=0·09), varied significantly during follow-up. With a restriction to 2 years, MRD (HR 5·82, 95% CI 2·62–12·91; p<0·0001), age (1·13, 1·08–1·18; p<0·0001), and the logarithm of white blood cell count (1·45, 1·24–1·70; p<0·0001) all affected relapse-free survival. After 2 years, only MRD was significant (3·36, 1·97–5·73; p<0·0001), although more follow-up is needed.

We recorded no difference in EFS or relapse risk between MRD low-risk patients whose MRD had become undetectable at day 29 and those with less than 0·01% MRD at day 29 but became undetectable by week 11. Additionally, we noted no difference between patients with undetectable MRD and those with less than 0·005% MRD at day 29.

We noted an interaction between MRD risk status and NCI risk for EFS (p=0·04). Within the MRD high-risk group, 5-year EFS was lower in NCI high-risk patients (72·8%, 95% CI 67·9–77·7) than in NCI standard-risk patients (85·8%, 82·1–89·5; p<0·0001; appendix).

On the basis of review by the chief investigator, 17 deaths were classified as having been caused by

	Univariate log rank*		Univariate Cox regression*		Multivariate (Cox regression)†	
	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
Sex (female *vs* male)	0·65 (0·49–0·86)	0·003	0·64 (0·47–0·86)	0·003	0·78 (0·54–1·13)	0·18
Age‡	1·84 (1·48–2·30)	<0·0001	1·09 (1·06–1·11)	<0·0001	1·10 (1·05–1·15)	<0·0001
White blood cell count§	1·36 (1·22–1·50)	<0·0001	1·32 (1·20–1·45)	<0·0001	1·35 (1·17–1·56)	<0·0001
MRD risk (high *vs* low)	3·83 (2·72–5·39)	<0·0001	4·69 (3·04–7·26)	<0·0001	4·02 (2·59–6·25)	<0·0001
NCI risk group (high *vs* standard)	2·06 (1·54–2·75)	<0·0001	2·01 (1·51–2·68)	<0·0001	0·83 (0·49–1·40)	0·48
Immunophenotype (T *vs* B)	2·47 (1·58–3·84)	0·0002	2·01 (1·42– 2·85)	<0·0001	0·61 (0·34–1·02)	0·06

MRD=minimal residual disease. NCI=National Cancer Institute. *Univariate analysis includes all available patients except MRD indeterminate patients in analyses of MRD risk. †Multivariate analysis presents a final model that includes MRD risk group, and is therefore based on a reduced number of patients. ‡Age as a continuous variable in Cox analyses, with groups of <2 years, 2–9 years, 10–15 years, and 16 years or older. §Logarithm of white blood cell count as a continuous variable in Cox analyses, with groups of $<10\times10^9$ per L, $10–19\times10^9$ per L, $20–49\times10^9$ per L , $50–99\times10^9$ per L, $\geq100\times10^9$ per L.

Table 3: **Prognostic factors for relapse-free survival in the trial overall**

induction therapy despite having occurred after day 35, because the onset of the causative event was before that timepoint. Most treatment-related deaths were due to infection (table 4). 34 (2%) of 1578 patients who received four drugs during induction (clinical intermediate or high risk) died compared with 12 (1%) of 1548 patients who received three drugs (clinical standard risk; p=0·001). The number of deaths in remission did not differ by clinical risk group (21 [1%] of 1536 standard-risk patients, 19 [2%] of 885 intermediate-risk patients, and 11 [1%] of 659 high-risk patients; p=0·35).

Clinical high-risk patients experienced more toxic effects that were attributable to asparaginase (hypersensitivity and pancreatitis) as a result of higher cumulative doses of asparaginase than did standard-risk and intermediate-risk patients (table 5, appendix). Encephalopathy was more frequent in patients aged at least 10 years (116 [14%] of 839) than in those younger than 10 years (129 [6%] of 2287; p<0·0001), as was osteonecrosis (100 [12%] *vs* 15 [1%]; p<0·0001), infection (168 [20%] *vs* 322 [14%]; p<0·0001), any thrombosis (41 [5%] *vs* 44 [2%]; p<0·0001), CNS thrombosis (28 [3%] *vs* 22 [1%]; p<0·0001), and mucositis (26 [3%] *vs* 15 [1%]; p<0·0001).

In the population of MRD low-risk patients who underwent randomisation, we recorded no difference in EFS, overall survival, or relapse risk between standard or reduced treatment groups (figure 4, table 6). 5-year EFS was 94·4% (95% CI 91·1–97·7) with one course of delayed treatment and 95·5% (92·8–98·2) with two courses. The difference in 5-year EFS was 1·1% (95% CI –5·6 to 2·5), which means the primary endpoint of the randomisation (to rule out a 7% reduction in EFS) was achieved. 5-year overall survival in the group given one delayed intensification (97·9%, 95% CI 95·7–100·0) and that given two delayed intensifications (98·5%, 96·9–100·0) did not differ significantly (OR 0·67, 95% CI 0·19–2·30; p=0·53). In the group given standard treatment, six of 261 patients relapsed (two isolated marrow, one isolated CNS, two combined marrow and CNS, and one combined marrow and skin), two had secondary tumours (one acute myeloid leukaemia and one lymphoblastic lymphoma), and three died in remission (one because of respiratory syncytial virus pneumonitis during maintenance treatment [patient with Down's syndrome], one veno-occlusive disease and herpes simplex virus pneumonitis with pulmonary haemorrhage in the second course of delayed intensification, and one Gram-negative sepsis in the first course of delayed intensification; table 6). In the reduced-treatment group, 11 of 260 patients relapsed (three isolated marrow, four isolated CNS, two combined marrow and CNS, one testes, and one isolated cervical lymph node). No patients in the reduced-treatment group died in remission. The numbers of deaths in remission, serious adverse events, and Common Terminology

	Induction (n=3126)	Remission (n=3080)	
		On protocol	Off protocol
Total	46 (1%)	51 (2%)	17 (<1%)
Infection	35 (1%)	39 (1%)	..
Bacterial infection	19 (1%)	22 (1%)	..
Fungal infection	9 (<1%)	6 (<1%)	..
Viral infection	2 (<1%)	7 (<1%)	..
Unknown infection	5 (<1%)	4 (<1%)	..
CNS thrombosis	1 (<1%)	1 (<1%)	..
Encephalopathy	1 (<1%)	2 (<1%)	..
Colitis	4 (<1%)	0	..
Steroid toxicity	2 (<1%)	1 (<1%)	..
Pancreatitis	0	1 (<1%)	..
SIADH	0	1 (<1%)	..
Other	3 (<1%)	5 (<1%)	..
After stem-cell transplantation	..	..	10 (<1%)
Secondary malignancy	..	..	5 (<1%)*
Unknown	..	1 (<1%)	2 (<1%)

SIADH=syndrome of inappropriate antidiuretic hormone secretion. *Two myelodysplasia, one T non-Hodgkin lymphoma, one glioblastoma multiforme, and one neuroblastoma.

Table 4: **Treatment-related deaths**

	Total (n=3126)	Clinical standard risk (n=1548)	Clinical intermediate risk (n=909)	Clinical high risk (n=669)	p value for standard risk *vs* intermediate risk	p value for standard/intermediate risk *vs* high risk
Any serious adverse event	1101 (35%)	369 (24%)	434 (48%)	298 (45%)	<0·0001	<0·0001
Any infection	490 (16%)	191 (12%)	192 (21%)	107 (16%)	<0·0001	0·80
Fungal infection	110 (4%)	35 (2%)	51 (6%)	24 (3%)	<0·0001	0·91
Seizure	135 (4%)	38 (2%)	46 (5%)	51 (8%)	0·001	<0·0001
Other encephalopathy	110 (4%)	21 (1%)	64 (7%)	25 (4%)	<0·0001	0·73
Asparaginase hypersensitivity	54 (2%)	3 (<1%)	8 (1%)	43 (6%)	0·11	<0·0001
Pancreatitis	50 (2%)	10 (1%)	18 (2%)	22 (3%)	0·003	<0·0001
Avascular necrosis	115 (4%)	8 (1%)	80 (9%)	27 (4%)	<0·0001	0·58
Any thrombosis	85 (3%)	27 (2%)	37 (4%)	21 (3%)	0·0005	0·45
CNS thrombosis	50 (2%)	17 (1%)	22 (2%)	11 (2%)	0·01	0·92
Colitis	47 (2%)	22 (1%)	17 (2%)	8 (1%)	0·39	0·46
Vincristine neurotoxicity	65 (2%)	26 (2%)	22 (2%)	17 (3%)	0·20	0·35
SIADH	11 (<1%)	3 (<1%)	4 (<1%)	4 (1%)	0·227	0·23
Mucositis	41 (1%)	6 (<1%)	8 (1%)	27 (4%)	0·12	<0·0001
Other serious adverse event	280 (9%)	82 (5%)	123 (14%)	75 (11%)	<0·0001	0·02

Some patients had more than one type of event. SIADH=syndrome of inappropriate antidiuretic hormone secretion.

Table 5: **Number of specific toxic effects by clinical risk groups**

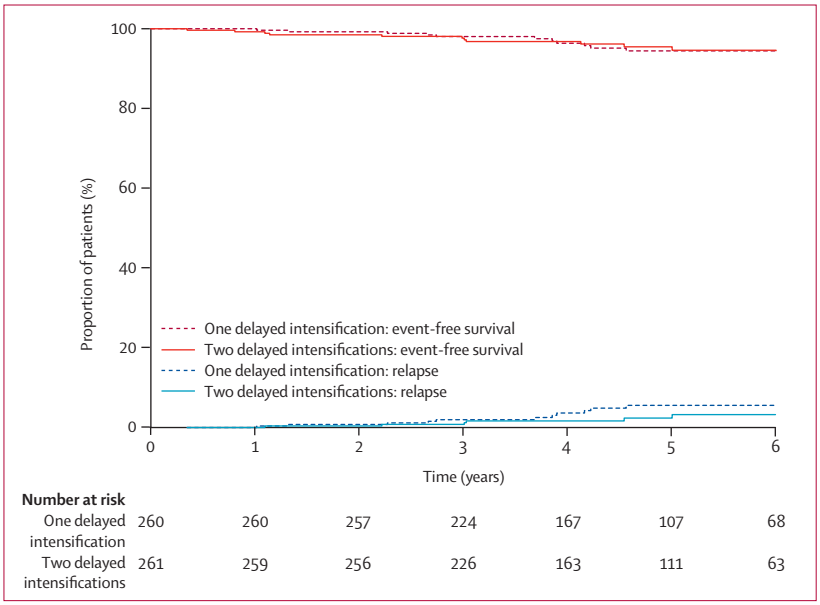

Figure 4: **Event-free survival and relapse in MRD low-risk patients**
MRD=minimal residual disease.

Criteria for Adverse Events grade 3 or 4 toxic effects in patients given reduced treatment and those given standard treatment did not differ significantly (table 7). However, the second delayed intensification course was associated with one (<1%) treatment-related death and 74 episodes of grade 3 or 4 toxic effects in 45 patients (17%) given standard treatment, of whom 21 had at least one grade 3 or 4 infection.

347 MRD low-risk patients were registered after closure of the low-risk randomisation in August, 2009 (figure 2). They received one course of delayed intensification. The outcome for these patients is included in that reported for the overall MRD low-risk group (appendix), because their follow-up is too short to be analysed separately.

Discussion

The results of our trial show that a reduction of post-remission treatment is feasible for children and young adults with ALL predicted to have a low risk of relapse on the basis of rapid clearance of MRD by the end of induction therapy. We have reported a 5-year EFS in the trial overall that is comparable with the benchmark of 85·6% established in a study of 498 patients.[8] A reduction in relapse risk in this study has resulted in a 7·2% improvement in 5-year EFS compared with our previous trial (UKALL 99),[1] in which only patients aged 18 years or younger were recruited. Combined with a significant reduction in treatment-related mortality, the improved EFS resulted in a 4% improvement in 5-year overall survival to 92·3% for that age group compared with UKALL 99.[16] Although the improvement was recorded in all risk groups, higher-risk patients benefited the most, with a 12% improvement in 5-year EFS for NCI high-risk patients and an 11·5% improvement in patients with T-lineage ALL,[16] leading to a significant increase in overall survival for these groups compared with UKALL 99.[1] The low frequency of isolated and any CNS relapse within 5 years is reassuring, and was equivalent to that reported in studies[2,3] in which a significantly higher proportion of patients received cranial irradiation than in our trial. Restricted use of cranial radiotherapy combined with a small proportion of patients who received an allogeneic haemopoietic stem-cell transplantation relative to other trials and the absence of etoposide from our treatment

	One delayed intensification (n=260)		Two delayed intensifications (n=261)		Unadjusted analyses		Adjusted analyses*	
	Number of events	Actuarial percentage at 5 years (95% CI)	Number of events	Actuarial percentage at 5 years (95% CI)	Unadjusted odds ratio for group given two delayed intensifications (95% CI)	Two-sided p value	Adjusted odds ratio for group given two delayed intensifications (95% CI)	Two-sided p value
Any event†	11	5·6% (2·3–8·9)	11	4·5% (1·8–7·2)	1·00 (0·43–2·31)	0·99	1·09 (0·47–2·53)	0·84
Relapse‡	11	5·6% (2·3–8·9)	6	2·4% (0·2–4·6)	0·55 (0·21–1·43)	0·23	0·60 (0·23–1·57)	0·30
Remission death	0	0%	3	1·2% (0–2·6)	7·40 (0·77–71·04)	0·08	8·39 (0·86–81·61)	0·06
Any death	6	2·1% (0–4·3)	4	1·5% (0–3·1)	0·67 (0·19–2·30)	0·53	0·71 (0·21–2·48)	0·61

MRD=minimal residual disease. *Adjusted for variables upon which randomisation was balanced: age (<10 years *vs* ≥10 years), sex (males *vs* female), white blood cell count (<50×10^9 per L *vs* ≥50×10^9 per L). †Includes two secondary tumours. ‡Includes relapse in patient who was incorrectly reported as low risk (allocated to receive two delayed intensifications).

Table 6: **Events in MRD low-risk patients who underwent randomisation**

regimens should hopefully reduce the risk of treatment-related cancers.[17,18]

The overall outcomes reported here and in other recent trials[19,20] have been obtained even though no new drugs for treatment of ALL have been introduced in the past 30 years; targeted drugs, such as monoclonal antibodies and protein kinase inhibitors, were not available for testing when our trial opened. Without a randomised or case-matched comparison, we cannot be certain of the reasons for the improvement in outcome. The randomised interventions in the trial are unlikely to provide the explanation, because less than half the patients underwent randomisation. The use of dexamethasone and pegylated asparaginase throughout treatment was probably an important contributor. Several large randomised clinical trials have shown that dexamethasone has a better efficacy in prevention of systemic and CNS relapse than does prednisolone.[21–23] Pegylated asparaginase has better pharmacokinetic[24,25] and pharmacodynamic properties,[26] and a lower risk of hypersensitivity reactions on re-exposure[27] than does the native formulation.

The non-relapse mortality in induction and in remission is conspicuous when considered in the context of low relapse risk. Deaths caused by toxic effects amount to half the deaths reported in our trial so far, although the proportion will diminish with longer follow-up as more patients relapse. Dexamethasone is more toxic than is prednisolone and is probably an important contributor to the risk of serious bacterial and fungal infection. In a recently concluded European study, AIEOP-BFM 2000,[23] twice as many patients in the group given dexamethasone died during induction than in the group given prednisolone; other studies[28,29] have had similar results. Additionally, dexamethasone might be associated with a higher risk of osteonecrosis than is prednisolone,[29] but that has not been a universal experience.[22,30] Dexamethasone affects quality of life more than prednisolone does,[31] although the effect does not persist in the long term.[32] Dose, scheduling, and interaction with anthracyclines are important determinants of the risk of steroid-associated toxic effects, and we are testing novel schedules of dexamethasone in our next trial in an attempt to reduce the toxic effects while retaining the efficacy of this drug.

	One delayed intensification (n=260)	Two delayed intensifications (n=261)	Relative risk for group given two delayed intensifications (95% CI)	Two-sided p value
Grade 3–4 toxic effect*	189 (73%)	200 (77%)	1·05 (0·95–1·16)	0·30
Serious adverse event	70 (27%)	82 (31%)	1·17 (0·89–1·53)	0·26
Cumulative toxicity†	195 (75%)	204 (78%)	1·04 (0·95–1·15)	0·39

MRD=minimal residual disease. *Measured with Common Terminology Criteria for Adverse Events. †Defined as remission death, grade 3–4 toxic effect, or serious adverse event.

Table 7: **Toxic effects in MRD low-risk patients who underwent randomisation**

Toxic effects attributable to pegylated asparaginase were similar to or lower than that reported with the native formulation. Most hypersensitivity reactions occurred in high-risk patients when re-exposed to the drug during consolidation or first interim maintenance course. Studies of native *Escherichia coli* asparaginase[26,33] have reported a frequency of 20–40% of hypersensitivity reactions associated with asparaginase intensification courses.

In view of these toxic effects, we were pleased to note that treatment reduction is feasible in a substantial subgroup of patients with a low risk of relapse (panel). MRD stratification identified 40–50% of patients (depending on age) who—irrespective of conventional risk factors—have a chance of surviving to 5 years relapse free of about 95%. We have shown that these patients do not require a second intensification course to achieve this outcome, thus avoiding exposure to acute toxic effects. Whether they also have decreased risk of late cardiac toxic effects and secondary cancers due to reduced exposure to anthracyclines and alkylating agents (appendix) will become apparent only after longer follow-up.

After UKALL 2003 opened, two US trials[34,35] also reported no benefit of a second intensification course for NCI standard-risk and high-risk patients. However, treatment was not stratified by MRD in either trial and the overall

Panel: Research in context

Systematic review

We did not do a formal systematic review when planning this trial. The need for the trial and the questions to be answered were determined by a combination of non-systematic literature review, discussions in the national childhood and adult leukaemia clinical study groups and clinician networks, and consultation with experts from the US Children's Oncology Group and European childhood leukaemia study groups (eg, French Acute Lymphoblastic Leukaemia Group, Nordic Society of Paediatric Haematology and Oncology, Dutch Childhood Oncology Group, Associazione Italiana Ematologia Oncologia, and Pediatrica-Berlin-Franklin-Munster). During planning, the evidence base indicated that on-treatment monitoring and detection of submicroscopic levels of leukaemia (minimal residual disease [MRD]) was the best predictor of relapse risk in children with acute lymphoblastic leukaemia (ALL), but whether treatment could be modified on the basis of MRD response was not known. We aimed to establish whether treatment for childhood ALL could be stratified by risk of relapse predicted by MRD response.

Interpretation

We have reported an improved outcome for children and young adults with ALL overall and have shown that post-remission therapy can be reduced for a subgroup of patients with rapid clearance of MRD during induction therapy without compromising the cure frequency. MRD monitoring should allow clinicians to select patients who have a chance of being cured and might benefit from treatment de-escalation to reduce their exposure to the side-effects of intensive therapy.

intensity of treatment differs significantly from our trial. The conclusion of the US trials[34,35] was that intensified interim maintenance with one delayed intensification course was the optimum therapy for NCI standard-risk and high-risk patients with a rapid morphological early response. Our trial has extended the previous findings by establishing that molecular MRD monitoring identifies a large group of patients with a rapid morphological early response who do not require a second delayed intensification course or intensified interim maintenance treatment to achieve a high chance of event-free survival to 5 years. Additionally, a small proportion of patients can be identified as low risk by karyotype and MRD response by the Children's Oncology Group criteria; the remaining subgroups can receive more intensive interim maintenance and delayed intensification therapy than was used in our protocol. An international trial, AIEOP-BFM 2000,[7,14] has also tested treatment reduction and intensification interventions for MRD high-risk and standard-risk groups, but the results are yet to be reported.

We note three main limitations of our study: an informative MRD result was not available for a third of patients enrolled; median follow-up of MRD low-risk patients was fairly short; and the reduction in treatment achieved by omitting the second delayed intensification is fairly modest. We are reasonably confident that the EFS for MRD low-risk patients will remain stable during extended follow-up, because no late relapses in the MRD low-risk group have been reported in the BFM 90 study[6] or our retrospective study of ALL (unpublished). Improvements in the quality of samples and ability to find MRD markers have meant that an informative MRD result is available for 92% of patients in our successor trial UKALL 2011 (ISRCTN64515327), which opened in April, 2012, and is testing ways to further reduce risk of treatment-related toxic effects. In future, new drugs[36,37] designed to target leukaemia-specific receptors and proteins could replace elements of conventional chemotherapy regimens that are the cause of some of the major toxic effects, thereby reducing toxicity while retaining overall treatment efficacy. Finally, translation of advances in understanding of the molecular biology of ALL and its effect on phenotype and clinical outcome[38–40] will help to define specific subgroups that might benefit from such an approach.

Contributors

AV, NG, CM, and SR designed the trial. AV was the trial's chief investigator and wrote the first draft of the report. NG was the clinical leader and JH was the laboratory lead for the laboratory network. NG, CM, RH, and CR collected data, analysed data, helped to address queries from local investigators, dealt with treatment difficulties, and contributed to the writing of the report. RW and SR collected and analysed data and contributed to the writing of the report.

Conflicts of interest

We declare that we have no conflicts of interest.

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