In Adults with Standard-Risk Acute Lymphoblastic Leukemia (ALL) the Greatest Benefit is Achieved from a Matched Sibling Allogeneic Transplant in First Complete Remission (CR) and an Autologous Transplant is less Effective than Conventional Consolidation/Maintenance Chemotherapy in All Patients: Final Results of the International ALL Trial (MRC UKALL XII/ECOG E2993)

Anthony H. Goldstone¹, Susan M. Richards², Hillard M. Lazarus³, Martin S. Tallman⁴, Georgina Buck², Adele K. Fielding⁵, Alan K. Burnet⁶, Raj Chopra⁶, Peter H. Wiernik⁸, Letizia Foroni⁵, Elisabeth Paietta⁸, Mark R. Litzow⁹, David I. Marks¹⁰, Jill Durrant⁷, Andrew McMillan¹¹, Ian M. Franklin¹², Selina Luger¹³, Niculae Ciobanu¹⁴, Jacob M. Rowe¹⁵.

1. UCL Hospitals, London, UK
2. Clinical Trial Service Unit, Oxford, UK
3. Ireland Cancer Center, University Hospitals of Cleveland, Cleveland, USA
4. Northwestern University Feinberg School of Medicine, Chicago, IL, US
5. Royal Free & University College Medical School, London, UK
6. University of Wales, Cardiff, UK
7. Christie NHS Trust Hospital, Manchester, UK
8. Our Lady of Mercy Cancer Center, New York Medical College, Bronx, New York, USA
9. Mayo Clinic College of Medicine, Rochester, MN, USA
10. Bristol Haematology & Oncology Centre, Bristol, UK
11. Nottingham University, Nottingham, United Kingdom
12. University of Glasgow, National Blood Transfusion Service, Glasgow, Scotland
13. Department of Haematology/Oncology, University of Pennsylvania, USA.
14. Stem Cell Sciences, Inc., New York, NY, USA
15. Rambam Medical Center and Technion, Israel Institute of Technology, Haifa, Israel

Short title: ALL: allogeneic transplant, autologous transplant, chemotherapy

Corresponding Author:
Prof. Anthony H. Goldstone
Director of Services
North London Cancer Network
UCLH
6th floor Rosenheim Wing
25 Grafton Way
London WC1 E 6DB
UK

Fax: 44-207-380-9153
Tel: 44-207-380-9983
E-mail: anthony.goldstone@uclh.nhs.uk

Copyright © 2007 American Society of Hematology
Abstract

An international collaboration was set up to prospectively evaluate the role of allogeneic transplantation for adults with ALL and compare autologous transplantation with standard chemotherapy. Patients received 2 phases of induction and, if in remission, were assigned to allogeneic transplantation if they had a compatible sibling donor. Other patients were randomized to chemotherapy for 2.5 years versus an autologous transplant.

A donor versus no donor analysis showed that Philadelphia chromosome-negative patients with a donor had a 5-year improved overall survival (OS), 53% versus 45% (p = .01) and the relapse rate was significantly lower (p = <.0001). The survival difference was significant in standard risk patients, but not in high-risk patients with a high non-relapse mortality rate in the high risk donor group. Patients randomized to chemotherapy had a higher 5-year OS, 46% than those randomized to autologous transplant, 37% (p = .03).

Matched related allogeneic transplants for ALL in first complete remission provide the most potent anti-leukemic therapy and considerable survival benefit for standard-risk patients. However, the transplant-related mortality for high-risk older patients was unacceptably high and abrogated the reduction in relapse risk. There is no evidence that a single autologous transplant can replace consolidation/maintenance in any risk group. This study is registered at [http://clinicaltrials.gov](http://clinicaltrials.gov) as NCT00002514.
Introduction

Treatment of ALL has improved enormously in the last 40 years particularly in children where a long-term survival of 80% is now achieved. Adults have fared much less well, the survival in the best series may not even reach 35 to 40% for those younger than 60 years and less than 10% for those older than 60 years.

For adults two separate approaches have been constructed, transplant based studies and attempts to optimise chemotherapy, reserving transplant only for patients with the Philadelphia chromosome.

The putative factors defining individual patients as “high risk” in adult ALL are numerous and include age, particularly over 35 years, elevated white cell count (WBC) which may well differ in relation to a “high risk” threshold between B and T Cell ALL, cytogenetics, and the presence or absence minimal residual disease (MRD) at particular points in the early phases of treatment. Molecular complete remission (CR) rates currently achieved may be as low as 60%.

The low incidence of the adult disease has meant that to study adequate numbers of patients collaboration by large co-operative groups is required.

In 1993 collaboration from the UK Medical Research Council (MRC) and the Eastern Cooperative Oncology Group of the USA (ECOG) developed a large study to ask two fundamental questions in this disease.
1. Given that the graft versus leukaemia effect (GvL) was first described in adult ALL and given published data supporting allogeneic transplant in CRI for Ph+ve and other high risk patients, could the allogeneic effect improve the outcome for all suitable adult patients?

2. Given the fact that protracted consolidation/maintenance therapy has been the mainstay of treatment for ALL, based on data mostly extrapolated from paediatric experience, could a single autologous transplant be at least as effective?

The design of the study was that all adult patients with a matched sibling donor would receive an allogeneic transplant whilst those without would be randomised to an autologous transplant versus consolidation maintenance/chemotherapy. The study design has been previously described in detail and the simplified outline is shown in Fig 1a.

Statistics

The target recruitment was based on 550 patients randomized, giving 95% power to detect an absolute difference of 15% in event free survival (EFS) between autologous transplant and chemotherapy. The randomization rate was lower than anticipated, and in 2006 the coordinators asked for disclosure of the results in order to plan the next trial. As the recruitment period had already been extended, the Steering Committee, in ignorance of the results, agreed to close the trial.

All patients were centrally registered at the Clinical Trial Service Unit in Oxford, for MRC patients, or at the ECOG operations office for ECOG patients. Randomization between
autograft and chemotherapy was done at these two centres, with minimisation (MRC) used to balance over sex, age (<20, 20-29, 40-49, 50+), WBC (<10, 10-49, 50+) and Ph status, or balanced blocks (ECOG) within strata by age (<50, 50+), time to remission (<4 weeks, >4 weeks) and Ph status.

The primary outcome measure was OS. Other outcomes analyzed were (i) EFS, defined as the time to relapse or death, (ii) relapse rate, and (iii) non-relapse mortality, defined as time to death censored at relapse. Kaplan-Meier curves were used and all treatment comparisons were by intention to treat. Comparisons between autologous transplant and chemotherapy were made by the logrank method. All event times were measured from the diagnosis, or from randomisation for the randomised comparison of autologous transplant and chemotherapy.

The comparison between those with versus those without a matched related donor was used as an unbiased assessment of the effect of matched related donor transplant. This comparison included only patients less than 50 or 55 years, commensurate with the upper age limit for related donor transplant. Differences between the Kaplan-Meier curves at 5 years were tested with a chi-square test. All p-values are two-sided. Subgroup analysis has been performed for risk groups based on reports from other trials and interim prognostic factor analyses from this trial27.

**Patients and Methods**

The trial recruited between 1993 and 2006. All patients from 15 to 59 years of age with newly diagnosed ALL, including Ph-positive, received identical induction therapy, irrespective of risk assessment, including central nervous system (CNS) prophylaxis and treatment of CNS disease, if present at diagnosis. In 2003 the upper age of the study was
raised to 64 years and for an allogeneic transplant was raised to 54 from 49 years. All patients who had an HLA-matched sibling donor were assigned to receive an allogeneic transplant. Patients with the Philadelphia chromosome could also receive a matched unrelated donor transplant. Those who did not have an HLA-matched sibling donor, or were over age 50 or (later) 55 years, were randomized to receive a single autologous transplant or consolidation/maintenance therapy. Prior to receiving the assigned or randomized therapy all patients received intensification with high-dose methotrexate. In this study patients over the age of 35 years or those with a high WBC count at presentation ($\geq 100 \times 10^9$/l for B-lineage and $\geq 30 \times 10^9$/l for T-lineage) along with all patients with the Philadelphia chromosome were deemed to be high risk. All the others were classified as “standard risk”. Time to remission was not an independent risk factor in this study\textsuperscript{27}. The study was approved by the relevant Institutional Review Boards of each centre and informed consent was given according to the Declaration of Helsinki. The precise details of the study regimen have been previously reported\textsuperscript{27}.

**Results**

A total of 1929 patients were registered to this study of whom 16 were excluded as misdiagnoses (Fig. 1b). The median follow-up is 4 years 11 months (1 month -13 years 11 months).

**Overall survival.**

The OS of all 1913 patients at 5 years was 39\% (Fig. 2a); it was 43\% for patients who were Ph-negative (Fig. 2b) and there was no difference in survival between patients
entered through MRC or ECOG (Fig. 2c). Details of the Ph positive patients have been presented and are being published separately.

**Donor vs No Donor analysis for Philadelphia chromosome-negative patients**

Figure 1b is a flowchart of patients in the study. Of the 1646 Ph-negative patients there were 1351 patients who were <50 or <55 years and achieved a complete remission on protocol. In 1031 patients HLA-typing information was available. Figure 2d demonstrates the overall survival benefit when all patients on study are included in this analysis with a 5-year survival of 53% (95% CI=48-58%) for patients with a donor versus 45% (95% CI=40-49%) for patients without a donor (p = .01). Patients at high risk had an OS of 41% versus 35% for donor versus no donor, respectively, which was not significantly different (p = .2) (Fig. 2e); however, the OS was significantly improved among patients at standard risk – 62% versus 52% for donor versus no donor, respectively (p = .02) for survival at 5 years (Fig. 2f), although an interaction test was not significant (p=.4). The relapse rate was significantly reduced in both risk groups, demonstrating the potent graft-versus-leukemia effect in an allogeneic transplant (Fig. 3a, b).

**Non-relapse mortality**

Figure 3c illustrates the high mortality rate post transplant among high-risk patients at 1 and 2 years, mostly due to graft-versus-host disease and infection. At 2 years 36% of high risk patients with a donor had died from non-relapse causes compared with 14% of patients who did not have a donor. Among standard risk patients the non-relapse mortality at 2 years was 20%, bearing in mind that among patients who did not have a donor there
was also a significant non-relapse mortality of 7% at 2 years. Surprisingly the non-relapse mortality did not change over the 13 years of this study.

Chemotherapy versus autologous transplant randomization for all patients, including Ph positive

Among the 456 patients randomized to chemotherapy versus autologous transplant, 16 were Ph-positive. Patients randomized to chemotherapy had significantly improved 5-year EFS (41% versus 32%; \( p = .02 \)); and OS 46% (95% CI=39-53%) versus 37% (95% CI=31-44%); \( p = .03 \) (Fig. 4 a, b).

Among patients at high risk the 5-year survival for chemotherapy versus autologous transplant was 37% versus 31%, respectively and for patients at standard risk this was 56% versus 46%, respectively (interaction \( p=.8 \) ) (Fig. 4 c, d).

In contrast to the donor versus no donor analysis, there was no difference in the non-relapse mortality between autologous transplant and chemotherapy (Fig. 4e), irrespective of the risk group (data not shown).

Effect of allogeneic transplant versus chemotherapy: donor versus no donor analysis for Ph negative patients censoring at autologous transplant

As patients randomized to chemotherapy had a better outcome than those undergoing autologous transplant, an analysis was made comparing patients with a donor versus those
without a donor, censoring at autologous transplant, to assess the effect of sibling donor transplant versus chemotherapy only.

Figure 5a demonstrates the superior OS for patients with a donor. As with the primary donor versus no donor analysis, this superiority could not be demonstrated among patients at high risk, but was significant for patients at standard risk with a 5-year survival of 63% for those with a donor versus 52% for those without a donor (interaction p=.6) (Fig. 5 b,c).

Discussion

The overall CR rate of 90% (Fig 1b) is very high and confirms the efficacy of the induction regimen, with relatively low toxicity allowing a very high percentage of patients to proceed to receive post remission therapy. The rate of randomisation was higher in ECOG at 60% than in the MRC 36% (Fig 1b) possibly reflecting somewhat different cultural practices in the trial groups regarding adherence to randomisation rules and potential penalties. There was no difference in survival between the MRC versus the ECOG patients (Fig 2c) indicating that the study was well balanced in all aspects on each side of the Atlantic.

The study originally included patients between 15 and 55 years although the age threshold, if there is one, at which “adult” ALL begins and “childhood” ALL ceases is a matter of current controversy. Indeed there may be evidence that patients up to age of 20 – 25 years or beyond might in 2007 achieve better outcomes on paediatric protocols.

Hitherto, allogeneic stem cell transplantation has been accepted as being of value in second remission and for high risk patients in first remission. In this study,
outcome of allogeneic transplant for all patients should best be estimated from a donor versus no donor analysis for patients between 15 and 50 years. This eliminates selection bias which would operate if only those transplanted were compared to those who were not. We regarded 50 years as the upper age limit initially for allogeneic transplant, at the beginning of the study in 1993. This may not be the case 14 years on. Survival at 5 years of 53% for those Ph-negative patients with a donor, versus 45% for those without, (p=0.02) indicates the superiority of allogeneic transplant overall whilst eliminating the biases of selection of transplant or not for those who have a donor.

Surprising though it might appear the high risk patients benefit less from having a donor than the standard risk patients in terms of overall survival. For high risk patients the donor versus no donor comparison shows a five year 41% versus 35% for OS which is not significantly superior (p=.2) (Fig 2e). This is an important finding since there is often a view that high risk patients should go immediately to allogeneic transplant. In fact the relapse rate for high risk patients is much reduced by the availability of a donor (Fig 3b) 63% versus 37% at 5 years (p=<.00005) so it is the toxicity of the transplant which is largely responsible for the lack of significantly improved survival for those patients who have a donor.

Somewhat unexpectedly, the significant overall benefits of having a donor are better for the standard risk Ph-negative patient who has a significantly superior survival at 5 years if he/she has a donor (62% versus 52%) p=.02 (Fig 2d). Relapse rates for these patients with a donor are also reduced as for high risk patients (49% versus 24% p=<.00005) (Fig 3a). With a donor the non-relapse mortality is far greater for high risk than for standard
risk patients (Fig. 3c). The non-relapse mortality was also higher for high risk patients compared to standard risk amongst those not undergoing a transplant. (14 versus 7%) (Fig.3c). Therefore a not insignificant number of patients were lost from treatment related causes other than transplant.

In the randomized group comparing chemotherapy and autologous transplantation the EFS and OS were superior for chemotherapy (p=.02 and .03, respectively). Differences were not statistically significant within subgroups, but these comparisons lack statistical power.

When comparing patients with a donor to the best “no donor” groups, i.e. by removing the effect of autologous transplant by censoring, the OS is once again significantly superior for standard risk patients with a donor but not for high risk patients (Fig 5a, 5b, 5c).

This study shows that the most potent anti leukaemia effect for adults with ALL derives from an allogeneic transplant as demonstrated by the significantly reduced relapse rate. This confirms the original hypothesis of a potential allogeneic effect and survival benefit therefrom. However, the transplant related mortality for high risk patients – due to the older age group – was unacceptably high. Although the size of the improvement in survival for the donor group was not statistically significantly different between the standard and high risk groups, this much higher mortality rate suggests that the difference is real. Thus benefit was confined to patients with standard risk disease for whom undergoing an allogeneic transplant demonstrates significant survival advantages over those undergoing conventional therapy.
For the younger patients with poor risk features a matched unrelated donor (MUD) allogeneic transplant may become a real option for the future \(^{30-35}\), ahead of conventional consolidation/maintenance chemotherapy.

Several relatively small, variously designed, studies of autologous transplant in ALL have been reported\(^ {10-13,36}\). The overall data suggest that autologous transplant offers little, if any, anti-leukemia benefit over conventional chemotherapy. However, as in no study was there a worse outcome for autologous transplant, its short duration offers a potentially significant benefit. In this large study, the outcome for autologous transplant was not equivalent and therefore it cannot be suggested as the preferred modality.

Adult ALL is a relatively uncommon disorder with perhaps fewer advances made in the last two decades than for other major haematological malignancies. It has taken a very large collaborative study lasting many years to demonstrate the value of a sibling allograft in this disease and the lack of additional value of an autograft over conventional consolidation/maintenance chemotherapy for those without a donor.

It is not easy to consider how to go forward. The very high remission rate on the present protocol makes the achievement of a higher “conventional” remission rate very difficult and it may be that interventions which attempt to reduce the amount of MRD are the way forward. This might potentially be achieved, as in so many other haematological disorders, by the addition of monoclonal antibody to chemotherapy given that both the CD20 and CD22 antigens are variably expressed in a considerable number of adult ALL patients \(^ {37}\).
Despite the high transplant-related mortality in older high risk patients, the GvL remains the single most potent strategy and efforts must be made to reduce the toxicity. There are only rare data regarding the use of reduced-intensity transplant conditioning in ALL.38 Never-the-less, some form of less toxic transplant must be studied in this high risk group of patients.

The toxicity of the induction phases for many adults might be reduced by using pegylated asparaginase39 and perhaps with the induction of hyper-CVAD40 or other alternative chemotherapy and studying whether delays in treatment which sometimes occur in the early phases on this protocol can be reduced or abrogated.

Because of the paucity of significant new agents for this disease it seems likely that the MUD transplant as a potential curative option will be offered to more patients in any new study with a risk-adapted approach; perhaps an ablative transplant for those under 40 years without a sibling and a non-ablative approach for those >40 years.

Sibling donor allogeneic transplant is the treatment of choice for adults with standard risk ALL in remission providing the greatest chance for a long-term survival. Autologous transplant has a less favourable outcome than consolidation/maintenance chemotherapy for those without a donor.
Acknowledgments

Author Contribution Statement:
Anthony H. Goldstone – designed and performed research, wrote the paper
Susan M. Richards – analyzed data
Hillard M. Lazarus – performed research
Martin S. Tallman – performed research
Georgina Buck – analyzed data
Adele K. Fielding – performed research
Alan K. Burnett – performed research
Raj Chopra – performed research
Peter H. Wiernik – performed research
Letizia Foroni – contributed vital data
Elisabeth Paietta – contributed vital data
Mark R. Litzow – performed research
David Marks – performed research
Jill Durrant – analyzed data
Andrew McMillan – wrote the paper
Ian M. Franklin – wrote the paper
Selina Luger – wrote the paper
Niculae Ciobanu – wrote the paper
Jacob M. Rowe – designed and performed research, wrote the paper

Conflict of Interest Disclosure: The authors declare no competing financial interests.
Figure Legends.

Figure 1.

(a) Simplified overall schema of the study.

MUD indicates matched unrelated donor transplantation; HD MTX – high-dose methotrexate

(b) Patient flow diagram

All randomized patients with the exception of 2 misdiagnoses were included in the comparison of autologous transplant and chemotherapy. A large number of patients were lost, as in all transplant studies, in the period from initial accrual to randomization. Only Ph-negative patients were eligible for the intent-to-treat donor versus no-donor analysis as Ph-positive patients without a donor were to have unrelated donor transplant if possible.

Figure 2.

Overall survival from diagnosis for:

(a) all patients entered on the study, including Ph-positive;

(b) Ph-negative and Ph-positive patients.

(c) patients entered via MRC or ECOG.

(d) donor versus no-donor for all Ph-negative patients.

(e) donor versus no-donor for Ph-negative patients with high risk.

(f) donor versus no-donor for Ph-negative patients with standard risk.
Figure 3.  
Relapse rate for:  
(a) Ph-negative patients at standard risk.  
(b) Ph-negative patients at high risk.  
(c) Non-relapse mortality for high-risk and standard-risk patients.  

Note the underlying mortality at 1 and 2 years among the no-donor group.  

Figure 4. Randomized chemotherapy versus autologous transplant, measured from time of randomization.  
(a) Event-free survival for all patients.  

Overall survival for (b) all  
(c) high-risk patients (d) standard-risk patients  
(e) Non-relapse mortality for all patients undergoing chemotherapy or autologous transplant.  

Figure 5.  
Overall survival from diagnosis for donor versus no-donor patients censoring at first remission autologous transplant in Ph-negative patients. Estimation of the effect of sibling donor transplant versus chemotherapy in  
(a) all patients  
(b) high-risk patients.  
(c) standard-risk patients.
References


27. Rowe JM, Buck G, Burnett AK, et al. Induction therapy for adults with acute lymphoblastic leukemia; results of more than 1500 patients from the international ALL trial; MRC UKALL XII/ECOG E2993. Blood. 2005;106: 3760-3767


Fig 1

A

MRC UKALL XII / ECOG 2993

INDUCTION

< 50 (or >50) yrs

Assign

No donor

Randomise

HD MTX X 3

Sitting

Autograft

(HUD for Ph+)

Consolidation/Maintenance

B

PATIENT FLOW DIAGRAM

1020 patients entered

1028 eligible for randomisation (770 MRC, 358 ECOG)

256 (48% of eligible) randomised (246 (38%) MRC, 214 ECOG (68%))

1051 eligible for tissue typing

1051 tissue typed

1027 Philadelphia positive

144 (6%) relapsed

152 failed induction

123 too old for autograft

135 missing typing information

104 not tissue typed

449 Donor

6 relapsed, 12 weeks

43 nonrelapsed SCT

508 No donor

6 relapsed, 12 weeks

43 nonrelapsed SCT

103 nonrelapsed SCT

*) age at entry: < 50 (original trial) or >50 (revised trial)

**) 133 no available siblings, 14 clinician choice (ie considered too old), 8 patient choice, 6 early death, 2 admin (untraceable), 4 unknown reason

Fig 2

A  Overall Survival

B  Overall Survival

C  Overall Survival

D  Overall Survival

E  Overall Survival

F  Overall Survival
Fig 3

A

Relapse Rate  
Ph negative Standard risk

B

Relapse Rate  
Ph negative High risk

C

Non-Relapse Mortality (%)

<table>
<thead>
<tr>
<th></th>
<th>3 months</th>
<th>6 months</th>
<th>1 year</th>
<th>2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Donor</td>
<td>1.5</td>
<td>7.3</td>
<td>26.0</td>
<td>35.8</td>
</tr>
<tr>
<td>No Donor</td>
<td>1.2</td>
<td>2.0</td>
<td>10.3</td>
<td>13.6</td>
</tr>
<tr>
<td>Standard Risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Donor</td>
<td>0.4</td>
<td>3.4</td>
<td>17.6</td>
<td>19.5</td>
</tr>
<tr>
<td>No Donor</td>
<td>0.3</td>
<td>1.2</td>
<td>5.3</td>
<td>6.9</td>
</tr>
</tbody>
</table>
Fig 4

A  Event-Free Survival

B  Overall Survival

C  Overall Survival (High risk)

D  Overall Survival

E  Non-Relapse Mortality (%)
Fig 5

A. Overall Survival

B. Overall Survival

C. Overall Survival

For personal use only.
In adults with standard-risk acute lymphoblastic leukemia (ALL) the greatest benefit is achieved from a matched sibling allogeneic transplant in first complete remission (CR) and an autologous transplant is less effective than conventional consolidation/maintenance chemotherapy in ALL patients: final results of the international ALL trial (MRC UKALL XII/ ECOG E2993)