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Efficacy and toxicity of a paediatric protocol in teenagers and young adults with Philadelphia chromosome negative acute lymphoblastic leukaemia: results from UKALL 2003

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Summary

Despite the substantial outcome improvements achieved in paediatric acute lymphoblastic leukaemia (ALL), survival in teenage and young adult (TYA) patients has remained inferior. We report the treatment outcomes and toxicity profiles observed in TYA patients treated on the UK paediatric ALL trial, UKALL2003. UKALL2003 was a multi-centre, prospective, randomized phase III trial, investigating treatment intensification or de-escalation according to minimal residual disease (MRD) kinetics at the end of induction. Of 3126 patients recruited to UKALL2003, 229 (7·3%) were aged 16–24 years. These patients were significantly more likely to have high risk MRD compared to 10–15 year olds (47·9% vs. 36·6%, $P = 0{\cdot}004$). Nonetheless, 5-year event-free survival for the TYA cohort (aged 16–24 years) was 72·3% [95% confidence interval (CI): 66·2–78·4] overall and 92·6% (95% CI: 85·5–99·7) for MRD low risk patients. The risk of serious adverse events was higher in patients aged ≥10 years compared to those aged 9 or younger ($P < 0{\cdot}0001$) and novel age-specific patterns of treatment-related toxicity were observed. TYA patients obtain excellent outcomes with a risk- and response-adapted paediatric chemotherapy protocol. Whilst those aged 10 years and older have excess toxicity compared with younger patients, the age association is specific to individual toxicities.

Keywords: acute lymphoblastic leukaemia, chemotherapy, efficacy, toxicity, teenage and young adult.

Survival rates in paediatric acute lymphoblastic leukaemia (ALL) have improved significantly over time, such that excellent sustained complete remission (CR) rates of around 90% are reproducibly achieved (Pui *et al*, 2012). However, outcomes in teenage and young adult (TYA) patients aged 16–24 years have remained inferior, as a consequence of multiple factors, including resistant leukaemia biology (Roberts *et al*, 2012), increased susceptibility to therapy-related toxicity, poorer recruitment to clinical trials (Fern *et al*, 2008) and poorer compliance (Kondryn *et al*, 2011).

Over the last decade, it has become apparent that TYA patients have improved survival outcomes when treated on paediatric chemotherapy-based protocols rather than transplant-focused adult protocols. Ramanujachar *et al* (2007) showed that 15–17 year olds treated on the UK Medical Research Council (MRC) ALL97/99 paediatric protocol had a 16% higher event-free survival (EFS) at 5 years compared those treated on the contemporary adult protocol, UKALL-XII/E2993 [65%; 95% confidence interval (CI): (52–78) vs. 49% (37–61) respectively]. Retrospective analyses from other international groups also demonstrated superiority of paediatric-inspired ALL protocols in TYA patients (Boissel *et al*, 2003; de Bont *et al*, 2004; Hallbook *et al*, 2006; Lopez-Hernandez *et al*, 2008; Ribera *et al*, 2008; Stock *et al*, 2008; Usvasalo *et al*, 2008; Huguet *et al*, 2009)' with higher CR rates, higher EFS, lower relapse risk and comparable non-relapse mortality. Given the complexities of ALL protocols, it is difficult to establish precisely why paediatric protocols are superior. However, key differences between the two approaches include higher cumulative doses of immunosuppressive drugs (asparaginase, vincristine and steroids), greater use of intrathecal methotrexate and lower exposure to

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myelotoxic drugs (daunorubicin, etoposide) (Ram *et al*, 2012) in the paediatric protocols. In addition, adult strategies have tended to incorporate allogeneic haemopoietic stem cell transplantation in first CR. Despite the potent anti-leukaemic effect of allograft in ALL (Goldstone *et al*, 2008) there is significant risk of transplant-related mortality in the TYA age group (Ramanujachar *et al*, 2007; Goldstone *et al*, 2008; Burke *et al*, 2013).

In light of emerging data, the upper age limit for the UK paediatric ALL trial that had started recruiting in 2003, UKALL2003, was increased from 18 years to the 20th birthday in April 2006 and 25th birthday in September 2007. The lower age limit of the contemporary adult trial, UKALL XII, was simultaneously increased to avoid overlapping age criteria.

Here we report the clinical characteristics, treatment outcomes and toxicity profiles for the cohort of TYA patients, aged 16–24 years, treated on UKALL2003.

Materials and methods

Study design

From 1 October 2003 to 30 June 30 2011 we recruited consecutive children and young people diagnosed with ALL at 45 centres in the UK and Ireland into the MRC UK UKALL 2003 randomized controlled trial (Supplementary Material). Details of the trial have been published previously (Vora *et al*, 2013, 2014). Patients with mature B ALL were not eligible and Philadelphia chromosome positive (Ph+) patients were treated on alternative trial protocols when available.

Patients were stratified at diagnosis according to initial clinical risk of relapse (RR) based on the National Cancer Institute (NCI) risk criteria, leukaemia cytogenetics (Moorman *et al*, 2010) and response to induction chemotherapy based on morphology and minimal residual disease (MRD) at day 29. By definition, all TYA patients were stratified as NCI high risk (>10 years) and received regimen B unless they had high risk cytogenetics at presentation [*KMT2A* (*MLL*) rearrangements, near haploidy (<30 chromosomes), low hypodiploidy (30–39 chromosomes), t(17;19)(q23;p13), intrachromosomal amplification of chromosome 21 (iAMP21) or t(9;22)(q34;q11)/*BCR-ABL1*]. High-risk patients were assigned regimen C treatment. TYA patients were not further stratified by early response at day 8 or 15. Morphological remission status was assessed at day 29 of induction and CR was defined as a marrow blasts <5%. Patients who were not in CR at day 29 of induction and clinical high-risk patients were not eligible for MRD stratification and randomization.

Minimal residual disease was measured by a standardized real-time quantitative polymerase chain reaction method for immunoglobulin and T-cell receptor antigen gene rearrangements. The quantitative range of the assay was 10^{-4}. MRD was performed in four laboratories in the UK that participated in a European quality-assurance scheme (Flohr *et al*, 2008; Bruggemann *et al*, 2010). All MRD results were centrally reviewed. Patients were classed as having low risk MRD if they had undetectable MRD after induction (day 29) and at the end of consolidation. Those with MRD less than 0·01% were also classed as low risk. Patients with detectable MRD of at least 0·01% after induction were classed as high risk. Patients in whom MRD could not be measured or where there was persistent disease below 0·01% at the end of consolidation were classified as MRD indeterminate.

The trial 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.

Randomizations

Within the intermediate clinical risk group, MRD low risk patients were randomly assigned (1:1) to receive one or two delayed intensifications. Within the same group, MRD high risk patients were randomly assigned (1:1) to continue with the intermediate treatment regimen (regimen B) with two delayed intensifications or to receive the intensive schedule for clinical high risk patients (regimen C).

Treatment allocation was obtained by telephone call to the central trials unit, where a computer randomization was performed, with stratification by MRD result and balancing for sex, age (<10 years vs. ≥10 years) and white cell count (WCC) at diagnosis ($<50 \times 10^9$/l vs. $>50 \times 10^9$/l) by method of minimization. Patients, clinicians and data analysts were not masked to treatment allocation.

The overall outcomes of the two randomizations have been previously published (Vora *et al*, 2013, 2014).

Treatment procedures (supplemental material)

All TYA patients received a four-drug induction with vincristine, dexamethasone, pegylated asparaginase and daunorubicin. All patients also received two doses of intrathecal methotrexate in induction and those who had blasts in their cerebrospinal fluid at diagnosis received an additional two doses. Patients who did not achieve a reduction in bone marrow blast count of less than 25% at day 29 of induction or those with high risk cytogenetics who did not achieve a morphological remission (<5% blasts) at the same time point were eligible for an allogeneic transplant in first remission. Patients assigned to both regimen B and regimen C received a Berlin-Frankfurt-Muenster (BFM) consolidation although patients assigned to regimen C received four additional doses of vincristine and 2 additional doses of pegylated asparaginase. Interim maintenance in regimen B

consisted of 8 weeks of daily oral mercaptopurine, weekly oral methotrexate and monthly vincristine and steroid pulses. Regimen C maintenance comprised increasing doses of intravenous methotrexate without folic acid rescue, and vincristine and pegylated asparaginase. Delayed intensification in regimen B included one dose of pegylated asparaginase, vincristine, dexamethasone and doxorubicin for 3 weeks followed by a 4-week BFM consolidation block. Regimen C delayed intensification contained 2 additional doses of vincristine and one of pegylated asparginase. Maintenance therapy for all patients consisted of oral mercaptopurine and methotrexate with monthly steroid and vincristine pulses plus intrathecal methotrexate every 3 months. Male patients received treatment for 3 years and female patients for 2 years from the start of interim maintenance.

Serious adverse event reporting

Serious adverse events (SAE) were defined as any adverse event that resulted in death, was deemed to be life-threatening, resulted in unexpected hospitalization or unexpected prolongation of an existing hospitalization, or resulted in permanent or significant disability or incapacity. Death due to relapse of leukaemia or hospitalization due to febrile neutropenia were excluded from analysis. In all cases the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf) grading was used for reporting and analysis. SAEs were prospectively collected with a stated intention in the protocol to subsequently perform analyses according to subgroups of biological interest. SAE data was extracted from the trial database on 31 October 2013 and reviewed (re-classifying if necessary) for inclusion in this report.

Statistical analysis

The primary outcome measures for the trial were EFS, defined as time from diagnosis to first event, either relapse, secondary tumour or death, and overall survival (OS). The secondary outcome measures were cumulative RR and treatment-related toxic effects.

We compared categorical variables with standard χ^2 tests. B-cell precursor (BCP)-ALL patients were classified into three cytogenetic risk groups according to the presence of chromosomal abnormalities: good risk: *ETV6-RUNX1*/t(12;21)(p13;q21), high hyperdiploidy (51–65 chromosomes), high risk: *KMT2A* (*MLL*) rearrangements, iAMP21, t(17;19), near haploidy, low hypodiploidy and t(9;22); intermediate (all others cases including t(1;19)(q23;p13)/*TCF3-PBX1*), a minor revision of a classification previously described (Moorman *et al*, 2010). 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 e.g., time to first SAE included censoring at death. Patients who died within 35 d of starting treatment or who never achieved remission, or both, were deemed to be induction failures. They were included in analyses of EFS and OS, but excluded from analyses of relapse or remission death.

All analyses were by intention to treat. *P* values were two-sided and considered significant when <0·05. We completed statistical analyses with in-house programs or SAS version 9.3 (SAS Institute Inc., Cary, NC, USA).

Specific molecular genetic abnormalities were not included within the analyses for this age group because they are highly heterogeneous at the genetic level with no distinct genetic subtypes accounting for more than 15% cases (Moorman, 2012). We are currently screening patient samples from UKALL2003 for the specific kinase abnormalities that are frequently found in 'BCR-ABL1-like' ALL and these results will be reported separately.

This trial is registered with the International Standard Randomized Controlled Trial Number (ISRCTN) registry, number ISRCTN07355119.

Results

Demographics

UKALL 2003 registered a total of 3207 patients, of whom 81 were excluded, leaving 3126 patients eligible for analysis (Fig 1). Of these, 229 (7·3%) were aged between 16 and 24 years at diagnosis (Table I), with the breakdown by single year of age as follows: 66 (2·1%) aged 16, 33 (1·1%) aged 17, 44 (1·4%) aged 18, 30 (1·0%) aged 19, 15 (0·5%) aged 20, 11 (0·4%) aged 21, 16 (0·5%) aged 22, 10 (0·3%) aged 23, 4 (0·1%) aged 24. All TYA patients were, by definition, NCI high risk. There were no significant age differences in presenting WCC, incidence of Down syndrome or presence of central nervous system (CNS) disease at diagnosis. There was an increase in the incidence of T-cell disease with advancing age; 63 (27·6%) in TYA patients compared to 79 (5·2%) in those age under 5 years, 109 (14·2%) in 5–9 year olds and 137 (22·6%) in 10–15 year olds, $P(\text{trend}) < 0{\cdot}0001$. BCP-ALL patients with good risk cytogenetics decreased with age from >70% in younger children (<5 years) to just 25% of TYA patients (Table I). The majority of good risk cytogenetic patients harboured high hyperdiploidy ($n = 33$) rather than *ETV6-RUNX1* ($n = 5$). A total of nine patients had high risk cytogenetics [near haploidy ($n = 1$), low hypodiploidy ($n = 2$), *KMT2A* ($n = 4$) and t(9;22) ($n = 1$)]. The frequency of high risk cytogenetics is somewhat lower than expected because the vast majority of t(9;22) patients were transferred to EsPhALL (Biondi *et al*, 2012), UKALLXII (Fielding *et al*, 2009) or UKALL14. Thus the majority of BCP-ALL patients (69%) had intermediate risk cytogenetics, which included t(1;19) ($n = 3$), but mostly comprised patients with B-other ALL ($n = 99$). A total of 21 patients harboured an *IGH* translocation with a range of different partner genes, including *CRLF2* as previously reported (Russell *et al*, 2014).

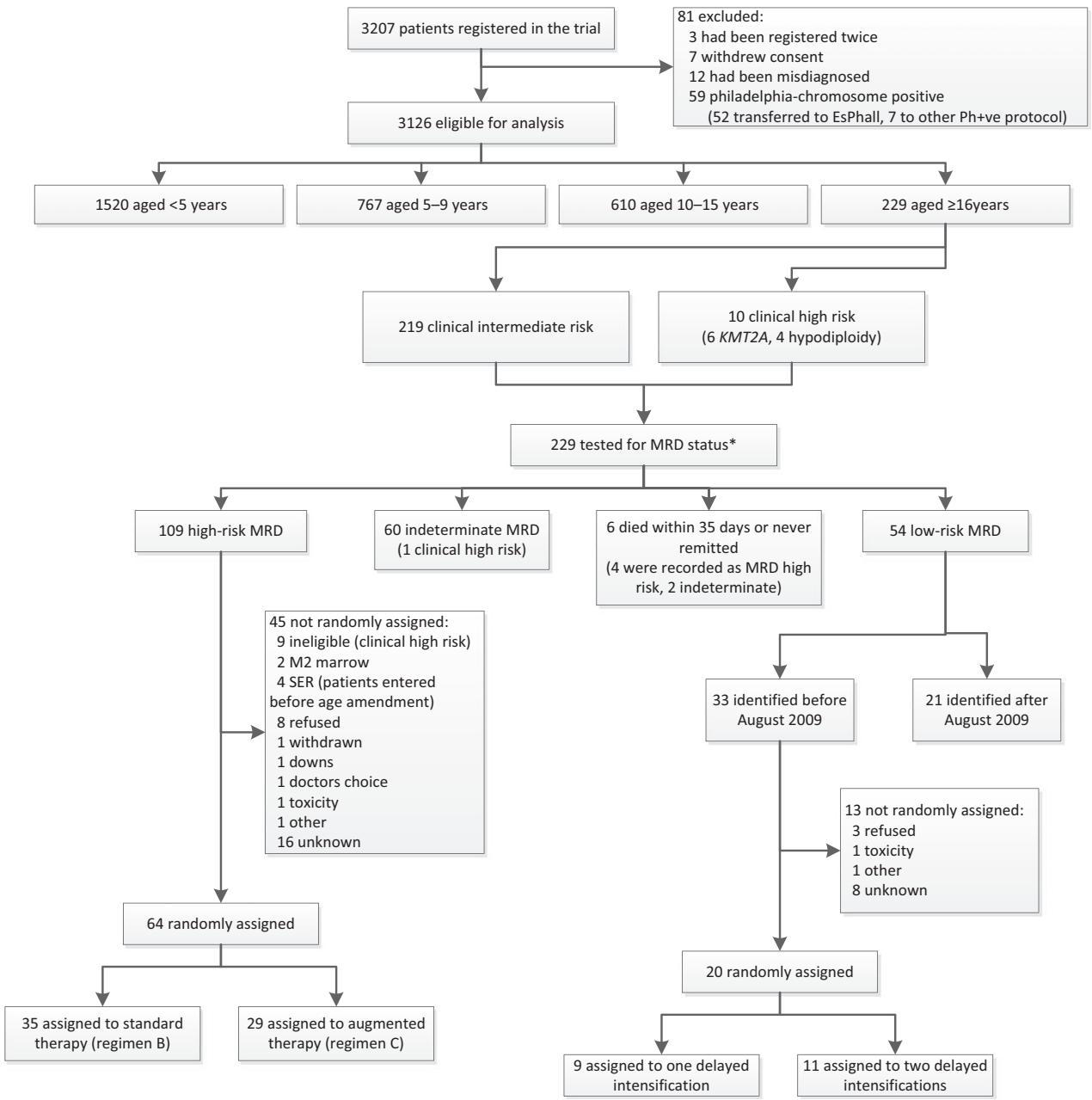

Fig 1. Trial Recruitment. *All eligible trial patients, with the exception of some of those who died within 35 d or never achieved remission, were tested for MRD status after induction and before first interim maintenance, but clinical high-risk patients were not eligible for MRD stratification and randomization. MRD, minimal residual disease; SER, slow early response; M2 marrow, between 5% and 25% leukaemic blasts in bone marrow.

Minimal residual disease risk status

Patients aged ≥16 years were more likely to be MRD high risk compared to younger patients (Table I). 109 (47·9%) TYA patients were MRD high risk at day 29 compared to 223 (36·6%) in the 10–15 year old group ($P = 0{\cdot}004$), 271 (35·3%) 5–9 year olds and 427 (28·1%) under 5 year olds. The proportion of patients with indeterminate MRD was the same across all age groups at approximately 30%, but decreased over time during the trial. Similar to the trial overall, there was an association between MRD risk group and cytogenetic risk group for the TYA patients. Among the cytogenetic good risk TYA patients 14 (38·9%), 11 (30·6%) and 11 (30·6%) were MRD low, indeterminate and high risk respectively, whereas among patients with intermediate risk cytogenetics the proportions were 27 (27·3%), 21 (21·7%) and 51 (51·5%); they were 0 (0%), 1 (11·1%) and 8 (88·9%) respectively, among high risk cytogenetic patients, P (trend) = 0·002.

Table I. Patient characteristics.

Age group (years)	<5 (n = 1520)	5–9 (n = 767)	10–15 (n = 610)	16 + (n = 229)	Total (n = 3126)	P-value* (<10 vs. 10+)	P-value* (10–15 vs. 16+)
Sex							
Female	683 (44·9)	338 (44·1)	255 (41·8)	74 (32·3)	1350 (43·2)	0·007	0·01
Male	837 (55·1)	429 (55·9)	355 (58·2)	155 (67·7)	1776 (56·8)		
Down syndrome							
No	1477 (97·2)	745 (97·1)	596 (97·7)	222 (96·9)	3040 (97·2)	0·6	0·5
Yes	43 (2·8)	22 (2·9)	14 (2·3)	7 (3·1)	86 (2·8)		
WCC ($\times 10^9$/l)							
<10	634 (41·7)	370 (48·2)	294 (48·2)	109 (47·6)	1407 (45·0)	0·1	0·6
10–	274 (18·0)	126 (16·4)	71 (11·6)	31 (13·5)	502 (16·1)		
20–	294 (19·3)	118 (15·4)	82 (13·4)	32 (14·0)	526 (16·8)		
50–	174 (11·4)	62 (8·1)	54 (8·9)	25 (10·9)	315 (10·1)		
100+	144 (9·5)	91 (11·9)	109 (17·9)	32 (14·0)	376 (12·0)		
NCI risk group							
Standard	1202 (79·1)	614 (80·1)	0	0	1816 (58·1)	n/a	n/a
High	318 (20·9)	153 (19·9)	610 (100·0)	229 (100·0)	1310 (41·9)		
Immunophenotype							
T	79 (5·2)	109 (14·2)	137 (22·6)	63 (27·6)	388 (12·4)	<0·0001	0·1
non-T	1440 (94·8)	656 (85·8)	470 (77·4)	165 (72·4)	2731 (87·6)		
Unknown	1	2	3	1	7		
CNS disease at diagnosis							
No	1502 (98·8)	756 (98·6)	589 (96·6)	226 (98·7)	3073 (98·3)	0·002	0·1
Yes	18 (1·2)	11 (1·4)	21 (3·4)	3 (1·3)	53 (1·7)		
Cytogenetic risk group§							
Good	993 (71·9)	395 (63·8)	159 (37·4)	37 (25·3)	1584 (61·6)	<0·0001	0·001
Intermediate	336 (24·3)	172 (27·8)	188 (44·2)	90 (61·6)	786 (30·6)		
Poor	21 (1·5)	13 (2·1)	25 (5·9)	10 (6·9)	69 (2·7)		
High	31 (2·2)	39 (6·3)	53 (12·5)	9 (6·2)	132 (5·1)		
Unknown	60	39	48	20	167		
MRD risk group							
n/a†	12 (0·8)	4 (0·5)	13 (2·1)	6 (2·6)	35 (1·1)	<0·0001‡	0·004‡
High	427 (28·1)	271 (35·3)	223 (36·6)	109 (47·6)	1030 (32·9)		
Indeterminate	491 (32·3)	237 (30·9)	183 (30·0)	60 (26·2)	971 (31·1)		
Low	590 (38·8)	255 (33·2)	191 (31·3)	54 (23·6)	1090 (34·9)		

Values within parenthesis are expressed in percentage. WCC, white cell count; NCI, National Cancer Institute; CNS, centra nervous system; MRD, minimal residual disease.
*Excluding 'unknown' categories.
†Induction failure.
‡High *versus* low.
§B-cell precursor acute lymphoblastic leukaemia only.

Outcomes

Follow-up to October 2013 is reported with a median follow-up for the trial overall of 5 years 10 months (range: 1 month – 10 years 1 month). Due to the sequential changes in age eligibility, the median follow up for TYA patients was shorter at 4 years 10 months (range 2 years 5 months – 10 years 0 months). Nonetheless, the median follow up for TYA patients aged 16–19 was over 5 years, and for those aged ≥20 was over 3 years. Five-year EFS for the entire trial population was 87·3% (95% CI: 86·1–88·5). When analysed by age, the 5-year EFS of patients age under 10, 10 – 15 and ≥16 years was 89·8% (88·4–91·2), 83·6% (80·5–86·7) and 72·3% (66·2–78·4) respectively [odds ratio (OR) = 2·1 (95% CI: 1·7–2·4), *P* (trend) < 0·00005, *P*(10–15 vs. ≥16) = 0·0004] (Fig 2A).

Five-year OS and cumulative risk of relapse (RR) for the trial population was 91·6% (90·6–92·6) and 8·8% (7·8–9·8) respectively. OS at 5 years, analysed by age group, was 76·4% (70·5–82·3) for 16–24 year olds, 87·5% (84·8–90·2) for 10–15 year olds and 94·2% (93·2–95·2) for under 10 year olds [OR = 2·7 (2·2–3·4), *P*(trend) < 0·00005, *P*(10–15 vs. ≥16) = 0·0004]. The RR was higher for TYAs, at 20·9% (15·0–26·8) at 5 years compared to 7·1% (5·9–8·3) for under 10 years and 10·7% (8·0–13·4) for 10–15 year) [OR = 2·1 (1·7–2·6), *P*(trend) < 0·00005, *P*(10–15 vs. ≥16) = 0·0003] (Fig 2A). In the trial overall 80 (2·6%) of the 3126 patients died in remission.

The risk of death in remission (DIR) was higher with increasing age: the 5-year DIR rate was 2·1% (1·5–2·7) in those aged under 10 years, 3·4% (1·8–5·0) in those aged 10–15 and 6·1% (2·8–9·4) in those aged ≥16, OR = 2·0 (1·4–3·9), *P* (trend) = 0·0007. However, the difference in DIR rates between the TYA group and the younger teenagers did not reach statistical significance (*P* = 0·1). The effect of treatment regimen (regimen B vs. C) on DIR was similar (with higher DIR for those on regimen C compared to B) in the older age groups [OR = 3·8 (1·6–9·4) for age 10–15, 3·3 (0·9–11·7) for age ≥16, *P*(heterogeneity) = 0·8], but different for the younger patients [0·5 (0·2–1·2) for age <10 years, *P*(heterogenetity <10 vs. 10+) = 0·001]. In the TYA group there were 13 remission deaths, 8 whilst still on treatment (four due to infection, one methotrexate encephalopathy, one CNS thrombosis, one pancreatitis, one secondary haemophagocytic lymphohistiocytosis) and 5 off-treatment (two post-transplant, two infection, one unknown). In all age groups most treatment-related deaths were due to infection. Thirty-five of the 3126 patients failed induction (either by not achieving remission or dying within 35 d of starting treatment) 6 of whom were TYA patients. The actuarial rates of induction failure by age group were: under 10 years 0·7% (0·3–1·1), aged 10–15 2·1% (0·9–3·3) and aged ≥16 2·6% (0·4–4·8), *P*(10–15 vs. ≥16) = 0·7.

Analysis of prognostic factors for the trial has been reported (Vora *et al*, 2013; Moorman *et al*, 2014) with MRD being the single most important determinant of outcome for patients in UKALL 2003. The effect of MRD risk group on outcome was similar by age group [OR for MRD high risk = 2·8 (2·0–3·8) age <10, 4·2 (2·6–6·7) age 10–15, 3·2 (1·7–6·0) age ≥16, *P*(heterogeneity for EFS) = 0·4]; and the difference in EFS between the MRD high and low risk TYA patients was highly statistically significant *P* = 0·0001 (Fig 2B). EFS for the TYA patients with low risk MRD was 92·6% (95% CI: 85·5–99·7) at 5 years, with no events occurring after the second year from trial entry (Fig 2B). Those with high risk MRD had an EFS of 63·2% (53·8–72·6) at 5 years. Patients with indeterminate MRD had similar results to patients with high-risk disease, with an EFS of 70·6% (58·4–82·8).

The effects of WCC and cytogenetic risk group on EFS did not differ significantly by age group. However, there was evidence of a difference in the effect of immunophenotype [OR for T-ALL vs. B-ALL = 2·8 (1·8–4·5) for age <10, 1·12 (0·7–1·8) for age 10–15, 1·0 (0·5–1·7) for age ≥16, *P* (trend) = 0·003], and a suggestion of a difference in the effect of sex [OR for boys = 1·4 (1·0–1·7) for age <10, 1·2 (0·8–1·7) for age 10–15, 0·6 (0·4–1·1) for age ≥16, *P* (trend) = 0·03].

Among TYA patients, there was a significant difference in EFS by cytogenetic risk group (Fig 2C). As in the trial overall, there was no difference in the effect of cytogenetic risk group (good vs. intermediate) on EFS by MRD risk group [OR for intermediate risk cytogenetics = 1·8 (0·6–5·6) for MRD high risk, 4·8 (0·4–50·4) for MRD low risk, *P*(heterogeneity) = 0·5].

Fourteen (6·1%) of the 229 TYA patients received a SCT in first CR. Indication for transplant was *KMT2A* gene rearrangement in 4, hypodiploidy in 2, *BCR:ABL1* positive in 1, patient/clinician choice in 3, >25% leukaemic blasts in the marrow at day 28 in 3 and unknown in 1. The first remission transplant rate for 10–15 year olds was also 6·1%, but was lower (1·4%) for those aged less than 10 years. Of the 14 TYA patients treated with SCT, 5 have died: 1 due to infection, 1 due to GVHD and 3 post-transplant relapse. The remaining 9 were in remission at last follow-up. A further 21 (9·2%) TYA patients received a transplant following first relapse.

In the light of data from both UK studies and other groups showing persisting high mortality for Down syndrome patients, a number of treatment modifications, applicable to all patients, were implemented in 2009 (Patrick *et al*, 2014). Of the seven TYA Down syndrome patients, three have died (two induction failures, one relapsed), one is alive post-bone marrow transplantation relapse and three are alive in first remission. There was no evidence of heterogeneity in the effect of Down syndrome on EFS, OS or relapse outcomes for subgroups defined by age (data not shown).

Toxicity

A total of 1835 SAEs were reported in 1164 (37·2%) patients in the trial overall. The overall incidence of SAEs was higher for those aged 10 or older compared to those under 10 years

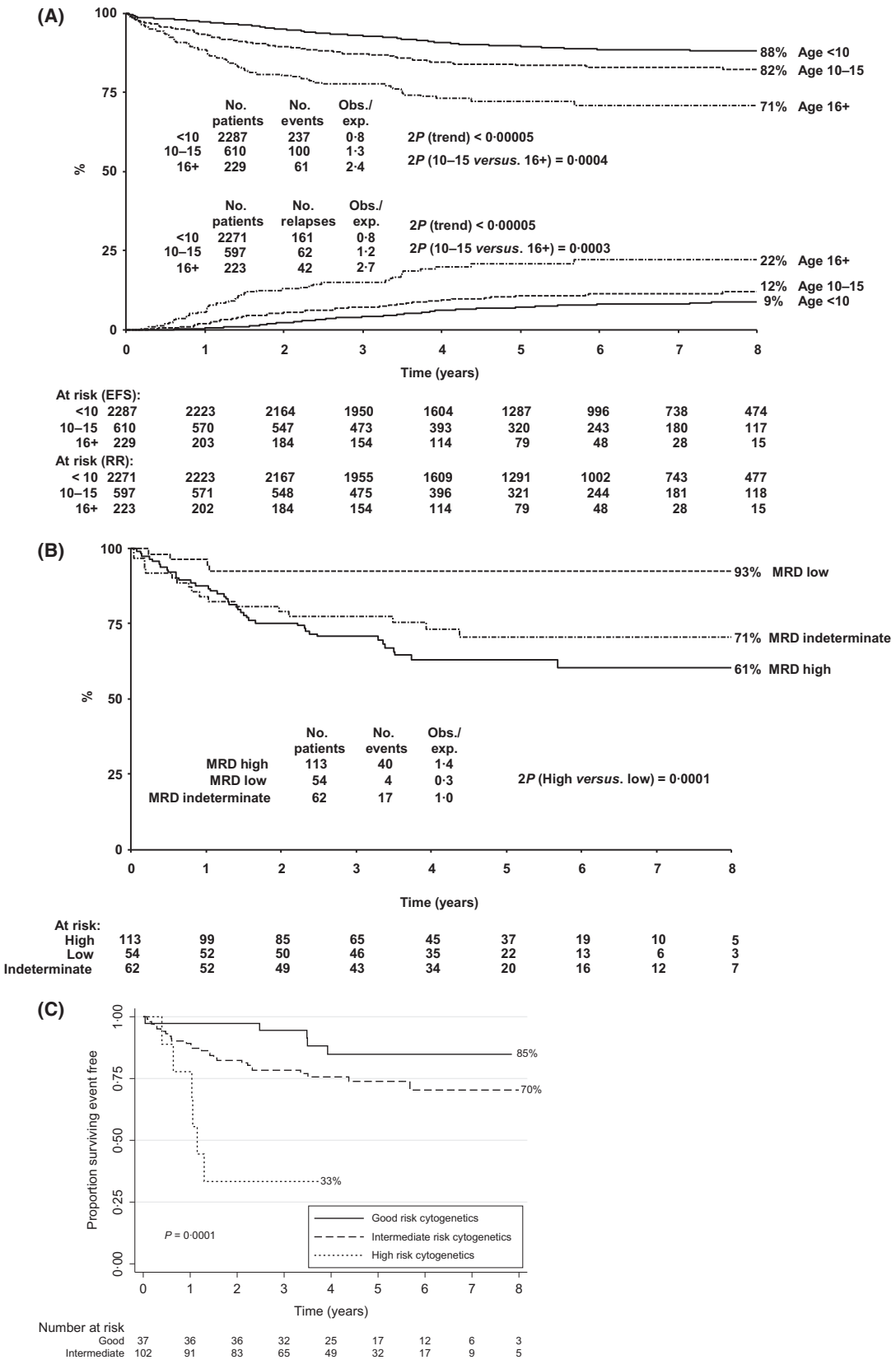

Fig 2. (A) EFS and RR by age group. (B) EFS by MRD risk at day 29 in the TYA population. (C) EFS by cytogenetic risk group in the TYA population. EFS, event-free survival; RR, risk of relapse; MRD, minimal residual disease; TYA, teenage and young adult.

(Table II), and there was a clear distinction in the time to first SAE by age group (Fig 3), OR (<10 years vs. 10–24 years): 2·58 (95% CI: 2·24–2·95), $P < 0{\cdot}00005$. This difference remained after stratifying for sex, NCI risk group, immunophenotype, MRD risk group and treatment allocation, adjusted OR 1·51 (95% CI: 1·28–1·77), $P < 0{\cdot}00005$. Analysis by treatment allocation simply accounted for whether the patient had regimen A, B or C. However, this does encompass many of the differences relating to intensity of treatment received. The magnitude of the effect of age was reduced after stratifying for the other covariates but nonetheless remained significant.

Broadly, four patterns of toxicity profiles were observed across the different age groups (Table II); (i) toxicities more frequently observed in patients aged 10 years or older compared to those age 1–9 years (pancreatitis, bacterial infection, mucositis, methotrexate encephalopathy and hyperglycaemia), (ii) toxicities that were observed with similar frequency across all age groups (vincristine neurotoxicity, asparaginase hypersensitivity and central venous catheter-related infection and thrombosis), (iii) toxicities that increased in frequency with increasing age (deep vein thrombosis, pulmonary embolism, infections and steroid induced psychosis) (Fig 4A), although the numbers except for infection are small and of borderline significance and (iv) toxicity observed predominantly in adolescents (avascular necrosis with 82% of events occurring in 10–19 year olds) (Fig 4B).

Discussion

We report that OS and EFS for TYA patients treated on an intensive, risk-adapted paediatric protocol, UKALL 2003, are substantially better compared to historical data from the adult UKALL 12 trial (Ramanujachar *et al*, 2007); EFS 45%

Table II. Impact of age on SAE frequency.

Age group (years)	Total (n = 3126)	<5 (n = 1520)	5–9 (n = 767)	10–15 (n = 610)	16+ (n = 229)	P-value* (<10 vs. 10 +)	P-value* (10–15 vs. 16 +)
All SAEs	1164 (37·2)	464 (30·5)	235 (30·6)	341 (55·9)	124 (54·1)	<0·0001	0·6
Toxicities more frequently observed in patients aged 10 years or older compared to those age 1–9 years							
Pancreatitis	50 (1·6)	9 (0·6)	16 (2·1)	19 (3·1)	6 (2·6)	<0·001	≥0·05
Bacterial infection	283 (9·1)	129 (8·5)	48 (6·3)	72 (11·8)	34 (14·8)	<0·0001	≥0·05
Septicaemia	182 (5·8)	81 (5·3)	34 (4·4)	48 (7·9)	19 (8·3)	<0·05	≥0·05
Pneumocystis	15 (0·5)	3 (0·2)	2 (0·3)	6 (1)	4 (1·7)	<0·0001	≥0·05
Methotrexate encephalopathy	250 (8)	73 (4·8)	57 (7·4)	93 (15·2)	27 (11·8)	<0·0001	≥0·05
Mucositis	42 (1·3)	10 (0·7)	6 (0·8)	20 (3·3)	6 (2·6)	<0·0001	≥0·05
Steroid-induced hyperglycaemia	40 (1·3)	11 (0·7)	4 (0·5)	17 (2·8)	8 (3·5)	<0·0001	≥0·05
CNS thrombosis	50 (1·6)	9 (0·6)	13 (1·7)	18 (3·0)	10 (4·4)	<0·0001	≥0·05
Toxicities which were observed with similar frequency across all age groups							
Asparaginase hypersensitivity	55 (1·8)	22 (1·4)	13 (1·7)	16 (2·6)	4 (1·7)	≥0·05	≥0·05
Line-related thrombosis	23 (0·7)	11 (0·7)	7 (0·9)	3 (0·5)	2 (0·9)	≥0·05	≥0·05
Line-related bacterial infection	43 (1·4)	26 (1·7)	6 (0·8)	6 (1)	5 (2·2)	≥0·05	≥0·05
Vincristine neurotoxicity	62 (2)	30 (2)	9 (1·2)	18 (3)	5 (2·2)	≥0·05	≥0·05
Viral infection	155 (5)	90 (5·9)	34 (4·4)	19 (3·1)	12 (5·2)	≥0·05	≥0·05
Toxicities which increased in frequency with increasing age							
Thrombosis other than line or CNS	18 (0·6)	3 (0·2)	3 (0·4)	5 (0·8)	7 (3·1)	<0·001	<0·05
Any infection	546 (17·5)	260 (17·1)	106 (13·8)	119 (19·5)	61 (26·6)	<0·0001	<0·05
Steroid-induced psychosis	18 (0·6)	4 (0·3)	6 (0·8)	3 (0·5)	5 (2·2)	≥0·05	<0·05
Toxicities seen predominantly in adolescence							
Avascular necrosis	138 (4·4)	5 (0·3)	13 (1·7)	92 (15·1)	28 (12·2)	<0·0001	≥0·05

Values within parenthesis are expressed in percentage. SAE, serious adverse event; CNS, central nervous system.
*P-values are not corrected for multiple testing

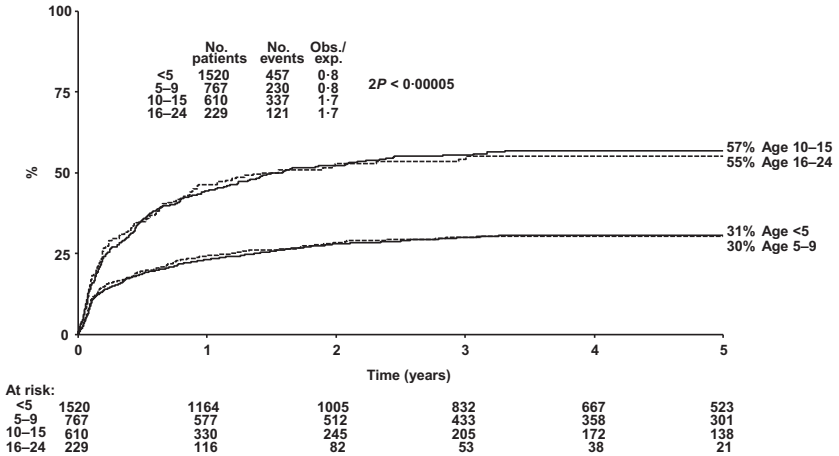

Fig 3. Time to first serious adverse event. Solid lines represent the age groups <5 and 10–15 years. Dashed lines represent the age groups 5–9 and 16–24 years. After stratifying for sex, National Cancer Institute risk group, immunophentype, minimal residual disease risk group and treatment allocation: adjusted odds ratio (<10 vs. 10–24) = 1·51, 95% confidence interval: 1·28–1·77, $2P < 0·00005$.

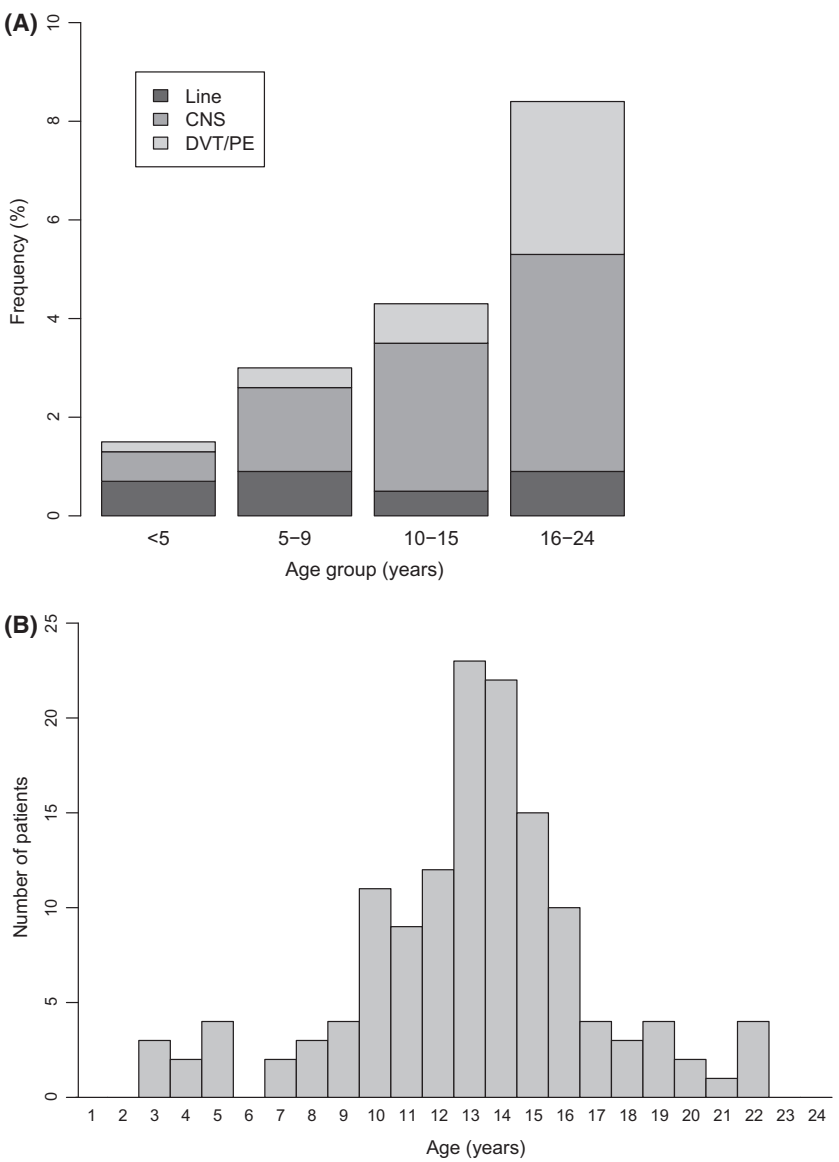

Fig 4. (A) Incidence of thrombotic events across different age groups. (B) Absolute number of episodes of avascular necrosis according to single year of age (at treatment start). DVT, deep vein thrombosis; PE, pulmonary embolism; CNS, central nervous system.

versus 72%, OS 45% *versus* 76% at 5 years, We also describe the presenting features, clinical outcomes and treatment-related toxicities of a large population of prospectively studied TYA ALL patients.

Many study groups, including our own, have reported excellent survival outcomes for paediatric patients with ALL who have undetectable MRD post-induction chemotherapy due to a low risk of relapse (Cave *et al*, 1998; van Dongen *et al*, 1998; Pui *et al*, 2011; Vora *et al*, 2013). More recently, MRD has been shown to be of equivalent predictive value in adult patients with low risk patients achieving long term disease-free survival of 72–80% (Bassan *et al*, 2009; Gokbuget *et al*, 2012). TYA patients with low risk MRD at the end of induction had a 92% EFS at 5 years with no events occurring after the second year from trial entry. This outcome compares favourably with the published data (Pui *et al*, 2011) and suggests that further improvement in outcomes for this low risk subset will primarily require reductions in treatment-related mortality.

The proportion of patients with MRD high-risk disease at the end of induction was significantly higher in TYA patients (50%) than in the younger teenagers (33%). This is in keeping with data from other groups (Pui *et al*, 2011); Toft *et al* (2013) previously noted a marked rise in persistent MRD post-induction with age in adults over 18 years compared to younger teenagers and children. Whilst outcomes for MRD high risk patients are better than previously reported for high risk adults, the relapse risk is higher than for MRD low risk patients. As slow MRD response is a sign of chemotherapy resistance, improvements in outcome for this group will require innovative treatment approaches. There is evidence that allogeneic transplantation can improve outcomes in adults with persistent MRD post-consolidation ($<10^{-3}$) (Bassan *et al*, 2009; Ram *et al*, 2012). In our current trial, UKALL 2011, patients with persistent high level MRD (>0·5%) post-augmented consolidation are candidates for treatment intensification followed by a first remission allogeneic transplant.

Our study demonstrates novel and important insights into the impact of age on therapy-related toxicity. The time to first SAE was significantly shorter and cumulative incidence of SAEs was significantly higher in those aged 10 years or older compared to those under 10 years of age. This difference is not solely a consequence of treatment allocation (regimen B in older vs. regimen A in younger) as these differences persisted after stratification for these and other risk factors. However, the impact of age was not consistent across specific toxicities and we observed four distinct profiles; (i) toxicities more frequently observed in patients aged 10 years or older compared to those age 1–9 years, (ii) toxicities that were observed with similar frequency across all age groups, (iii) toxicities that increased in frequency with increasing age and (iv) toxicity observed predominantly in adolescents.

These data suggest that the development of toxicity with increasing age is complex and dependent on multiple factors that are likely to include pubertal changes, body mass index, drug metabolism, environmental factors and compliance. The observation that age had no impact on certain toxicities suggests that other risk factors are dominant in these circumstances, such as genetic predisposition (Barthelemy Diouf *et al*, 2013) (vincristine neuropathy), presence of a central venous catheter (line-related infection or thrombosis) or environmental (increased exposure to viruses in children at school). Interestingly, 82% of episodes of avascular necrosis were documented in patients aged 10–19 years, suggesting that principle risk factors for this complication may include pubertal changes in bone growth or drug metabolism. Further investigation of age-specific toxicity risk may help to find ways of reducing treatment-associated morbidity and mortality for all patients.

As reported previously (Barry *et al*, 2007; Nachman *et al*, 2009; Pui *et al*, 2011; Moorman, 2012; Toft *et al*, 2013), we found an increase in proportions of patients with unfavourable biological characteristics with increasing age, including an increased frequency of T cell disease, unfavourable cytogenetics and tumour response kinetics, as measured by MRD. Recent genomic studies have identified several novel classes of genetic abnormality underpinning B-other ALL, the dominant genetic subtype among TYA patients. These aberrations include kinase activating abnormalities (e.g. *EBF1-PDGFRB*, *CRLF2* deregulation), copy number alterations (e.g. *IKZF1* deletions and *ERG* deletions) and *IGH* translocations targeting a variety of oncogenes (Clappier *et al*, 2014; Moorman *et al*, 2014; Roberts *et al*, 2014; Russell *et al*, 2014). Further studies are needed in order to establish the frequency of these abnormalities in the TYA population and to assess whether they can further refine the cytogenetic risk classification presented in this study.

The main limitation of this study is the shorter follow-up of TYA patients due to the late and sequential changes in age eligibility criteria. However there are at least 2·5 years follow-up for all TYA patients and median follow-up is more than 5 years in all but the subset of patients aged 20 and over, in which median follow up is still more than 3 years. The majority of events occur before these time points and we will continue to monitor this group for late events. We also note the relatively high proportion of cases for which an informative MRD result was not available. This proportion declined over the course of the trial as sample quality and laboratory procedures improved.

In conclusion, an MRD risk-stratified approach using paediatric treatment regimens results in excellent outcomes for TYA patients with Philadelphia chromosome-negative ALL. Future improvements will be realised through reducing treatment-related mortality for MRD low risk patients and relapse risk for MRD high-risk patients.

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Authorship contributions

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

Conflicts of interest

We declare that we have no conflicts of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. Medical Research Council Working Party on Leukaemia in Children.

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