Prospective outcome data on 267 unselected adult patients with Philadelphia-chromosome positive acute lymphoblastic leukaemia confirms superiority of allogeneic transplant over chemotherapy in the pre-imatinib era: Results from the international ALL trial MRC UKALLXII/ECOG2993.

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Short Title: Ph pos adult ALL, UKALL12/ECOG2993

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Abstract

Prospective data on the value of allogeneic haematopoietic stem cell transplant (alloHSCT) in Philadelphia chromosome positive (Ph pos) acute lymphoblastic leukaemia (ALL) are limited. The UKALLXII/ECOG2993 study evaluated the outcome of assigning alloHSCT – with a sibling (sib) or matched unrelated donor (MUD) - to patients below the age of 55 achieving complete remission (CR). The CR rate of 267 patients, median age 40, was 82%. Twenty-eight percent of patients proceeded to alloHSCT in CR1. Age > 55 or a pre-HSCT event were the most common reasons for failure to progress to alloHSCT. At 5 years, OS was 44% following sib alloHSCT, 36% following MUD alloHSCT, and 19% following chemotherapy. After adjustment for sex, age and WBC and excluding chemotherapy-treated patients who relapsed or died before the median time to alloHSCT, only RFS remained significantly superior in the alloHSCT group (OR 0.31, CI 0.16-0.61). An intention-to-treat analysis, using the availability or not of a matched sibling donor, showed 5-year OS to be non-significantly better at 34% with a donor versus 25% with no donor. This prospective trial in adult Ph pos ALL indicates a modest but significant benefit to alloHSCT. This trial has been registered with clinicaltrials.gov under identifier NCT00002514 and as ISRCTN77346223.
Introduction

Patients with ALL in whom the Philadelphia chromosome, is detected (Ph pos) constitute the largest, molecularly-defined sub-group of approximately 25% of adults with ALL. The poor prognostic relevance of the Ph pos ALL is well-established. It has long been concluded that the outcome with standard ALL chemotherapy alone is sufficiently poor to recommend a sibling haematopoietic stem cell transplant (sib alloHSCT) in first complete remission (CR1). A recent retrospective case series from the City of Hope National Medical Centre/Stanford University, the largest study of allogeneic HSCT to date in Ph pos ALL, details the outcome of 79 patients (10 of whom were children) treated with alloHSCT in CR1 or CR2 and demonstrates that survival of 54% can be achieved in patients in CR1. However such a study is unlikely to be generally representative of all patients with Ph pos ALL and may overestimate the potential benefits of alloHSCT, due to selection bias.

The international adult ALL trial UKALLXII/ECOG E2993, initiated in 1993, was designed to evaluate the overall hypothesis that alloHSCT was the optimal therapy for adults with ALL. Patients with Ph pos ALL were assigned to a ‘high-risk’ arm, in which all eligible patients who achieved CR after standard induction were allocated to sib alloHSCT (if sibling donor available) or to matched unrelated donor HSCT (MUD HSCT). Patients without a donor or those unsuitable for alloHSCT were eligible for the autologous HSCT versus chemotherapy randomisation. In practice, very few individuals were randomised and the majority of patients not receiving alloHSCT were treated with chemotherapy alone. The present analysis reports on the results of 267 patients in the Ph pos arm of the study, diagnosed between 1993 and 2004, before the general implementation of imatinib therapy in the treatment of this disease. For more recent patients on this study, a protocol modification introduced imatinib into intensification and then later into induction, but these
patients are not reported here. This report documents the largest prospective study of patients with Ph pos ALL and is also the largest study of alloHSCT in this disease. The data set defines the limits of application and the outcome of HSCT in a real-world, multi-centre patient population with Ph pos ALL in the pre-imatinib era and provides an important baseline comparator against which the addition of newer and more targeted therapies can be evaluated.

**Methods**

**Study Eligibility**

This trial was jointly conducted by the Medical Research Council (MRC) of the United Kingdom and the Eastern Co-operative Oncology Group (ECOG) of the USA. Eligible patients were aged 15-60 years (ECOG) or 55 years (MRC) with newly diagnosed, untreated ALL and no prior malignancy. The Ethics Committee or Institutional Review Board of each participating centre approved the study. All subjects gave informed consent in accordance with the Declaration of Helsinki. There were no exclusion criteria for abnormal renal or hepatic function or poor performance status at diagnosis. All comers with a confirmed diagnosis were eligible for inclusion.

**Diagnosis**

Diagnosis of ALL was established by documenting > 25% marrow lymphoblasts. Confirmation of the diagnosis of ALL by central morphology or immunophenotyping (ECOG only) review was required in both the UK and the USA. The Philadelphia chromosome [t(9;22)(q34;q11.2)] or BCR-ABL fusion was detected by conventional cytogenetics, FISH, RT-PCR or a combination in all cases and was confirmed centrally in both the UK and USA, as previously described ².

**Treatment**

Induction phases I and II were administered as described by Goldstone et al. ¹⁰
Those patients deemed to be in haematological CR after completion of phases I and II who were aged 50 years or more, lacked a suitable allogeneic donor - or had contraindications to allogeneic transplantation - were eligible for the randomisation between autologous HSCT and continuing chemotherapy. Patients who were in remission then received intensification as previously described. After intensification, those aged less than 50 years (USA) or 55 years (UK) with a sibling donor proceeded immediately to either an HLA-identical sib alloHSCT, or MUD HSCT if no sibling donor was available. Patient awaiting transplant continued chemotherapy as per protocol. Patients randomized to autograft were also to receive their transplant at this stage. In practice, very few patients received autograft (N=7). In the early years of the protocol, bone marrow was used as a source of stem cells. Latterly, mobilized peripheral blood stem cells were recommended. Mobilization of stem cells was achieved after administering mitoxantrone 30 mg/m2 on days 1 and 2 of week 15, combined with Ara-C 2g/m2 on days 1-3 and rhuG-CSF daily.

The conditioning regimens for transplant consisted of fractionated total body irradiation (TBI) 1320 cGy in 6 fractions twice daily (days –6 to –4), along with 400 cGy testicular boost in males and high-dose etoposide 60 mg/kg IV day –3 originally proposed by Blume et al. T cell depletion was not recommended but the final decision was left to the transplant centre. Recommended graft versus host disease prophylaxis was standard cyclosporine and short course methotrexate. Response was measured at day 21 (although in many cases the day 21 result was indeterminate, due to hypocellular marrow) and at the end of phases I and II of induction, i.e. approximately days 28 and 56 since the start of induction therapy. Haematologic remission was defined as less than 5% lymphoblasts. The date of remission is taken as the date that the patient’s doctor recorded remission to the data reporting centre.
Statistical analysis

All patients were centrally registered by telephone, at the Clinical Trial Service Unit (CTSU) in Oxford for MRC patients, or at the ECOG operations office for ECOG patients. All outcomes were measured from the start of treatment. The primary outcome measure was overall survival (OS). Other outcomes analysed were (i) event free survival (EFS), defined as the time to relapse or death, (ii) relapse free survival (RFS), defined as time to relapse, excluding patients who never entered remission and censoring at death in remission, and (iii) 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 date of last contact, or 31st October 2007 if earlier.

Chi-square tests were used for comparing groups by initial characteristics. The Mann Whitney U-test was used to test for differences between remitters and non-remitters for continuous variables, and between treatment groups. Kaplan-Meier curves were used and univariate comparisons were made by the log rank method. Odds ratios (OR) were calculated and are quoted along with their 95% confidence intervals. Unless otherwise indicated, an OR of less than unity (<1) indicates a worse prognosis in the second group compared to the first group.

An intention to treat analysis on related donor transplantation was planned for the entire trial. For this, information on whether tissue typing was being carried out, and if so, whether a sibling donor was found, was prospectively collected in order to obtain an unbiased estimate of the effect of aiming to carry out a sibling donor transplant on all those with a suitable donor. For the Ph pos group the number of patients who had an unrelated donor HSCT considerably weakens this comparison, so these analyses were repeated censoring at unrelated donor transplant.

Multivariate Cox regression analysis was carried out using stepwise regression, adding variables age, WBC, gender, BCR-ABL breakpoint and cytogenetics to the model.
one at a time in order of most to least significance (as long as their p-value was <0.05).

Age and white blood count (WBC) were treated as continuous variables. Due to the high number of missing cases for central nervous system (CNS) disease at entry this was not included. Analyses were carried out on the subsets of patients with data for;

Age, WBC and gender (n=265 for OS and EFS; n=218 for RFS and death in remission)
Age, WBC, gender and CNS disease at entry (n=185 for OS and EFS; n=151 for RFS and death in remission)
Age, WBC, gender and BCR-ABL breakpoint (n=140 for OS and EFS; n=109 for RFS and death in remission)
Age, WBC, gender and cytogenetics (n=220 for OS and EFS; n=183 for RFS and death in remission)

**Results**

**Patients**

Recruitment ran from January 1993 to May 2004. Only patients registered onto the original protocol, before an amendment introduced imatinib to the therapy are included in this analysis. Out of a total of 1533 patients registered, 268 were registered as Ph pos. One patient was later excluded because of misdiagnosis. Thus a total of 267 patients are included in this report. The median follow-up in the 51 survivors is 8 years 2 months (range 3 years 2 months to 14 years 3 months). Five patients were lost to follow-up, 3 after relapse, and two cases (lost at 1 day and 2 months) are known to have later died. A further 4 patients are being followed up for survival only, with no information available on disease status, from 2 months, 3 months (n=2), and 15 months. Patient characteristics are summarised in table 1.

**Response to induction therapy**

Two hundred and sixty two of 267 patients were fully assessable for remission, since there were 5 in whom the date of remission was not known. They are assumed to
have achieved remission at some point (two relapsed, one died at 13 months and the other 2 are still alive at 6 and 7 years). Figure 1 is a flow chart, which details the outcomes of all patients in the study. 176 of 262 (67%) patients achieved remission after protocol induction therapy phases I and II. This is in contrast with 87% for those patients with Ph negative disease\(^2\). A further 39 remitted with additional (non-protocol) therapy (19 stopped induction early and 20 had not remitted by the end of phase II; remission followed transplant in 9 cases). Together with the 5 who remitted at an unknown time this gives an overall remission rate of 82%, compared with 93% for those with Ph negative disease.

There were 13 deaths during induction (5%). Nine patients died of infection alone, one of infection plus bleeding, one of infection plus necrotising enterocolitis, and one with an acute respiratory syndrome plus myocardial infarction. There was one suicide. Of the 34 further patients who did not achieve remission at any point, including 3 patients who received an allogeneic transplant (2 MUD, 1 sibling donor), all died at a median of 7 months (range 2 – 20 months).

Factors predicting for achievement of CR at any point, were age (88% CR rate in those aged under 30, 85% in age 30-49, falling to 67% in those aged ≥50 years, \(p=0.03\)) and presenting WBC (89% CR rate in WBC<30x10^9/l v 75% CR rate in WBC ≥30x10^9/l, \(p=0.005\)). There were no statistically significant differences in overall CR rate by sex, CNS disease at diagnosis or additional cytogenetic abnormalities.

Outcome by post-remission therapy.

**Survival**

The median event free survival (EFS) in all 267 Ph pos patients was 9 months and the median overall survival (OS) was 13 months. Estimated EFS at 5 years and 10 years was 17% (95%CI = 13%-22%) and 15.5% (95% CI = 11%-20%). Estimated OS at 5 and 10 years was 22% (95%CI = 17%-27%) and 18% (95% CI = 13%-23%).
Of the 220 patients who achieved remission at some point, 181 remained on protocol and were eligible for analysis of post-remission therapy (as shown in flow chart in Figure 1). Twelve patients who received non-protocol transplants were excluded from the analysis, leaving 76 patients who received a per-protocol myeloablative alloHSCT in first remission (45 with cells from a sibling and 31 with cells from a MUD). Sibling donor alloHSCT was carried out significantly earlier during therapy (median 153 days, range 79-284 days from start of therapy) than unrelated donor alloHSCT (median 191 days, range 113-276 days), p<0.0001. Eighty-six received chemotherapy alone. The reasons for these patients not receiving a transplant are shown in the flow chart in figure 1. Among those receiving transplant, there was no statistically significant difference between patients receiving MUD and sib alloHSCT in terms of age, gender, WBC, CNS disease at diagnosis or additional cytogenetic abnormalities. Only seven patients were treated with autologous transplantation, too few to carry out meaningful analysis.

Comparison of chemotherapy and alloHSCT

For those who achieved remission on protocol, the outcome of patients who received transplant was compared with the outcome of those who received chemotherapy. Only 82 of the 86 chemotherapy-treated patients who remained in remission at 12 weeks, which was the scheduled time for transplant, were included in the comparative analysis. Table 2 shows the outcomes, OS, RFS, EFS and survival free from death in remission by treatment received and Figure 2 illustrates OS by treatment received. At 5 years OS was 44% for siballoHSCT, 36% for MUD alloHSCT, and 19% for chemotherapy, respectively. At 10 years, OS was 39% for sib alloHSCT, 31% for MUD alloHSCT, and 13% for chemotherapy, respectively.

The difference in outcome between sib alloHSCT and MUD alloHSCT groups was not statistically significant, but this may be due to the small numbers involved in the analysis. Sib alloHSCT had a non-significant 9% higher actuarial relapse risk at 5 years
than MUD alloHSCT, but MUD alloHSCT had a non-significant 20% higher actuarial risk of
death in remission at 5 years. Comparing the outcome after any alloHSCT with the
outcome after chemotherapy alone, OS (p=0.0002), EFS (<0.0001) and RFS (<0.0001)
were all significantly superior for patients receiving any alloHSCT over those receiving
chemotherapy alone. There was a marked difference in the cause of death between
alloHSCT and chemotherapy recipients. Whereas the leading cause of death in
chemotherapy-treated patients was relapse, the leading cause of death after transplant
was treatment related mortality (TRM), which was 27% after sib HSCT and 39% after MUD
HSCT.

As expected, the groups receiving alloHSCT and chemotherapy differed
significantly from each other in age (Mann Whitney U-test p = 0.004) with a preponderance
of older patients among the patients treated with chemotherapy. Ninety five percent of
patients who received alloHSCT were aged <50 years (72/76) compared to 77% (63/82) of
the chemotherapy patients. This clear selection bias is explained by both the upper age-
limit for HSCT years and the relative increase in contraindications to HSCT in older
patients. There was also a significant difference in presenting WBC between the groups,
with those receiving alloHSCT tending to have lower presenting WBC than those receiving
chemotherapy (Mann Whitney U test p = 0.007). There is no obvious explanation for this
difference, but it might reflect the fact that patients with lower presenting WBC were more
likely to enter CR and progress to alloHSCT, or the fact that patients with high presenting
WBC were more likely to relapse prior to HSCT or that an association between WBC and
some other, unknown, factor exists. There was no significant difference between the
groups by gender, CNS disease at presentation or additional cytogenetic abnormalities.

Although chemotherapy-treated patients who relapsed or died before the 12 week
transplant schedule date were excluded from the previous analysis, an additional 32
chemotherapy patients relapsed or died before the median time to alloHSCT (day 160)
whereas none relapsed within this time frame in the HSCT arm. In order to take as many known differences between the groups into account as possible, the data were re-analysed, adjusting for sex, age and WBC and excluding chemotherapy-treated patients who relapsed or died before the median time to alloHSCT. RFS remained significantly superior in the HSCT group as compared to the chemotherapy group (unadjusted OR 0.17 (0.11-0.26), adjusted OR 0.31 (0.16-0.61)). However, following adjustment, the difference in TRM between those receiving alloHSCT and those receiving chemotherapy alone reached significance (unadjusted OR 1.54 (0.69-3.45), adjusted OR 6.22 (1.98-19.56)). As a consequence, there was no longer a significant difference in OS (unadjusted OR 0.48 (0.33-0.69), adjusted OR 1.31 (0.73-2.35)) or EFS (unadjusted OR 0.27 (0.19-0.40), adjusted OR 0.67 (0.37-1.19)) between the two groups.

Since analyses by treatment received are potentially biased, we also carried out an intention-to-treat analysis, using the availability or not of a matched related sibling donor. Information on sibling donor availability was available for 158 patients (see flow chart, Figure 1). Figure 3 shows the Kaplan Meier survival analysis of the sib donor vs. no sib donor analysis. OS was non-significantly better (OR 0.80 (0.55-1.15), p=0.2) for the group with a sibling donor. At 5 years, OS was 34% (95% CI = 24-45%) with a sibling donor, and 25% (95% CI = 15-34%) without a sibling donor. At 10 years, OS was 30% (95% CI = 19%-40%) and 19.5% (95% CI = 10% - 29%) for these groups.

Since a substantial proportion of patients in the no sibling donor group received a MUD or mismatched HSCT (30 full intensity and 3 non-myeloablative), this analysis was repeated, but censoring at MUD/mismatched and non-myeloablative HSCT. This slightly increased the difference between the groups, with an OR of 0.74 (0.50-1.11), 5 year survival at 36% (95% CI = 25-46%) for the sibling donor group and 23% (95% CI = 12-34%) for the no donor group. Although not statistically significant, these results suggest that the apparent
superiority of sib HSCT over chemotherapy partly truly reflects an inherent - though moderate - superiority of HSCT, and is not entirely due to selection bias.

Prognostic factors for outcome

Effect of graft versus host disease

In order to assess the contribution of a graft-versus-leukaemia (GvL) effect to the superior EFS and RFS seen after HSCT, we analysed the relationship between graft-versus-host disease (GvHD) and outcome in patients who achieved remission on protocol. Acute GvHD of any grade was reported in 29 of the 45 sib HSCTs (6 patients had grade 3/4 GvHD) and 15 of the 31 MUD HSCTs (2 patients had grade 3/4 GvHD). The occurrence of GvHD was unknown in 7 sib and 5 MUD HSCTs, respectively. We examined relapses and deaths in remission by the presence or absence of GvHD. The data are shown in table 3. There were significantly more relapses at 5 years from HSCT in the absence of GvHD (65%, 95% CI 43-87%), than in the presence of any grade of acute GvHD, (32%, 95% CI 15-49%) (Log rank p=0.01), There was also an apparent increase in deaths in remission (14% (95% CI 0-32%) at 5 years in the absence of GvHD versus 43% (95% CI 27-59%) in the presence of GvHD but this was not statistically significant (p=0.2). There was no significant difference in EFS.
**Impact of additional cytogenetic abnormalities and BCR breakpoint**

The impact of additional chromosome abnormalities and BCR breakpoint on OS, EFS, RFS and death in remission were examined by univariate analysis (Table 4). Both an extra Ph chromosome [+der(22)] and high hyperdiploidy (HeH) were associated with a significantly better RFS. It should be noted that 25/28 (89%) cases with HeH also had +der(22). The RFS results were broadly consistent with the effects seen on OS and EFS but these did not reach statistical significance. BCR breakpoint was a marginally significant prognostic factor for RFS and del(9p) had worse RFS but this was not reflected in OS.

**Other factors affecting outcome**

Presenting WBC was significant for all endpoints, with a worse prognosis with increasing WBC (p<0.0001 for OS, EFS and RFS; p=0.05 for death in remission) in this group of 267 Ph positive patients. Increasing age corresponded to increasingly worse prognosis for OS (p=0.005) and death in remission (p=0.03) but was only marginally significant for EFS (p=0.06) and was not significant for RFS (p>0.1). Gender and CNS disease at presentation were not found to be statistically significant. The source of stem cells for transplant was not routinely collected but the majority of transplants in the first half of the study would have been bone marrow whereas peripheral blood was more common in the second half of the trial. Analysis of outcome by era of transplant (first versus second half of study) did not show any statistically significant differences.

**Multivariate analysis**

By multivariate analysis, age and presenting white cell count were prognostic factors for several outcome measures as shown in table 5. As most HeH cases also had +der(22) only the latter was considered in the multivariate model. The existence of +der(22) remained prognostic for better RFS, whilst del(9p) was still significant for a poorer
RFS. BCR breakpoint and CNS disease at diagnosis were not statistically significant on multivariate analysis.

Discussion

This is the largest prospective study of Ph pos ALL. The data confirm the generally poor outcome for patients with Ph pos ALL with an overall CR rate of 82%, considerably less than in Ph neg disease. The need for a 3rd course of induction therapy to achieve remission in 20 patients is consistent with the data reported from the LALA94 study in which the corresponding figure was 18% \(^6\). The OS was 22 % at 5 years. These remission and survival figures are entirely consistent with previously published, smaller studies \(^{13,4,6}\). The factors predicting achievement of CR in our study were age and presenting white cell count.

The first striking finding is the number of patients (76 of the 267, 28%) who actually received the proposed HSCT. The reasons for patients not receiving HSCT were, in the majority of cases, either being beyond the age limits or having an early event which prevented transplant (even where a donor was available). In some cases patient or physician choice was the reason given. ‘Lack of donor availability’ was also common - our understanding of this situation is not precise, since in some cases tissue typing was not carried out in cases where this is given as a reason, which may indicate no sibling, were available but does not explain why an unrelated donor was not sought. However, since this was a multi-centre international study, the low transplant rate was unlikely to have been due to individual physician or national bias and likely represents a realistic assessment of the therapeutic milieu in Ph pos ALL. The relevance of such a low transplant rate in a prospective study of Ph pos ALL is two-fold. First, it sets the valuable results from transplant-only series into a more realistic context by supplying a denominator, which can illuminate the potential magnitude of the selection bias, which can
occur in such studies. Second, these data provide an international transplant rate baseline, against which studies of novel induction therapies including tyrosine kinase inhibitors can be evaluated.

Despite the low transplant rate overall, sufficient numbers of patients received transplant to enable comparisons between outcomes of those who received HSCT and chemotherapy. Adjusting as far as possible to allow for the selection bias favouring the receipt of transplant by adjusting for sex, age and presenting WBC as well as excluding chemotherapy-treated patients who relapsed or died before the median time to HSCT (160 days), RFS remained significantly superior in the HSCT group as compared to the chemotherapy group (p=0.0007) but the difference in TRM between the groups became statistically significant, so that the odds ratio for OS changed from 0.48 95% CI (0.33-0.69) unadjusted (i.e. OS significantly better in the HSCT group) to an adjusted figure of 1.31 95% CI (0.73-2.35) i.e. OS non-significantly worse in the HSCT group This suggests that the advantage of HSCT over chemotherapy alone in terms of relapse must be carefully weighed up against the disadvantage in terms of TRM. This finding is consistent with high TRM in high-risk Ph negative patients on the UKALLXII/ECOG2993 study. The only factor clearly associated with the high TRM in the high-risk group was older age.10

The adoption of MUD HSCT in this study paradoxically provides a barrier to assessing the true role of HSCT, since the sibling donor vs. no donor analysis is complicated by the fact that those with no sibling donor can also receive alloHSCT, considerably weakening the power of this analysis to demonstrate the true role of alloHSCT. With this in mind, it is not surprising that the sib donor vs. no donor analysis of this study did not demonstrate a statistically significant advantage to HSCT, However despite the limitations of the analysis in this context, the data shown in figure 4 show a trend towards a survival advantage for the ‘sib donor’ arm which is entirely consistent with the hypothesis that HSCT provides a survival advantage in Ph pos ALL in adults. Hence
our data support and extend previous “transplant-only” studies 9,14-18 and are consistent with the conclusions of LALA94 6. Peri-transplant care remains an important area to focus on, with a view to reducing post transplant TRM. It is a possibility that reduced intensity conditioned transplant 19 may benefit the older individuals at highest risk of TRM but the benefit of this procedure for Ph pos ALL remains untested in prospective study.

As confirmation of the therapeutic relevance of the graft versus leukaemia effect in this disease, the occurrence of any acute GvHD was associated with a significant reduction in relapse, although unsurprisingly, a concomitant significant increase in death in remission was seen when GvHD was reported. Overall, EFS was better in the presence of GvHD but this difference was not statistically significant. This contrasts with the findings of Laport et al. 9 in whose study acute GVHD was associated with less good OS and EFS. One speculative explanation for this difference may be that the widespread use of CAMPATH (alemtuzumab) in conditioning regimens in the UK cohort was a possible limiting factor in the severity of acute GvHD only 8 of 41 (20%) of patients with acute GvHD level recorded had level 3 or 4 GvHD. We did not collect sufficient data on CAMPATH administration to formally test this hypothesis. Similarly, chronic GvHD was not sufficiently well documented to assess an effect.

In concordance with our previous analysis we found that none of the additional chromosomal abnormalities impacted on EFS or OS. 2 However, this more extensive analysis revealed that patients with +der(22) or del(9p) impacted on RFS. We found that patients with +der(22) had a lower risk of relapse which is in contrast to previous studies by CALGB 20 and the Japanese Adult Leukaemia Study Group (JALSG). 21 However, both these studies were based on fewer patients and neither result was confirmed by multivariate analysis. In our study, virtually all HeH patients also had +der(22). Therefore it was not surprising that univariate analysis of HeH also showed a reduced RFS. HeH is known to confer a good prognosis when it occurs alone 2 and it has been hypothesised to
improve outcome when co-existing with t(9;22).\textsuperscript{22} We observed that patients with del(9p) had a increased risk of relapse which is in agreement with the recent JALSG study.\textsuperscript{21} Deletions of 9p, which are a surrogate marker for \textit{CDKN2A} deletions, occur in all cytogenetic subgroups at varying frequencies and their prognostic relevance has yet to be firmly established \textsuperscript{23}. It is noteworthy that, in similarity to the present study, other investigators observed differences in RFS only and not on other outcome measures. The therapeutic relevance of these additional chromosome abnormalities is not clear, but since the chromosome abnormalities in the JALSG study retained their poor prognostic significance in an entirely imatinib-treated cohort, it is tempting to speculate that knowledge of these cytogenetic abnormalities and further investigation of their pathological significance could contribute to a possible therapeutic stratification of adult Ph pos ALL in the future.

In summary the UKALLXII/ECOG2993 study demonstrates the prognostic relevance of additional chromosome abnormalities in Ph pos ALL. We also show for the first time in an unselected cohort, that alloHSCT, using either a sibling, or a matched unrelated donor, may be a better treatment for Ph pos ALL than conventional chemotherapy alone. However, TRM remains a significant problem. The data provide an important baseline against which developments in HSCT technology and promising novel therapies with tyrosine kinase inhibitors\textsuperscript{24-27} can be evaluated.

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\textbf{Authorship:} AKF wrote the paper. All contributed to writing the paper and checked the final version. All authors participated in data collection, study design and co-ordination. SMR and GB controlled and analyzed data. AVM, EP, GD and LF supervised cytogenetic
or molecular diagnosis or review. AHG and JMR were study chairs in the UK and USA respectively. The authors have no conflicts of interest to declare.

We thank all participating centers, physicians and patients. A list of the participating centers of the United Kingdom Medical Research Council Adult Leukemia Working Party and Eastern Cooperative Oncology Group can be found in the appendix.
References


Table 1: Patient characteristics at diagnosis

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<td>&lt;30</td>
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<td>≥30</td>
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<td>Median (range)</td>
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</tr>
<tr>
<td>BCR breakpoint: (124 unknown)</td>
<td></td>
</tr>
<tr>
<td>Major</td>
<td>42 (29)</td>
</tr>
<tr>
<td>Minor</td>
<td>100 (70)</td>
</tr>
<tr>
<td>Both</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Additional cytogenetic abnormalities: (46 unknown)</td>
<td></td>
</tr>
<tr>
<td>Extra Ph chromosome [+der(22)]</td>
<td>49 (22)</td>
</tr>
<tr>
<td>-7</td>
<td>31 (14)</td>
</tr>
<tr>
<td>+8</td>
<td>24 (11)</td>
</tr>
<tr>
<td>del(9p)</td>
<td>24 (11)</td>
</tr>
<tr>
<td>High Hyperdiploidy (HeH)</td>
<td>28 (13)</td>
</tr>
<tr>
<td>t(4;11), t(1;19), t(8;14) or HoTr</td>
<td>0</td>
</tr>
</tbody>
</table>

* 115 cases were positive by cytogenetics and RT-PCR; 47 by RT-PCR alone; 45 by all three methods; 29 by cytogenetic alone; 17 by cytogenetics and FISH; 12 by RT-PCR and FISH; and 2 by FISH alone.
Table 2. Outcome at 5-years (95% CI) by treatment received, excluding those who did not achieve remission on protocol and chemotherapy-treated patients in whom treatment failed within 12 weeks.

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Sib alloHSCT (n=45)</th>
<th>MUD alloHSCT (n=31)</th>
<th>Chemo (n=82)</th>
<th>Auto (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>% event-free at 5y (CI)</td>
<td>Events</td>
<td>% event-free at 5y (CI)</td>
</tr>
<tr>
<td>Survival</td>
<td>27</td>
<td>44% (29-59%)</td>
<td>21</td>
<td>36% (19-52%)</td>
</tr>
<tr>
<td>Event free survival</td>
<td>27</td>
<td>41% (27-56%)</td>
<td>21</td>
<td>36% (19-52%)</td>
</tr>
<tr>
<td>*Relapse free survival</td>
<td>15</td>
<td>57% (40-73%)</td>
<td>9</td>
<td>66% (48-85%)</td>
</tr>
<tr>
<td>*Survival free from death in remission</td>
<td>12</td>
<td>73% (59-87%)</td>
<td>12</td>
<td>53% (33-74%)</td>
</tr>
</tbody>
</table>

* Actuarial survivals. For relapse, a relapse is counted as an event and times are censored at death in remission; for death in remission, relapses are censored and death in remission is counted as an event.
Table 3. Relationship between acute graft versus host disease and outcome in patients who achieved remission on protocol and went on to receive an HSCT in first remission

<table>
<thead>
<tr>
<th></th>
<th>GVHD</th>
<th>Odds ratio * (95% CI), log rank p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Number of patients</td>
<td>44</td>
<td>20</td>
</tr>
<tr>
<td>Relapses</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>Deaths in remission (TRM)</td>
<td>17</td>
<td>3</td>
</tr>
<tr>
<td>Any event</td>
<td>27</td>
<td>15</td>
</tr>
<tr>
<td>Actuarial risk of relapse at 5 years (95% CI)</td>
<td>32% (15-49%)</td>
<td>65% (43-87%)</td>
</tr>
<tr>
<td>Actuarial risk of TRM at 5 years (95% CI)</td>
<td>43% (27-59%)</td>
<td>14% (0-32%)</td>
</tr>
<tr>
<td>Actuarial risk of any event at 5 years (95% CI)</td>
<td>62% (47-76%)</td>
<td>70% (50-90%)</td>
</tr>
</tbody>
</table>

* Odds ratio >1 indicates an increased risk of the observed event in the absence of GVHD
Table 4.
Relationship between additional chromosome abnormalities, BCR breakpoint and outcome

<table>
<thead>
<tr>
<th></th>
<th>Death</th>
<th>Any event</th>
<th>Relapse</th>
<th>Death in CR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds ratio, 95% CI, P</td>
<td>Odds ratio, 95% CI, P</td>
<td>Odds ratio, 95% CI, P</td>
<td>Odds ratio, 95% CI, P</td>
</tr>
<tr>
<td>BCR breakpoint (minor v major)</td>
<td>1.22 (0.82-1.83), &gt;0.1</td>
<td>1.31 (0.88-1.96), &gt;0.1</td>
<td>1.78 (1.03-3.08), <strong>0.05</strong></td>
<td>0.77 (0.31-1.94), &gt;0.1</td>
</tr>
<tr>
<td>Extra Ph chromosome [+der(22)]</td>
<td>0.82 (0.58-1.16), &gt;0.1</td>
<td>0.77 (0.55-1.07), &gt;0.1</td>
<td>0.64 (0.42-0.99), <strong>0.04</strong></td>
<td>1.38 (0.70-2.72), &gt;0.1</td>
</tr>
<tr>
<td>HeH</td>
<td>0.72 (0.47-1.08), &gt;0.1</td>
<td>0.69 (0.46-1.03), 0.06</td>
<td>0.55 (0.33-0.91), <strong>0.01</strong></td>
<td>1.29 (0.58-2.85), &gt;0.1</td>
</tr>
<tr>
<td>-7</td>
<td>1.11 (0.72-1.70), &gt;0.1</td>
<td>1.10 (0.72-1.66), &gt;0.1</td>
<td>1.06 (0.60-1.89), &gt;0.1</td>
<td>1.37 (0.56-3.38), &gt;0.1</td>
</tr>
<tr>
<td>+8</td>
<td>0.72 (0.46-1.12), &gt;0.1</td>
<td>0.72 (0.47-1.11), &gt;0.1</td>
<td>0.76 (0.44-1.34), &gt;0.1</td>
<td>0.69 (0.29-1.67), &gt;0.1</td>
</tr>
<tr>
<td>del(9p)</td>
<td>0.92 (0.58-1.45), &gt;0.1</td>
<td>1.40 (0.84-2.34), &gt;0.1</td>
<td>2.45 (1.27-4.72), <strong>0.01</strong></td>
<td>0.59 (0.21-1.71), &gt;0.1</td>
</tr>
</tbody>
</table>

An odds ratio >1 indicates an increased risk of the event observed in relationship to the presence of the particular chromosome abnormality studied. In the case of major BCR breakpoint, the comparator is to minor breakpoint. Statistically significant P values are listed in bolded type face.
Table 5
Multivariate analysis of prognostic factors

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>Death</th>
<th>Any event</th>
<th>Relapse</th>
<th>Death in CR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>WBC at presentation</td>
<td>1.004 (1.002 – 1.005)</td>
<td>1.003 (1.001 – 1.004)</td>
<td>1.004 (1.002 – 1.006)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.0002</td>
<td>NS</td>
</tr>
<tr>
<td>Age</td>
<td>1.02 (1.007 – 1.034)</td>
<td>1.013 (1.000 – 1.025)</td>
<td>NS</td>
<td>1.032 (1.005 – 1.061)</td>
</tr>
<tr>
<td></td>
<td>0.002</td>
<td>0.04</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Extra Ph chromosome</td>
<td>NS</td>
<td>NS</td>
<td>0.569 (0.342-0.946)</td>
<td>NS</td>
</tr>
<tr>
<td>[+der(22)]</td>
<td></td>
<td></td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>del(9p)</td>
<td>NS</td>
<td>NS</td>
<td>1.742 (1.036-2.928)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.04</td>
<td></td>
</tr>
</tbody>
</table>

HR: hazard ratio, CI: confidence interval, NS: not significant,

Hazard ratio >1 unity indicates increased risk of the event in relationship to the characteristic studied.
**Figure legends**

Figure 1. Flow chart showing all patients and treatments received

Figure 2. Kaplan Meier plot of Overall Survival by treatment received. Patients who failed to achieve remission on protocol and chemotherapy-treated patients who relapsed or died within 12 weeks of the start of treatment (the scheduled time for transplant) are excluded from the analysis.

Figure 3. Kaplan Meier plot of Overall Survival by availability of sibling donor among those in whom tissue typing was carried out and reported.
267 recruited.

262 assessable

215 remitted at known date
170 in remission on protocol <56 days
6 in remission on protocol >56 days
*39 achieved remission with either additional non-protocol induction therapy OR post-transplant

220 achieved remission

181 available for on-protocol Therapy

169 Continued On Protocol Therapy
45 sib allo

12 non-protocol transplant:
4 mismatched related
1 syngeneic
1 cord blood-MUD
3 mini-sib allo
2 mini-MUD allo
1 mini-haplo

Donor vs no donor analysis: 158 tissue typing results available

81 sib donor
44 sib allo,
1 MUD,
2 mismatch siballo
3 mini-siballo
31 chemotherapy

77 no sib donor:
38 chemo,
29 MUD,
6 autograft
1 mismatchedsibHSCT
2 mini-MUD
1 mini-haplo

Reasons for chemotherapy alone N= 86
19 aged >50
37 relapsed before the median time to transplant
45 no sib donor
2 donor status unknown

5 remitted, but date unknown.

13 died in induction.
34 failed to achieve remission incl 3 transplanted (1 MFD, 2 MUD).

*39 off protocol in induction or before remission, including 9 transplanted in failed remission (6 sib, 1 mini-sib, 1 MUD, 1 mismatched related)
Figure 2

At risk:

- Sib allo HSCT: 45, 35, 29, 25, 19, 18
- MUD allo HSCT: 31, 23, 12, 12, 11, 11
- Chemotherapy: 82, 43, 23, 19, 15, 12

TIME IN YEARS

PERCENT

Sib allo HSCT 44%
MUD allo HSCT 35%
Chemotherapy 19%
Figure 3

At risk:

<table>
<thead>
<tr>
<th></th>
<th>No donor</th>
<th>Donor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time in Years</td>
<td>52</td>
<td>52</td>
</tr>
<tr>
<td>0-1</td>
<td>26</td>
<td>39</td>
</tr>
<tr>
<td>1-2</td>
<td>22</td>
<td>33</td>
</tr>
<tr>
<td>2-3</td>
<td>19</td>
<td>27</td>
</tr>
<tr>
<td>3-4</td>
<td>18</td>
<td>24</td>
</tr>
</tbody>
</table>

PERCENT

TIME IN YEARS

Donor: 34%
No donor: 25%
Prospective outcome data on 267 unselected adult patients with Philadelphia-chromosome positive acute lymphoblastic leukaemia confirms superiority of allogeneic transplant over chemotherapy in the pre-imatinib era: Results from the international ALL trial MRC UKALLXII/ECOG2993