Outcome of 609 Adults After Relapse of Acute Lymphoblastic Leukaemia (ALL); An MRC UKALL12/ECOG 2993 Study.

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Abstract

The majority of adults with ALL who achieve complete remission (CR) will relapse. We examined the outcome of 609 adults with relapsed ALL, all of whom were previously treated on the MRC UKALL12/ECOG2993 study, where the overall survival (OS) of newly diagnosed patients is 38% (95% confidence interval (CI) = 36-41%) at 5 years. By contrast, OS at 5 years after relapse was 7% (95% CI = 4-9%). Factors predicting a good outcome after salvage therapy were young age (OS 12% in patients <20 years versus OS 3% in patients >50 years, 2P <0.00005) and short duration of first remission (CR1) (OS 11% in those with CR1>2 years versus OS 5% in those with CR1 <2 years, 2P <0.00005). Treatment received in CR1 did not influence outcome after relapse. In a very highly selected sub-group of patients who were able to receive HSCT after relapse, some were long-term survivors. We conclude from a large, unselected series with mature follow-up that most adults with relapsed ALL, whatever their prior treatment, cannot be rescued using currently available therapies. Prevention of relapse is the best strategy for long-term survival in this disease.

Abstract word count: 189
Introduction

In contrast to the fate of children with the disease, the majority of adults who develop ALL do not become long-term survivors. Although rates of CR in adult ALL are high - 78- 93% in large, prospective clinical trials - long term disease-free survival ensues in only approximately 40% of patients. Salvage therapy can sometimes achieve second remissions for adults with relapsed ALL. In patients who have not already been treated with haematopoietic stem cell transplantation (HSCT), achievement of a second remission is usually followed by high-dose therapy and HSCT wherever donor availability, patient age, performance status and vital organ function permit. Typically, matched unrelated donors or previously unconsidered higher risk options such as transplants from haploidentical donors or cord blood transplants will be considered at this stage. Unfortunately, post-relapse strategies rarely result in long-term survival. Consequently, most studies in ALL now attempt to identify patients at highest risk of relapsing and apply higher risk therapies at an earlier time-point. However, the optimal risk: benefit delineation for application of high-risk therapies in first remission is far from clear. In particular, it is unknown what, if any, are the effects of prior therapy on the possibility of salvage after relapse. To address this issue, we analysed the fate of 609 adult patients who relapsed following treatment on the UKALLXII/ECOG2993 protocol. The length of the study and the number of patients enrolled affords a unique opportunity to examine the fate of a very large, mature series of prospectively enrolled adult patients with ALL who relapsed after a uniform approach to initial therapy.

In examining the data, we specifically asked whether patients who had not already received high dose chemoradiotherapy followed by HSCT as part of their initial therapy could be salvaged by autologous or allogeneic HSCT after relapse. The analysis provides a clear answer to this question, which is extremely relevant to the therapy of ALL and to the design of future therapeutic trials in adults with ALL.
Furthermore the data also provide guidance concerning which patients are most likely to benefit from post-relapse therapy, as currently conceived. The data allow identification of which patients will fare particularly poorly, for whom alternative and novel therapeutic strategies should be explored at relapse.

Methods

Study Eligibility

Eligible patients were aged 15-60 years (15-55 years in UK) with newly diagnosed, untreated ALL (FAB L1 or L2 only for ECOG patients) and no prior malignancy. The Institutional Review Board of each participating centre approved the study. All subjects gave informed consent.

Initial Diagnostic Procedures and treatment

Diagnosis of ALL was established by documenting > 25% marrow lymphoblasts. Confirmation of the diagnosis of ALL by central morphology review was recommended as well as submission of blood or marrow samples for cytogenetic analysis and immunophenotyping. Assessment of Philadelphia chromosome status was by cytogenetic analysis and by molecular methods, where applicable. All patients were treated according to the UKALL12/ECOG E2993 protocol. A simplified schema of original therapy is given in figure 1. Complete remission was defined as less than 5% bone marrow blasts with maturation of all other cell lines, peripheral blood neutrophils >1,000 x10^6/µL, platelets >100,000 x10^6/µL and no evidence of extramedullary leukaemia.

Treatment and data collection post-relapse
After relapse following initial on-protocol therapy, patients were followed up but choice of therapy was left to the discretion of physician and patient. Limited data were collected on therapy after relapse, but transplants, subsequent relapses, and survival or date of death were recorded. Data on achievement of second or subsequent complete remission were not collected.

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 Coordinating Center for ECOG patients. Randomisation between autograft and chemotherapy was done on computer at these two centres, who were also responsible for the collection of follow-up forms. Data entry and analyses for the whole trial were done at CTSU.

Analyses by prognostic factors and treatment used Kaplan-Meier curves and the log rank statistic for comparisons. Relative risks are indicated by the observed number of deaths (O) divided by the number which would be expected on the assumption of no difference between groups (E), but using time to event analysis to allow for the variable lengths of follow-up. The main analyses were of survival from the date of relapse. Independence of prognostic factors was confirmed by Cox regression analysis, with age and log (WBC+1) included as continuous variables. This trial is ongoing. This report includes all patients who started treatment before 1/11/2003, with follow-up to 31/10/2005.

Results

Patients and Patient characteristics

Of 1508 trial patients who were eligible for analysis, 74 patients died in induction and 62 failed to achieve remission. Of the 1372 patients who entered remission, 609 (44%)
relapsed, at a median of 11 months from the start of treatment. The outcome of these 609 adult patients with ALL in first relapse is the subject of this report. Median follow-up of the 50 survivors is 4 years 1 month (range = 12 days to 10 years 11 months).

Three hundred and eighty two (63%) were male. Five hundred and fifty six (91%) patients relapsed within the bone marrow and this was the sole site of relapse in the majority (90%) of those patients. Forty-five patients (8%) relapsed at solely extra-medullary sites, while for 8 (1%) the site was unknown. Sites of extramedullary relapse were as follows: central nervous system (CNS) N = 22, skin/soft tissue N = 8, testes N = 5, lymph nodes/mediastinum N = 5, and N= 1 each of ovary, bone, prostate, kidney, serous effusion. One hundred and twenty patients (20%) were Philadelphia chromosome positive (Ph+), which is similar to the percentage (25%) of patients with Ph + disease registered to the trial as a whole.

Most patients relapsed within 2 years of diagnosis (81%), although a significant minority (19%) relapsed beyond 2 years of diagnosis. Out of the 440 chemotherapy treated patients, 349 relapsed within 2 years of diagnosis, and 87 later. Those on chemotherapy who relapsed within 2 year can be considered “relapses on therapy” since the duration of therapy was set to be 18 months from the point of initiation of the consolidation therapy, i.e. 23 months.

Risk groups were defined as: standard (T cell ALL with presenting WCC<100 x 10^9/l, or non-T cell ALL with presenting WCC <30 x 10^9/l), high (T cell ALL with WCC >100 x 10^9/l, or non-T with WCC>30 x 10^9/l) and very high (Ph + ALL). 287 (47%) of patients who relapsed were in the standard risk category, 135 (22%) were in the high-risk category, and 67 (11%) were unclassified. In terms of initial treatment received at diagnosis 440 (72%) had received chemotherapy alone and the remainder had been treated with high dose therapy and bone marrow transplantation (with the exception of 3 cases where an off-protocol low intensity
conditioning regimen was used). These and other patient characteristics are summarised in table 1.

**Outcome after relapse**

The median survival post-relapse was 24 weeks. Survival at 1 year was 22% (95% CI = 18%-25%), and 7% (95% CI = 4%-9%) at 5 years. Data on achievement of a second remission and time to CR2 were not available in sufficient number for analysis. Only 42 of 609 relapsed patients remain alive without further relapse. Length of follow-up for these patients is median = 54 months; range = 1 – 131 months

**Prognostic factors for survival from relapse**

Four factors, age, gender, site of relapse and time from diagnosis to relapse were statistically significant as prognostic factors for outcome following relapse. Table 2 details the prognostic factors analysed and shows the deaths per total number of patients, the relative risk (as observed/expected - O/E), the P value, 5 year OS and confidence intervals.

Stratified analyses showed the independence of these 4 factors. Stepwise Cox regression analyses, with age, sex, relapse (<2 yrs or ≥2yrs), involvement of bone marrow, involvement of CNS, log (WBC+1), and immunophenotype in the initial model, confirmed this. Other factors analysed, such as Ph status, WBC at diagnosis, immunophenotype at diagnosis, and, notably, therapy received in first remission, were not significant prognostic indicators for survival after relapse. The data on analysis of prognostic factors are shown in full in table 2, with the hazard ratios in table 3. Relevant survival curves are shown in figure 3a-e. Inclusion of post-relapse therapy (transplant or not) as a time dependent variable in the Cox analyses made little difference to the hazard ratios, although female gender (hazard ratio =
1.21; 95% CI = 0.98-1.50) and BM involvement (hazard ratio = 1.48; 95% CI = 0.95-2.30) were no longer formally significant (both p=0.08)

**Therapy in relapse - Efficacy of transplantation after relapse**

In view of the demonstration that initial therapy received was not prognostic for outcome after relapse we were interested to examine the prognostic value of treatment received after relapse. In particular we wished to determine the role of HSCT since this is typically regarded as the only potentially curative therapeutic option. Patients who had already received transplant as part of their prior therapy (N=169) were excluded from this analysis, since the possibility of receiving a transplant was not equal with those who had never before received transplant, and information on second transplants was not systematically collected. In addition, those who had received non-myeloablative or mismatched transplant or transplant of unknown type after relapse (N=13) were excluded from comparisons. To adjust for the lead-time bias present in comparisons between transplant and chemotherapy 125 patients treated with chemotherapy post relapse, who had sustained relapse or died within the median time to transplant (103 days) were also excluded. A flow chart depicting the patient groups and the analyses performed is given in figure 2. The data for the patients analysed show that those treated with HSCT, had a superior OS (15% (95% CI = 0-35%) for autograft (N = 13), 16% (95% CI = 7-26%) for matched unrelated donor transplant (N = 65) and 23% (95% CI = 10-36%) for sibling allograft (N = 42)) to those receiving chemotherapy alone (N = 182) whose (OS only 4% (95% CI = 1-7%) at 5 years). The differences between the transplant groups and chemotherapy group were statistically significant (2P< 0.00005). Figure 4 shows the Kaplan-Meier survival curves illustrating these data. This result was not materially changed when allowance was made (by stratified analysis) for sex, age, time to relapse (<2 or >2 yrs), and type of relapse. Multivariate Cox regression analyses, excluding only those who had a
transplant before relapse and the few who had a mini, mismatched or cord blood transplant, including transplant as a time dependent variable, confirmed that those who received a transplant had better survival. Comparisons by treatment received, no matter how analysed, should be treated with caution, since no statistical method can adjust for the unmeasured selection factors involved. However, in this large but selected group of patients with relapsed ALL who were able to receive HSCT in relapse, some were long-term survivors, although the best expected survival was only 23% at 5 years.

Discussion

This is the largest series of adults with relapsed ALL ever reported. The magnitude of the dataset, homogeneity of initial therapy, and the maturity of follow-up have allowed us to detect some highly statistically significant prognostic factors which are informative, both to practising clinicians and their patients and to those involved in the design of clinical trials in adult ALL. The prognostic factors identified do not depend on response to salvage therapy and therefore could be used to guide a more focussed approach to the treatment of relapsed ALL by delineating patients in whom a small but important chance for long-term salvage exists from those in whom there is very little realistic opportunity for long-term survival. Our study confirms the findings of smaller /single center studies with respect to the prognostic value of age and duration of first remission and newly identifies female gender and site of relapse, as prognostic factors for a poor outcome.

Another important question for this study was the role of initial therapy in determining outcome after relapse. Our data, in contrast to the results of a smaller study of 61 patients with ALL, demonstrate that initial therapy of ALL does not affect the outcome after relapse. Patients who relapsed had the same long-term outcome whether or not they received chemotherapy or high dose therapy and transplant as part of their initial therapy. Taken
together with studies suggesting a survival benefit for allogeneic HSCT in adult ALL, the results presented here suggest that the survival benefits of high dose chemoradiotherapy in adult ALL are largely in preventing relapse. Once the patient has relapsed, subsequent cure becomes unlikely, whatever the initial therapy.

Despite this, our data do indicate that a small number of the patients who received chemotherapy alone as initial treatment can be rescued and survive long-term if they receive subsequent high-dose therapy and HSCT at relapse. Only about one quarter (108/429) of the patients who initially received chemotherapy were treated with a sibling or unrelated donor HSCT post relapse. Our data do not address whether this was due to lack of attainment of CR2, performance status of the patients or donor availability. However, it is clear that such patients constitute a very highly selected group and there is no suitable comparator, either within our study or within other studies. Probably as few as one half of those who relapse will even reach another remission and many will not reach the point of HSCT for other reasons, hence those who do undergo HSCT following relapse are already destined to have a better outcome than those who do not. The survival rates are clearly much lower than for those treated on this study with HSCT in CR1 - 42% for autograft, 45% for matched unrelated donor allograft, and 52% for sibling allograft - suggesting, unsurprisingly, that HSCT is much more beneficial if used in CR1 rather than in CR2.

Our study has limitations. Since the study did not collect information on which regimens were used to achieve a second remission, nor on the rate of attainment of CR2, we are unable to address which regimens can be recommended in relapsed ALL. Nor have we documented to what intensity and with what overall aim our relapsed patients were treated. Therefore, we cannot exclude the fact that a palliative strategy may have been pursued in a proportion of the patients. There is still no broad agreement on which regimens would be best suited to treat patients with relapsed ALL. Smaller series have demonstrated some utility to a
number of regimens, but it is clear that results obtained are far from ideal whatever therapy is applied.

Our data, although pertaining to patients with relapsed ALL, also contribute to the debate about how patients with de-novo disease should be treated. Since the outcome after relapse is so poor, our study underscores the importance of treating adults to maximal benefit ‘up-front’. There are data from large studies suggesting that allografting in CR1 can result in a better outcome than chemotherapy alone 14,15, although this approach is not yet substantiated for all age/risk groups in adult ALL. However, since our data demonstrate so conclusively that the prognosis after relapse is dismal for most patients, the substantial risk of transplant-related mortality as initial therapy is worth taking in patients with high-risk disease. Indeed, there is increasing evidence that the morbidity and mortality of unrelated donor HSCT may differ little from that of sibling donor transplant in ALL. 16. Hence, we draw the conclusion that a strategy to ‘reserve’ HSCT as a post-relapse option is not the best therapeutic approach for most adults. With regard to adolescents and younger adults whose relapse risk is lower - most especially those patients under the age of 20 we conclude from the data in our study that such patients - who are already at the lowest risk of relapse - are also among the most likely to be rescued following relapse. As evidence accumulates that the initial therapy of such patients should be with paediatric’ protocols 17,18,19, our study gives additional weight to the benefit of employing ‘paediatric’ strategies, to treat intensively with chemotherapy but to avoid the short and long-term toxicity of HSCT. For older adults, risk-adapted therapies, in which the higher –risk therapies are applied as early as possible to those patients destined to have the higher rates of relapse, are now the subject of numerous on-going studies, for example the German study GMALL 07/2003, Italian studies GIMEMA ALL0904 and NILG-ALL 09/00, and French study GRAALL 02/2005.
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In summary our data suggest that the vast majority of adult patients with relapsed ALL (in contrast to adults with relapsed acute myeloid leukaemia 20,21, whatever their prior therapy, cannot be rescued using currently recognised therapies, even if HSCT is an option. However, in choosing among current available therapies for patients who have relapsed, the best possible results can be obtained in a select subset of patients who are fit and eligible for a high dose procedure. We suggest that every eligible adult with relapsed ALL be included in a prospective study involving novel therapeutic agents 22.

ACKNOWLEDGEMENTS
The authors would like to thank all the doctors in the United Kingdom, United States, Israel, Italy and New Zealand who participated in the MRC UKALLXII / ECOG 2993 trial. A full list is provided in Rowe et al1.
Table One: Clinical Characteristics of 609 adults with relapsed ALL

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<th>Age at First Diagnosis (Years)</th>
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<td>227</td>
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<td>409</td>
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<th>Risk Group at First Diagnosis</th>
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<th>V. High</th>
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<td>135</td>
<td>120</td>
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<th>Initial Treatment at First Diagnosis</th>
<th>In first remission</th>
<th>Pre-remission ^</th>
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<tr>
<td>Diagnosis **</td>
<td>Chemo</td>
<td>Sib allo</td>
</tr>
<tr>
<td></td>
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<td>160</td>
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<th>Site of Relapse</th>
<th>BM alone</th>
<th>BM + CNS</th>
<th>CNS alone</th>
<th>Extramedullary</th>
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<td>(8 unknown)</td>
<td>523</td>
<td>33</td>
<td>22</td>
<td>23</td>
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</tbody>
</table>

** 1 BMT on unknown date

*Other = 1 reduced-intensity sibling allogeneic HSCT, 1 reduced-intensity MUD allogeneic HSCT, 1 reduced-intensity haploidentical HSCT, 1 fully conditioned haploidentical HSCT, 1 unknown type

^ Pre-remission = HSCT performed in absence of achieving CR1
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<th>Ph status</th>
<th>Gender</th>
<th>Age at diagnosis</th>
<th>WBC (x 10⁹/l) at diagnosis</th>
<th>Immunophenotype</th>
<th>Therapy in CR1*</th>
<th>Time, diag. to relapse</th>
<th>Site of relapse</th>
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<tr>
<td>- +</td>
<td>M F</td>
<td>&lt;20 20-34 35-49  &gt;50</td>
<td>&lt;10 10-49 &gt;50</td>
<td>B pre. T Mat. B Null Mix</td>
<td>Chem Auto Allo</td>
<td>&lt;2 &gt;2</td>
<td>BM BM+CNS CNS Ex</td>
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<td>Deaths</td>
<td>397 109</td>
<td>348 211</td>
<td>101 212 174 72</td>
<td>227 161 169</td>
<td>368 87 12 30 21</td>
<td>390 76 70</td>
<td>463 96</td>
</tr>
<tr>
<td>Total No.</td>
<td>433 120</td>
<td>382 227</td>
<td>117 236 182 74</td>
<td>248 178 181</td>
<td>409 92 12 30 22</td>
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<td>.09 1.2</td>
<td>0.7 0.9 1.2 1.5</td>
<td>.09 1.0 1.1</td>
<td>0.9 1.1 1.2 1.3 1.5</td>
<td>1.0 1.05 1.0</td>
<td>1.0 0.7</td>
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<td>5 yr OS (%)</td>
<td>6 9</td>
<td>8 3</td>
<td>12 7 4 3</td>
<td>5 9 6</td>
<td>8 5 0 0 5</td>
<td>7 3 9</td>
<td>5 11</td>
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<tr>
<td>CI</td>
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<td>5-11 0-6 6-18</td>
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<td>0-6 2-8 4-13</td>
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<td>Log-rank P value</td>
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<td>&lt;0.00005 (trend)</td>
<td>0.05 (trend)</td>
<td>0.06 (heterogeneity)</td>
<td>1.0 (heterogeneity)</td>
<td>&lt;0.00005</td>
<td>0.004 (heterogeneity)</td>
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</table>

*24 patients were excluded: 7 transplanted before remission, 3 with reduced intensity conditioning regimens, 1 mismatched related, 1 with unknown type SCT, 1 with SCT on unknown date and 11 who died before 12 weeks and hence could not possibly have reached transplant.

Ph = Philadelphia, - = negative, + = positive, WBC = white blood count, B pre. = precursor B, MatB = mature B, mix = mixed lineage, chem = chemotherapy, auto = autologous HCST, allo = matched or unrelated donor HSCT, BM = bone marrow, CNS = central nervous system, Ex = extramedullary
Table 3.

Results of multivariate Cox regression analysis of all relapsed patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio</th>
<th>95% confidence interval</th>
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<tr>
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<td>1.02</td>
<td>1.01-1.02</td>
</tr>
<tr>
<td>Female gender</td>
<td>1.27</td>
<td>1.06-1.51</td>
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<tr>
<td>Relapse &lt; 2 years</td>
<td>1.63</td>
<td>1.30-2.04</td>
</tr>
<tr>
<td>BM involvement</td>
<td>1.51</td>
<td>1.06-2.17</td>
</tr>
<tr>
<td>CNS involvement</td>
<td>1.68</td>
<td>1.22-2.31</td>
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</table>
Figure Legends

Figure 1
Simplified Schema of Initial treatment on MRC UKALLX11/ECOG E2993

Figure 2
Flowchart depicting the patients included and the analyses performed to assess efficacy of HSCT in relapse.

Figure 3
Probabilities of survival from first relapse – an analysis of prognostic factors
a. Gender b. Age at diagnosis c. Time from diagnosis to relapse d. Site of relapse e. Therapy in CR1
Numbers at risk are shown beneath the graph
BM = bone marrow, CNS = central nervous system
Sib Allograft = allogeneic HSCT from fully matched sibling donor. MUD allograft = allogeneic HSCT from matched unrelated donor.

Figure 4
Probability of survival according to therapy given in relapse
Those who died within a hundred days of relapse and those patients who had a prior transplant in CR1 are excluded from this analysis to allow more appropriate comparison of high dose therapy and HSCT with chemotherapy alone.

Sib Allograft = allogeneic HSCT from fully matched sibling donor. MUD allograft = Allogeneic HSCT from unrelated donor.
Reference


21. Song KW, Lipton J. Is it appropriate to offer allogeneic hematopoietic stem cell transplantation to patients with primary refractory acute myeloid leukemia? Bone Marrow Transplant. 2005;36:183-191

Fig. 1.

INDUCTION
Phase 1
Phase 2

Ph positive

Ph negative

High dose MTX x 3

50 years old and/or no donor

< 50 years old, HLA matched sibling donor

Assign

Randomise

Assign

Sibling or MUD HSCT
(Etoposide/TBI)

Autologous HSCT
(Etoposide/TBI)

CNS DXT Consolidation Maintenance

Relapse: therapy at physician discretion, data on outcome collected
Fig. 2.

Relapsed adult ALL N = 609

Excluded from analysis of therapy post relapse
- not equal chance of receiving BMT

Received chemotherapy
sustained relapsed/died within median time to HSCT
(103 days)
N = 125

HSCT as original therapy
N = 169*

Non-myeloablative or unknown transplant type
N = 13

Included in analysis of outcome of therapy post-relapse

Sibling allogeneic HSCT
N = 42

MUD HSCT
N = 65

Autologous HSCT
N = 13

Chemotherapy
N = 182

*Outcome of these patients who received HSCT as part of original therapy is shown in Fig 3e
(N = 157, 12 excluded from analysis due to HSCT prior to CR1 or non-standard transplant)
Fig. 3a.

At risk:

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<td>11</td>
</tr>
<tr>
<td>4</td>
<td>23</td>
<td>6</td>
</tr>
<tr>
<td>5</td>
<td>19</td>
<td>2</td>
</tr>
</tbody>
</table>

2P = 0.006

Male: 8%
Female: 3%
Fig. 3b.

![Graph showing survival rates by age group and time (years)]

- **At risk:**
  - <20: 117
  - 20-34: 236
  - 35-49: 182
  - 50+: 74

- **Time (years):**
  - 0: 117
  - 1: 35
  - 2: 17
  - 3: 14
  - 4: 11
  - 5: 10

- **Survival rates by age group:**
  - Age 50+: 3%
  - Age <20: 12%
  - Age 20-34: 7%
  - Age 35-49: 4%

- **Statistical significance:**
  - $2P < 0.00001$
Fig. 3c.

At risk:

<table>
<thead>
<tr>
<th>Time (years)</th>
<th>&lt;6 months</th>
<th>6 m. - 1 yr</th>
<th>1-2 yrs</th>
<th>&gt;2 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-6 mo.</td>
<td>153</td>
<td>177</td>
<td>163</td>
<td>116</td>
</tr>
<tr>
<td>6 mo. - 1yr</td>
<td>24</td>
<td>27</td>
<td>34</td>
<td>40</td>
</tr>
<tr>
<td>1-2 yrs</td>
<td>12</td>
<td>11</td>
<td>16</td>
<td>19</td>
</tr>
<tr>
<td>&gt;2 yrs</td>
<td>7</td>
<td>10</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td>1-2 yrs b%</td>
<td>6</td>
<td>9</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>6 mo. - 1yr 6%</td>
<td>5</td>
<td>6</td>
<td>6</td>
<td>4</td>
</tr>
</tbody>
</table>

Percent

100
75
50
25
0

2P < 0.00001

> 2 years, 11%
Fig. 3d.

At risk:

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>BM</td>
<td>523</td>
<td>105</td>
<td>47</td>
<td>33</td>
<td>25</td>
<td>19</td>
</tr>
<tr>
<td>BM+CNS</td>
<td>33</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CNS</td>
<td>22</td>
<td>6</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Extramedullary</td>
<td>23</td>
<td>7</td>
<td>3</td>
<td>2</td>
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<td>0</td>
</tr>
</tbody>
</table>

$Z = 0.04$ (heterogeneity)
Fig. 3e.

At risk:

<table>
<thead>
<tr>
<th></th>
<th>Allo/MUD</th>
<th>Chemo</th>
<th>Auto</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>100</td>
<td>100</td>
<td>100</td>
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<tr>
<td>1</td>
<td>77</td>
<td>80</td>
<td>129</td>
</tr>
<tr>
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<td>21</td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>7</td>
<td>39</td>
</tr>
<tr>
<td>4</td>
<td>9</td>
<td>4</td>
<td>27</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>3</td>
<td>22</td>
</tr>
</tbody>
</table>

2P = 1.0

Allo/MUD: 9%
Chemo: 7%
Auto: 5%
Fig. 4.
Outcome of 609 adults after relapse of acute lymphoblastic leukaemia (ALL); an MRC UKALL12/ECOG 2993 study

Adele K. Fielding, Susan M Richards, Rajesh Chopra, Hillard M Lazarus, Mark Litzow, Georgina Buck, Jill Durrant, Selina M Luger, David I Marks, Andrew K McMillan, Martin S Tallman, Jacob M Rowe and Anthony H Goldstone