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Outcomes in older adults with acute lymphoblastic leukaemia (ALL): results from the international MRC UKALL XII/ECOG2993 trial

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Summary

Although the incidence rate of acute lymphoblastic leukaemia (ALL) is slightly higher in older than in younger adults, response rates to induction chemotherapy and survival rates are poorer. The contribution of disease-related *versus* treatment-related factors remains unclear. We analysed 100 older patients (aged 55–65 years) treated on the UKALLXII/ECOG2993 trial compared with 1814 younger patients (aged 14–54 years). Baseline characteristics, induction chemotherapy course, infections, drug reductions and survival outcomes were compared. There were more Philadelphia-positive (Ph+) patients in the older group (28% vs. 17%, $P = 0{\cdot}02$), and a trend towards higher combined cytogenetic risk score (46% vs. 35%, $P = 0{\cdot}07$). The complete remission rate in older patients was worse (73% vs. 93%, $P < 0{\cdot}0001$) as was 5-year overall survival (21% vs. 41%, $P < 0{\cdot}0001$) and event-free survival (EFS) (19% vs. 37%, $P < 0{\cdot}0001$). Older patients had more infections during induction (81% vs. 70%, $P = 0{\cdot}05$), and drug reductions (46% vs. 28%, $P = 0{\cdot}0009$). Among older patients, Ph+ and cytogenetic risk category as well as infection during induction predicted for worse EFS. Poorer outcomes in these patients are partly due to cytogenetic risk, but there is significant morbidity and mortality during induction chemotherapy with frequent delays and drug reductions. New approaches, including better risk stratification and use of targeted therapies, could improve treatment for these patients.

Keywords: acute lymphoblastic leukaemia, chemotherapy, elderly, infection.

Acute lymphoblastic leukaemia (ALL) is often seen as a disease of the young, but the age-specific annual incidence for individuals over 60 years is 0·9–1·6 per 100 000, compared to 0·4–0·6 per 100 000 in those between 25 and 50 years (Larson, 2005). Estimates for the proportion of new cases that present in older patients range from 16% to 31% (Taylor *et al*, 1992; Pagano *et al*, 2004).

The outcomes for older patients have consistently been found to be worse, both in response to induction chemotherapy, and in long term survival. Furthermore, based on an analysis of Surveillance, Epidemiology and End Results (SEER) data from the United States, in contrast to younger patients there has been no significant improvement in outcomes for this group over the last 25 years (Pulte *et al*, 2009). Despite these differences there are few large cohorts of older patients described, and conclusions about their management are largely extrapolated from younger patients. All of the major cooperative groups are heavily biased towards trials for those under 55 years, with inclusion of very few patients aged over 70 years.

Disease-based differences have been shown in older patients, with a higher proportion of B-lineage immunophenotype reported by some groups (Gökbuget *et al*, 2000; Robak *et al*, 2004; Larson, 2005), as well as cytogenetic differences, particularly a higher proportion of Philadelphia chromosome positive (Ph+) (33–54%) cases (Groupe Fran-

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çais de Cytogénétique Hématologique, 1996; Wetzler *et al*, 1999; Gökbuget *et al*, 2000; Appelbaum, 2005; Moorman *et al*, 2007). However, most treatment protocols include an intensive induction phase with significant toxicities, [often based on paediatric regimens (Huguet *et al*, 2009)], and the extent to which treatment-based toxicity contributes to poorer outcomes remains unclear.

An increased understanding of the relative importance of disease-related *versus* treatment-related factors could make a considerable difference when planning optimal treatment strategies. This report describes the characteristics and outcomes of those patients aged ≥ 55 years enrolled on the Medical Research Council (MRC) UKALL XII/Eastern Cooperative Oncology Group (ECOG) 2993 trial. This constitutes one of the largest cohorts of older ALL patients treated prospectively on a standard protocol. Analysis provides insight into the reasons for their poorer outcomes, and suggests future strategies to mitigate these.

Methods

Patients

The study was conducted jointly by the MRC of the United Kingdom, and the ECOG of the United States. Patients with newly diagnosed, untreated ALL and no prior malignancy were recruited between 1993 and 2006. The Ethics Committee or Institutional Review Board of each participating centre approved the study. Informed consent was obtained from all subjects in accordance with the Declaration of Helsinki. There were no exclusion criteria for abnormal renal or hepatic function, or poor performance status at diagnosis. Beginning in 2003 (MRC) or 2004 (ECOG), patients with Ph+ disease were entered into an imatinib substudy, and these patients have been excluded from this analysis. The initial age range for MRC patients was 15–55 years, whereas it was 15–59 for ECOG patients. When the imatinib sub-study began, the upper age limit for all ECOG and Ph+ MRC patients was subsequently increased to 64, but remained at 55 for MRC patients with Ph− disease. However, two Ph− MRC patients aged 56–59, were entered into the trial.

Diagnosis, treatment and response assessment

Diagnosis of ALL was established by documenting more than 25% marrow lymphoblasts. Confirmation of the diagnosis by central morphology review was recommended as well as submission of blood or marrow samples for cytogenetic analysis and immunophenotyping. A combined cytogenetic risk score was subsequently calculated on all patients, with high risk cytogenetics, defined as t(9;22), t(4;11), t(8;14), low hypodiploidy/near-triploidy (HoTr) or complex karyotype (Moorman *et al*, 2007). Central nervous system (CNS) involvement was assessed by the presence of lymphoblasts in cerebrospinal fluid.

All patients were treated according to the protocol as previously described (Table SI) (Rowe *et al*, 2005; Goldstone *et al*, 2008), receiving the identical two stage induction therapy irrespective of risk assessment, including CNS prophylaxis and treatment of CNS disease if present at diagnosis (Fig S1). Antifungal prophylaxis was recommended, but participating centres adhered to local policies. *Pneumocystis jiroveci* pneumonia (PCP) prophylaxis was recommended, with co-trimoxazole or, if the white blood cell (WBC) count would not tolerate this, inhaled pentamidine.

Patients were evaluated for response by bone marrow aspirate at the end of each of the two phases of induction. Those who achieved complete remission (CR) went on to the intensification and post-remission consolidation parts of the study. Younger patients achieving CR with a matched sibling donor were to receive an allogeneic matched sibling donor transplant (or a matched unrelated donor for those with Philadelphia positive disease). Patients aged 50 years or more (55 years or more from 2003) and those with no suitable donor, were eligible for randomization between autologous transplantation and consolidation/maintenance chemotherapy. Patients not achieving CR were taken off protocol, but followed for survival.

Randomization, data collection and statistical analysis

All patients were centrally registered at either the Clinical Trial Service Unit (CTSU) for MRC patients, or the ECOG Coordinating Center for ECOG patients. These centres were also responsible for the randomization and collection of follow-up information.

Chi-square tests (for categorical variables) and the Mann–Whitney *U*-test (for continuous variables) were used for comparing age groups by initial characteristics and for remission rates by age group. The primary outcome measure was event-free survival (EFS), defined as the time to relapse or death. Other outcomes analysed were overall survival (OS), relapse-free survival (RFS) defined as time to relapse excluding patients who never entered remission and censoring at death in remission, and death in remission, excluding non-remitters and censoring at relapse. Patients who did not relapse or die within the follow-up period were censored at the earlier of (1) the date of last contact or (2) October 31, 2010. All event times were measured from the time of diagnosis. Kaplan–Meier curves were used for survival analyses, and univariate comparisons were made by the log-rank method. P values $< 0{\cdot}05$ were considered statistically significant. Odds ratios (ORs) were calculated and are given with their 95% confidence intervals (CIs). Unless otherwise indicated, an OR of $<1{\cdot}0$ indicates a worse prognosis in the second group compared with the first.

Results

Patient characteristics

A total of 1914 patients were recruited from 1993 up to the study's closure in 2006, of whom 100 were aged 55 years or more (median 56, range 55–65) and 1814 were aged under 55 years (median 30, 14–54). ECOG centres enrolled a larger number of older patients into the trial compared to MRC centres (80% vs. 20%), in contrast to the younger group (34% vs. 66%, $P < 0{\cdot}0001$), as the upper age limit for eligible MRC patients was 55 years but was 60 years (later 65) for ECOG patients.

There was no significant difference between the age groups in terms of sex distribution, white blood cell (WBC) count or B *versus* T immunophenotype. The proportion of those with enlarged lymph nodes was lower in the older age group (17% vs. 31%, $P = 0{\cdot}004$), as was splenomegaly (16% vs. 29%, $P = 0{\cdot}005$) and hepatomegaly (9% vs. 17%, $P = 0{\cdot}04$). There was no difference in the presence of anterior mediastinal mass or CNS involvement.

Restricting the analysis to only those patients enrolled to the separate Ph+ substudy before the addition of imatinib, a higher proportion of older patients were Ph+ (28% vs. 17%, $P = 0{\cdot}02$). No other individual cytogenetic abnormalities varied significantly between groups, although there was a trend towards a higher proportion of older patients within the cytogenetic high-risk group (46% vs. 35%, $P = 0{\cdot}07$) (Table I).

Outcomes

Median follow-up was 8·7 years. The CR rate for older patients was 73%, compared to 93% in the younger group ($P < 0{\cdot}0001$). The rate of death in induction was 18% in the older group compared to 4% within the younger group. Nine percent of the older group survived induction without attaining CR compared to 3% in the younger group (Table II).

Overall outcomes were worse in the older group compared to the younger: 5-year OS 21% (95% CI 12–29%) vs. 41% (39–43%) ($P < 0{\cdot}0001$) and 5-year EFS 19% (11–27%) vs. 37% (34–39%) ($P < 0{\cdot}0001$). Five-year OS among those who achieved CR was also significantly worse in the older group: 30% (18–41%) vs. 44% (42–47% ($P = 0{\cdot}03$). There was a non-significant difference in RFS in the older compared to the younger group – 40% vs. 50% ($P = 0{\cdot}1$), as well as the proportion of deaths in remission at 5 years: 65% v 79% ($P = 0{\cdot}07$). Survival curves are shown in Fig 1.

Causes of death in induction without ever achieving remission were similar in both groups. Infection contributed to death in approximately 50% of the older group, compared to around 60% in younger patients ($P = 0{\cdot}2$). Infection was a contributing cause in 10 of the 17 older patients who achieved remission but died without further relapse. Only 26 of the older group underwent randomization after achieving CR, of which 13 were randomized to chemotherapy and 13 to autograft. These numbers were too small for meaningful log rank comparison.

Infections during induction

Infection rates during induction chemotherapy varied significantly between the two age groups. As shown in Table SII, the rate of reported infections was higher in the older group in phase 1 (67% vs. 45%, $P < 0{\cdot}0001$) but similar between the groups in phase 2 (59% vs. 55%, $P = 0{\cdot}6$).

Bacterial infections were the commonest infections reported, with the difference between the two age groups being much more pronounced in phase 1 (50% vs. 33%, $P = 0{\cdot}0009$). Viral and fungal infections were reported for all patients in both phases, while all except two cases of pneumocystis pneumonia (PCP) occurred in phase 2, with none at all reported in the older group.

Drug reductions during induction

There were significantly more drug reductions, omissions or delays in the older group in phase 1 (30% vs. 15%, $P = 0{\cdot}0001$), phase 2 (30% vs. 19%, $P = 0{\cdot}02$) and either phase 1 or 2 (46% vs. 28%, $P = 0{\cdot}0009$). In phase 1, the commonest recorded reason for drug reductions in both age groups was hepatotoxicity, but again the rates were significantly higher in the older age group (14% vs. 5%, $P = 0{\cdot}0001$) (Table SIII). Review of the data sheets for the older age group showed that asparaginase was the drug most commonly omitted (20 of 66 cases where a drug was specified), with liver toxicity the reason given in most cases.

Prognostic features within older group

Among disease-related factors, presenting WBC count $>50 \times 10^9$/l predicted a significantly worse outcome (5-year EFS 0% vs. 23%, $P = 0{\cdot}0005$), while immunophenotype had no effect. Ph+ was associated with a worse outcome (5-year EFS 0% vs. 22%, $P = 0{\cdot}008$) as was high *versus* standard cytogenetic risk group (5-year EFS 7% vs. 25%, $P = 0{\cdot}02$) (Table III).

Significant infections during induction chemotherapy were associated with a worse outcome, especially for those patients who had infections during both phase 1 and 2 compared to neither phase or one phase only (5-year EFS 8% vs. 39%, $P = 0{\cdot}002$).

Comparison of outcomes based on the whether significant drug reductions took place did not show a clear trend when patients who died in induction were excluded. There was no difference in EFS in those who had full dose chemotherapy compared to those who had reductions in phase 1 (5-year EFS 23% vs. 29%, $P = 0{\cdot}6$), phase 2 (33% vs. 15%, $P = 0{\cdot}1$) or both phases (32% vs. 21% phase 1 or 2 reductions vs. 25% both phase 1 and 2 reductions, $P = 0{\cdot}4$).

Table I. Patient characteristics.

Characteristic	Age		*P* value
	<55 years	≥55 years	
Number	1814	100	
Median age at entry, years (range)	30 (14–54)	56 (55–65)	
Group (%)			
MRC	1204 (66)	20 (20)	<0·0001
ECOG	610 (34)	80 (80)	
Sex (%)			
Male	1113 (61)	53 (53)	0·1
Female	701 (39)	47 (47)	
Lineage (%)			
B	1401 (77)	81 (81)	0·2
T	350 (19)	14 (14)	B *versus* T
Other/unknown	63 (3)	5 (5)	
Disease bulk (%)			
CNS disease	91 (5)	5 (5)	1·0
Lymph nodes enlarged	554 (31)	17 (17)	0·004
Splenomegaly	527 (29)	16 (16)	0·005
Hepatomegaly	305 (17)	9 (9)	0·04
Anterior mediastinal mass	158 (9)	4 (4)	0·1
Comorbidities (%)			
Creatinine raised	141 (8)	3 (3)	0·08
Bilirubin raised	246 (14)	11 (11)	0·5
AST raised	493 (27)	30 (30)	0·5
Presenting WBC (%)			
$<50 \times 10^9$/l	1334 (74)	78 (78)	0·2
$\geq 50 \times 10^9$/l	468 (26)	20 (20)	(excluding
Unknown	12 (<1)	2 (2)	missing)
Ph t(9;22)*			
All patients (%)			
Positive	247 (14)	20 (20)	0·07
Negative	1370 (76)	67 (67)	Ph+ *versus*
Unknown	197 (11)	13 (13)	Ph−/unknown
Ph t(9;22)*			
Pre-imatinib sub-study (%)			
Positive	246 (17)	20 (28)	0·02
Negative	1064 (73)	44 (62)	Ph+ *versus*
Unknown	141 (10)	7 (10)	Ph−/unknown
Other cytogenetics* (%)			
t(8;14)	18/1258 (1)	1/60 (2)	0·8
t(4;11)	74/1327 (6)	3/60 (5)	0·8
t(1;19)	28/1214 (2)	2/59 (3)	0·6
Complex	58/1213 (5)	3/59 (5)	0·9
HeH*	130/1226 (11)	6/59 (10)	0·9
HoTr*	39/1224 (3)	3/59 (5)	0·4
Cytogenetic risk group* (%)			
Standard	811 (65)	35 (54)	0·07
High	437 (35)	30 (46)	

MRC, Medical Research Council; ECOG, Eastern Cooperative Oncology Group; CNS, central nervous system; AST, aspartate transaminase; WBC, white blood cell count.

Genetic data was obtained from a mixture of cytogenetic, fluorescent *in situ* hybridization and polymerase chain reaction results. No genetic data was available in 87 cases in the younger age group and 7 in the older. In some cases the full set of cytogenetic abnormalities were not analysed, accounting for the differences in results seen.

*HeH:High hyperdiploidy (51–65 chromosomes), HoTr: Low hypodiploidy/near-triploidy, High risk cytogenetics: t(9;22)(q34;q11), t(4;11)(q21;q23), t(8;14)(q24;q32), low hypodiploidy/near-triploidy (HoTr) or complex karyotype.

Table II. Outcome by age group.

All patients			
	Age <55 years	≥55 years	*P* value
Number	1814	100	
CR* (%)	1683 (93)	73 (73)	<0·0001
No CR (%)			CR *versus*
All	131 (7)	27 (27)	no CR*
Survived induction, but no CR	61 (3)	9 (9	
Died in induction	70 (4)	18 (18)	
5-year overall survival, % (95% CI)	41 (39–43)	21 (12–29)	<0·0001
5-year event-free survival, % (95% CI)	37 (34–39)	19 (11–27)	<0·0001
5-year relapse-free survival, % (95% CI)	50 (48–53)	40 (27–53)	0·1
5-year death in remission, % (95% CI)	79 (76–81)	65 (49–81)	0·07
5-year overall survival, % (95% CI) in those who achieved CR†	44 (42–47)	30 (18–41)	0·03

CR, complete remission; CI, confidence interval.

*Those with undocumented date of CR but who continued as per protocol treatment (42 aged < 55 years and three aged ≥55 years) are assumed to have achieved remission.

†Excludes those who died in induction and those who never achieved remission.

Discussion

The MRC UKALL XII/ECOG E2993 trial included 100 patients between the ages of 55 and 65 years, representing one of the largest single cohorts of older ALL patients treated prospectively according to a standard protocol.

The CR rate in the older group was 70%, which, while significantly worse than for the younger patients treated on this protocol (91%), is similar to or better than other cohorts of this age group. The OS and EFS were also significantly reduced in the older age group – a common finding in other cohorts, although direct comparisons are made more difficult by differences in follow-up, age-group categories and censoring definitions for disease-free survival or EFS (Kantarjian *et al*, 2000; Petersdorf *et al*, 2001; Annino *et al*, 2002; Larson, 2005; Sancho *et al*, 2007; Goekbuget *et al*, 2008; O'Brien *et al*, 2008; Pullarkat *et al*, 2008). (Table IV).

The key issues addressed in this study are the reasons for the difference between younger and older patients with ALL, and whether changes in treatment strategy could improve outcomes. As shown in Fig 2, a numeric analysis of the outcomes of the patients in this group illustrates the extent of the problem. Of the 100 older patients in this trial only 20 were alive and in CR at analysis. Of the remaining 80, nine never achieved CR and although 36 did, they subsequently

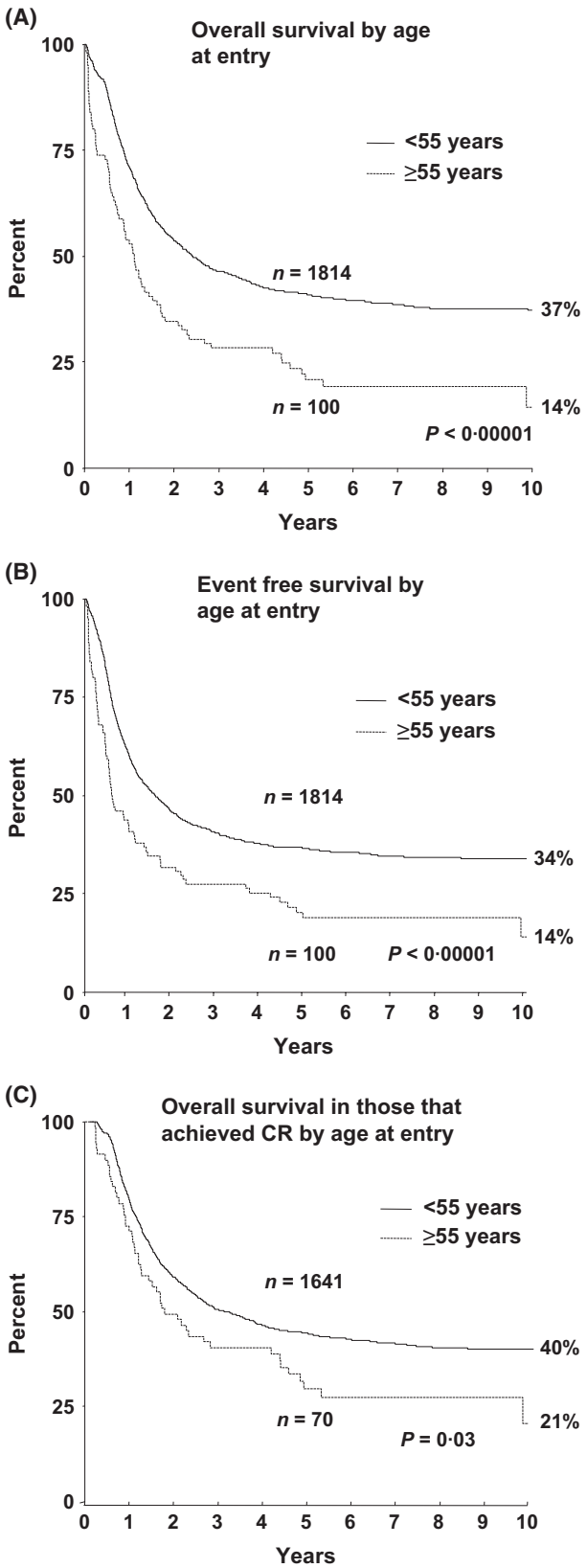

Fig 1. Survival of patients by age at entry to study showing (A) overall survival and (B) event-free survival in all patients and (C) overall survival in those who acheived complete remission.

Table III. Prognostic features within older patient group.

Variable	5-year EFS, % (95% CI)	Odds ratio (95% CI)	*P* value
Patient factors			
Sex			
Male	20 (8–31)	1·25 (0·80–1·94)	0·3
Female	18 (6–29)		
WBC			
$<50 \times 10^9$/l	23 (13–33)	3·96 (1·96–7·99)	0·0005
$\geq 50 \times 10^9$/l	0		
Immunophenotype			
B lineage	17 (8–26)	0·69 (0·39–1·24)	0·8
T lineage	36 (11–61)		
Ph (pre-imatinib study)			
Positive	0	0·38 (0·20–0·75)	0·008
Negative	22 (10–34)		
Cytogenetic risk*			
Standard	25 (10–41)	2·03 (1·15–3·59)	0·02
High	7 (0–16)		
Treatment factors			
Full dose induction phase 1			
No	22 (5–38)	0·98 (0·59–1·62)	0·9
Yes	20 (10–30)		
Full dose induction phase 2			
No	15 (0–31)	0·59 (0·31–1·13)	0·1
Yes	32 (18–46)		
Full dose induction phase 1 and 2			
Neither	25 (0–55)	0·86 (0·57–1·28)	0·4
Phase 1 or 2	21 (4–38)		
Both	31 (15–47)		
Significant infection induction phase 1			
No	34 (16–51)	1·76 (1·10–2·80)	0·02
Yes	14 (5–23)		
Significant infection induction phase 2			
No	40 (21–59)	2·00 (1·14–3·50)	0·01
Yes	17 (5–28)		
Significant infection induction phase 1 and 2			
Neither	35 (6–63)	1·70 (1·14–2·53)	0·008
Phase 1 or 2	40 (22–59)		
Both	8 (0–18)		

EFS, even-free survival; CI, confidence interval; WBC white blood cell count.

*High risk cytogenetics: t(9;22)(q34;q11), t(4;11)(q21;q23), t(8;14)(q24;q32), low hypodiploidy/near-triploidy (HoTr) or complex karyotype.

Table IV. Comparative prospective ALL trials looking at older patients.

Group and trial	Age group (years)	No.	CR rate (%)	OS (%) 2-year	3-year	5-year	8-year
MRC/ECOG UKALL12/E2993	55–65	100	70	35	28	21	19
CALGB (Cumulative*) (Larson, 2005)	>60	129	57		12		
MD Anderson Cancer Center (Kantarjian *et al*, 2000)	>60	44	79			17	
SWOG 8419 (Petersdorf *et al*, 2001)	50–84	85	41	–			
GIMEMA 0288 (Annino *et al*, 2002)	50–60	121	68				15
PETHEMA ALL96 (Sancho *et al*, 2007)	56–67	33	58	39			
SWOG 9400 (Pullarkat *et al*, 2008)	50–65	43	63			23	
EWALL (Goekbuget *et al*, 2008)	56–73	40	85	–			

MRC, Medical Research Council; ECOG, Eastern Cooperative Oncology Group; CALGB, Cancer and Leukemia Group B; SWOG. Southwestern Oncology Group; GIMEMA, Gruppo Italiano Malattie Ematologiche dell'Adulto; PETHEMA, Programa para el Estudio y Tratamiento de las Hemopatias Maligna; EWALL, European Working Group on Adult Acute Lymphoblastic Leukaemia.

*CALGB 8811, 9111, 9311, 9511, and 19802.

relapsed; all except one of these patients had died at the time of analysis. The remaining 35 patients died either during induction chemotherapy (18) or in CR (17). This population therefore is at significant risk of dying due to both a highly aggressive disease and a highly toxic treatment strategy.

At least some of the difference in outcomes is likely to be due to biological differences in the leukaemia itself. The incidence of Ph positivity was significantly higher in the older group (28% vs. 17%, $P = 0{\cdot}02$), a finding well established in other cohorts (Groupe Français de Cytogénétique Hématologique, 1996; Wetzler *et al*, 1999; Gökbuget *et al*, 2000; Thomas *et al*, 2001; Moorman *et al*, 2010). Although the combined cytogenetic risk score showed a trend towards higher risk in the older group, none of the other individual cytogenetic abnormalities showed a significant difference by age. This partly reflects the difficulty in collecting sufficient data for rarely occurring individual abnormalities, even in a large dataset. In contrast to other groups (Thomas *et al*, 2001), we found no significant difference in the presenting WBC count or immunophenotype between age groups.

The poor remission rates and longer-term outcomes are also related to issues related to toxicity of treatment. The first major point to note is the higher incidence of significant infections reported during induction in the older group. As the infection rate is a reflection of the treatment toxicity rather than underlying disease, this supports the contention that in this age group, the treatment itself contributes to the poor outcomes. Most ALL induction regimens consist of high doses of steroids (prednisolone or dexamethasone), vin-

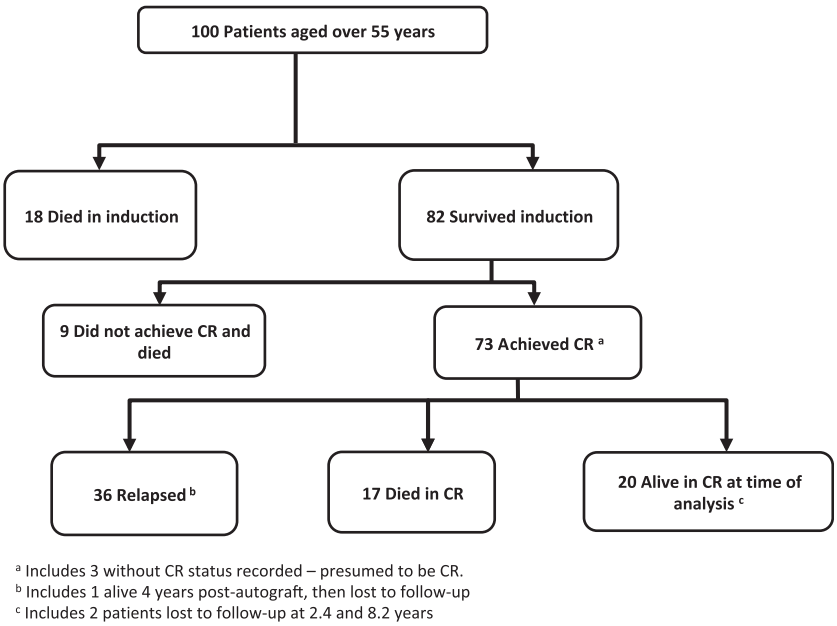

Fig 2. Patient flow diagram showing outcomes following induction in all patients aged 55 years and over.

cristine, daunorubicin and asparaginase, with later exposure to cyclophosphamide and cytarabine. The HyperCVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone) regimen does not include asparaginase (Kantarjian *et al*, 2000), and appears to have similar results in CR rates, but has not been shown to be superior to more traditional protocols.

The combination of myelosuppresssion with high dose steroids probably increases the infection risk. Over 80% of those $\geq$55 years were recorded as having a significant infection in induction, and this figure was 70% even in the younger group. By comparison, the major infection rate in induction has been estimated at 29–35% for acute myeloid leukaemia (Gardner *et al*, 2008). Within the older group, infection rates during induction had a clear prognostic correlation with EFS, even when those patients who died in induction were excluded (data not shown). Although part of the explanation for this could be the identification of those less fit patients who would be predicted to do worse, we believe that at least part of the explanation is that treatment-induced infections themselves have an impact on longer-term survival, in an already vulnerable patient group.

The second area that we examined in detail was drug reductions, delays and omissions. Here the correlation with EFS within the older groups is less clear, and a causative argument is less obvious. However the proportion of patients who had drug reductions was substantially higher in the older patient group throughout both induction phases, with 46% of the older group having some reduction in phase 1 or 2 compared to 28% in the younger group. This indicates that the induction protocol for this trial, which is fairly typical for ALL induction regimens, is too intensive for many older patients. Hepatotoxicity – a common complication in adult ALL patients undergoing induction – was an important cause of this attenuation of therapy, and the data suggest that asparaginase was poorly tolerated. Although this drug is critical to outcome, its use in the older age group requires re-evaluation.

The long recruitment time required for a trial of this size looking at a relatively uncommon disease, means that some features of the trial protocol have been superseded by the time of analysis. With regards to drug toxicity, patients on this trial were treated with daily asparaginase, which has now been effectively replaced by pegylated-asparaginase. There is less toxicity data in adults using the pegylated form of the drug, but it appears that liver toxicity remains an issue as elevated liver enzymes in 52% of cases were reported in a recent series (Rytting, 2010). The Ph+ patients reported here exclude those who were treated from 2003 (MRC) or 2004 (ECOG) on a separate substudy utilizing imatinib (Fielding *et al*, 2010). Given the efficacy and tolerability of imatinib, this drug would certainly be used in treatment protocols for older Ph+ patients.

In our analysis, we defined older patients as those between 55 and 65 years, and within this group the median age was 56 years. This demonstrates the difficulty in providing a substantial evidence base for the treatment of genuinely old patients. The conclusions that we have drawn here regarding toxicity and intolerance of standard chemotherapy, must be assumed to hold even more so for an older population. Many older patients off-protocol are treated with a less intensive regimens consisting of steroids and vincristine with or without targeted agents. These patients are presently poorly represented in the medical literature, but they almost certainly outnumber those treated with intensive approaches.

In conclusion, the poor outcomes of older patients with ALL are only partly due to differences in leukaemia biology, and an inability to tolerate intensive induction chemotherapy regimens plays a large part in the poorer outcomes. Better risk stratification based not only on age may help to identify those fitter patients who are able to manage standard therapy, and those who are less fit and should be treated less aggressively. There may be benefit in early consolidation with reduced-intensity conditioning allografts in selected patients and the use of minimal residual disease (MRD) monitoring early on to make decisions on further treatment. Combinations of less intensive protocols with targeted therapies, such as rituximab in CD20 positive disease (Thomas *et al*, 2010), nelarabine in T cell lineages (DeAngelo *et al*, 2007) and dasatinib in Ph+ disease (Rousselot *et al*, 2010), should play a larger part in these patients' management. In addition, newer agents, such as blinatumomab, appear to have the potential to eliminate MRD, with limited toxicity (Topp *et al*, 2011). Some of these questions are being addressed in prospective trials, and the coming years should allow a more subtle approach to treatment of ALL, as a disease of the old as well as the young.

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Author's contributions

J.I.S. wrote the paper. All authors contributed to the manuscript, checked the final version, and participated in data collection, study design, and coordination. G.B. and S.M.R. analysed the data. A.H.G. and J.M.R. were study chairs in the United Kingdom and United States, respectively.

Conflicts of interest

The authors declare no competing financial interests.

Supporting Information

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

Fig S1. Simplified overall schema of study.

Table SI. Induction chemotherapy schedule.

Table SII. Significant infections during induction chemotherapy.

Table SIII. Drug reductions during induction chemotherapy.

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