The role of post-transplant maintenance chemotherapy in improving the outcome of autotransplantation in adult acute lymphoblastic leukemia

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Summary

Extending the principle of conventional acute lymphoblastic leukemia (ALL) therapy to transplantation, 77 adult patients autografted in first remission after melphalan ± total body irradiation were scheduled to receive 6-mercaptopurine (6MP), methotrexate (MTX) and vincristine-prednisone (VP) for 2 years post-transplant to reduce relapse. 71% of patients received 6MP, 57% received MTX and 38% received VP. 30 patients relapsed at 1.5-80 months (median 12.5); 15 in the first year and 7 beyond 3 years. The cumulative incidence of relapse at 10 years was 42% (95% CI: 31-55). The 10-year probabilities of disease-free (DFS) and overall (OS) survival were 50% (95% CI: 38-62) and 53% (95% CI: 41-65) respectively. Age >30 years, >4 weeks to attain remission and high-risk karyotypes [t(9;22) or t(4;11)] were adverse features contributing to the identification of 3 prognostic risk groups with 0, 1, and 2 adverse features respectively: standard (47%), intermediate (36%), and high (17%). The 10-year cumulative incidences of relapse (20%, 48%, 85%; P<0.0001) and probabilities of disease-free survival (72%, 41%, 10%; P=0.0003) were significantly different amongst these groups. In Cox analysis of the 71 patients alive and well 120 days post-transplant, those receiving 2 or 3 maintenance chemotherapy agents had significantly lower relapse and superior DFS compared with those receiving 0 or 1 agent. Our data suggest that maintenance chemotherapy improves the outcome of autografted ALL patients. However, it is unlikely that autograft-based
strategies are optimal for the high-risk group of patients who should be considered for alternative-donor allograft procedures.
Introduction

Improvement in the outcome of adults with acute lymphoblastic leukemia (ALL) has lagged developments in childhood ALL [1,2], although the use of intensive regimens [3] has resulted in better outcome. The results of further intensification of therapy by using autotransplantation in adult ALL patients have also been generally disappointing with relapse being the commonest eventuality [3-16].

We have extended the principle of prolonged maintenance chemotherapy in ALL to the autograft setting by administering 6-mercaptopurine (6MP), methotrexate (MTX), and vincristine-prednisone (VP) after autotransplantation in an attempt to decrease relapse rates [17,18]. The pilot results have been encouraging [17,18]. We now provide long-term follow-up on a group of 77 patients with a minimum follow-up of 2.5 years. This is also the largest single-center series of autotransplantation in first complete remission (CR) ALL.

Patients and methods

Prospectively-gathered data [19] on 77 consecutive patients over the age of 15 who were autografted for ALL in first CR between July 1984 and December 1998 at the Leukaemia Unit of the Royal Marsden Hospital were analyzed. Table 1 shows the patient characteristics.
Thirty-five patients underwent autologous bone marrow transplantation (ABMT) after conditioning with melphalan and total-body irradiation (TBI) between July 1984 and December 1992. The subsequent 42 patients underwent autologous peripheral blood stem cell transplantation (PBSCT) between January 1993 and April 1994 after conditioning with high-dose melphalan alone. The ABMT population represented patients without HLA-identical sibling donors since adults with suitable sibling donors underwent allogeneic BMT in first remission until December 1992. After December 1992, PBSCT was offered as the procedure of first choice irrespective of the availability of matched sibling donors as part of our “sequential high-dose therapy” approach [20,21]. The idea behind sequential high-dose therapy was to perform a low-morbidity autograft as the first step – followed by a salvage allograft in second remission in relapsing patients. Exceptions to the sequential high-dose therapy approach included patients taking >8 weeks to attain CR, those with CNS disease and t(9;22) – who were allografted in first CR if an HLA-matched sibling donor was available.

Patients with lymphoid blast crisis of chronic myeloid leukemia were not included. Patients with biphenotypic disease (presence of myeloid markers) received different initial chemotherapy and were excluded. All research protocols were approved by the local institutional review board. All patients gave informed consent for the transplant.
Induction chemotherapy

Forty-nine patients received induction (weeks 1-4) and early intensification therapy (weeks 5-6) according to the United Kingdom Medical Research Council's adult UKALL X Regimen B combination chemotherapy protocol or similar combination induction-intensification. Twenty-eight patients received phase I (weeks 1-4) and phase II (weeks 5-9) induction therapy according to the United Kingdom Medical Research Council's adult UKALL XII chemotherapy protocol, which is more intense. Induction chemotherapy was administered either at the Royal Marsden Hospital or at other regional hospitals from where the patients were referred for autografting in first CR.

Central nervous system prophylaxis

Patients treated with melphalan-TBI as part of the conditioning received an additional 800 cGy cranial (no CNS disease at presentation) or craniospinal (CNS disease at presentation) irradiation in 5 daily fractions the week before the TBI. Patients treated with melphalan alone received 2400 cGy cranial irradiation in 15 fractions after hematologic recovery from intensification or phase II induction and before leukapheresis. No patient received testicular irradiation.

Patients without CNS disease received 6 injections of intrathecal MTX (usually 15 mg) over the treatment period prior to the transplant, and those with CNS
disease received triple intrathecal chemotherapy with MTX (usually 15 mg), cytarabine (usually 30 mg) and hydrocortisone (usually 100 mg) until 6 consecutive spinal fluid samples were free of disease. No intrathecal chemotherapy was administered post-transplant [22].

Bone marrow harvest

Bone marrow was harvested from the posterior iliac crests under general anesthesia, usually 6-8 weeks after completion of the intensification therapy. Seven patients received marrow that was purged in vitro with Campath-1M [23], whereas the remainder received unmanipulated marrow. Back-up marrow was harvested from the first 7 PBSCT recipients prior to leukapheresis and cryopreserved in case of secondary failure of engraftment with maintenance chemotherapy. This was not used, and the practice was subsequently discontinued.

Peripheral blood stem cell harvest

The first 7 PBSCT recipients received G-CSF (filgrastim) at the dose of 125 µg/m² subcutaneously q12h starting 2 weeks after the marrow harvest for a period of 7 days. Stem cells were harvested on days 5 to 8 (4 consecutive days). The next 35 patients received 12-16 µg/kg filgrastim subcutaneously q24h on days 1-4, and stem cells were harvested on days 4 and 5. Leukapheresis was
performed on a Cobe Spectra (Cobe Industries, Lakewood, CO) continuous-flow cell separator with 150-200% of the patient's calculated blood volume being processed at each session.

*Cryopreservation and infusion*

Cells were cryopreserved with 10% dimethylsulfoxide using a controlled-rate freezer, and were stored in the vapor phase of liquid nitrogen. The cells were rapidly thawed in a water bath at 37°C by the bedside and infused within 2 weeks of collection.

*High-dose therapy and transplant*

The conditioning regimen for ABMT was 110 mg/m² melphalan on day -1 and single-fraction TBI on day 0, and 950 cGy (n=2), 1050 cGy (n=31), or 1150 cGy (n=2). TBI was delivered from opposed ⁶⁰Co sources at a low dose rate (4 cGy/min). Autologous marrow was infused on day 0. PBSCT recipients received a single dose of 200 mg/m² melphalan with hydration on day -1. All cryopreserved cells (excluding back-up marrow) were infused on day 0; 24 hours after the administration of melphalan. No growth factors were administered post-transplant.
Supportive care

All patients were treated in protective isolation in rooms with positive-pressure ventilation. Blood products transfused were not screened for cytomegalovirus (CMV) antibody in CMV-seropositive patients. Antibiotic prophylaxis and therapy varied in accordance with prevalent practices and research programs. Broad-spectrum antibiotic therapy was started for fever in the neutropenic phase. Irradiated random platelets were transfused to maintain the platelet count at 20 x 10^9/L, and packed cells to maintain the hemoglobin at 100 g/L.

Maintenance chemotherapy

Maintenance chemotherapy with daily 6MP was usually begun when the leukocytes reached 3 x 10^9/L and the platelets 100 x 10^9/L, and was continued for 2 years. Commencement of chemotherapy was not delayed by any factor except for poor hematologic recovery, relapse or ongoing medical problems (e.g. interstitial pneumonitis) which could potentially be exacerbated by starting chemotherapy. Therapy was started with 25 mg 6MP and this was increased weekly or fortnightly in 25-50 mg steps. Weekly oral MTX at the dose of 5 mg (increasing in 2.5-5 mg steps) was added when the dose of 6MP reached 75 mg. All maintenance chemotherapy was discontinued 2 years after starting the first agent (6MP).
Drug doses were adjusted to maintain the absolute neutrophil count over 1 x $10^9$/L. Initially, monthly vincristine (1.4 mg/m$^2$; maximum 2 mg) with prednisone (40 mg/m$^2$ for a week) were administered to patients who could not tolerate myelosuppressive chemotherapy. After 1995, this was added routinely to all patients.

The target doses of 6-MP and MTX were 80 mg/m$^2$ daily and 20 mg/m$^2$ weekly respectively. Patients received folic acid and prophylaxis for *Pneumocystis carinii* pneumonia with oral trimethoprim-sulfamethoxazole (if on 50% of the target 6-MP dose) or aerosolized pentamidine (if on less than 50% of target 6-MP dose) while on maintenance chemotherapy. Acyclovir was administered to prevent reactivation of *Varicella zoster* virus.

The average dose of 6-MP and MTX administered was determined by calculating the actual total amount of drug administered after the transplant and dividing this amount by the number of days (6-MP) or weeks (MTX) from the date of the transplant to the last date of the chemotherapy. The latter was the day on which chemotherapy was electively discontinued after completion of 2 years or the day of relapse or TRM. The body surface area used for calculations was that at the time of the transplant.
Statistical analysis

The $\chi^2$ test was used to compare categoric variables and the Wilcoxon rank-sum test was used to compare continuous variables. The probabilities of disease-free survival (DFS) and overall survival (OS) were estimated by the Kaplan-Meier method, and compared using the log-rank test. The cumulative incidence of transplant-related mortality (TRM) and relapse was estimated using each type of event as a competing risk for the other [24,25]. The significance of differences in TRM and relapse was calculated using the likelihood-ratio statistic for proportional-hazards regression models. Two patients dying in CR of causes obviously unrelated to the transplant and the underlying disease (homicide and pre-existing ischemic heart disease at 8 and 36 months respectively) were censored at the time of death for OS and DFS, and were considered competing events for calculating the cumulative incidence of TRM and relapse.

The disease risk stratification was based upon age, cytogenetics and the time taken to attain CR (Tables 2 and 3), and was a modification of the German classification proposed by Hoelzer et al [26]. The following factors were analyzed in Cox proportional-hazards regression models for effect on relapse, DFS and OS: disease risk (standard vs intermediate vs high), gender, CR-transplant interval (<4 vs $\geq$4 months), stem cell source (marrow vs blood), type of induction therapy (UKALL X or similar vs UKALL XII or similar), WBC count at presentation (<30 vs $\geq$30 x $10^9$/L), intensity of maintenance therapy (0/1 agent vs 2/3 agents),
and immunophenotype (null vs others). The conditioning regimen was not included in the model because of 100% concordance between the stem cell source and conditioning.

Patient follow-up data are current through 1 August 2001 when the median, minimum and maximum follow-up duration for surviving patients was 6.9, 2.5 (excluding the patient who was murdered 8 months post-autograft), and 17 years respectively.

Results

Neutrophil recovery to 0.5 x 10^9/L was complete and sustained in all patients, occurring earlier in PBSCT recipients than ABMT recipients. The stem cell source did not influence platelet recovery significantly.

Transplant-related morbidity and mortality

Six patients died due to transplant-related causes 2-8 months (median 5.5) after ABMT, and none after PBSCT (P=0.007; Fisher’s exact test). All deaths were due to interstitial pneumonitis, and were most likely the result of TBI which was used for ABMT but not for PBSCT (Table 1). The cumulative 10-year incidence of TRM was 8% (95% CI: 4-17%).
Maintenance chemotherapy

Table 4 shows the time to starting each maintenance chemotherapy agent and the proportion of patients starting it for the entire group as well as for ABMT and PBSCT recipients separately. The only significant difference – the higher proportion of PBSCT recipients receiving VP – is the result of changed treatment strategy (routine use of VP rather than only in patients with poor marrow function). None of the 22 patients who did not receive 6MP received MTX, whereas 5 received VP.

17 patients received no maintenance chemotherapy at all because of early TRM within 4 months (n=3), pulmonary problems subsequently terminating in TRM beyond 4 months (n=2), relapse within 4 months (n=3), sluggish hematologic recovery terminating in relapse beyond 4 months (n=3), unknown/patient preference (n=5), and non-compliance/lifestyle (n=1; this patient eventually became a homicide victim). 9 patients received only 1 drug (5 VP and 4 6MP), 34 patients received 2 drugs (27 6MP-MTX and 7 6MP-VP), whereas 17 patients received all 3 drugs.

The average daily dose of 6MP administered was 3-109 mg/m² (median 33). The average weekly dose of MTX administered was 0.2-18.1 mg/m² (median 2.8). Maintenance chemotherapy was tolerated well, and other than transient
myelosuppression requiring dose reduction or temporary cessation of therapy, no other side effects were seen.

Relapse and post-relapse therapy

30 patients (39%) relapsed at 1.5-80 months (median 12.5); 15 in the first year, 7 in the second year, 1 in the third, 5 in the fourth, 1 in the fifth and 1 at almost 7 years. All relapses were confirmed to be immunophenotypically and cytogenetically (where applicable) identical to the original disease. No case of second or secondary leukemia was seen. Figure 1 shows the cumulative incidence of relapse.

18 patients died of relapsed disease or toxicity of salvage chemotherapy. 11 patients underwent an allograft from an HLA-matched sibling (n=6) or a matched unrelated donor (n=5) in second CR, and 1 is awaiting allograft. 9 died of transplant-related toxicity (n=7) or relapse (n=2), and 2 are alive and well in second CR at 7 y (HLA-identical sibling) and 1.5 y (unrelated donor).

Overall and disease-free survival

As of 1 August 2001, 44 of 77 patients were alive and in remission 8 months to 17 y (median 6.9) after the transplant; 41 in continuous first CR, 2 in second CR after allogeneic BMT, and 1 in second CR after chemotherapy (awaiting
allograft). Figures 2 and 3 show the actuarial probabilities of DFS and OS. All patients are off maintenance chemotherapy.

**Identification of risk groups**

The 3 adverse risk factors; age >30 y, t(9;22), t(4;11), and >4 weeks to attain CR (Table 2); were identified to be high-risk factors for relapse, DFS and OS (Table 3). As Table 2 shows, these factors could be combined to produce 3 risk groups. The outcome of these 3 groups in terms of relapse (Figure 4), DFS (Figure 5), and OS (P=0.003) was highly significantly disparate.

**The effect of maintenance chemotherapy**

Amongst patients alive and well at 120 days, those getting 2 or 3 maintenance chemotherapy agents had a significantly lower relapse rate (Figure 6), higher DFS (Figure 7), and OS (P=0.0008). This time point was chosen to eliminate the 6 patients dying early; 3 of relapse and 3 of TRM; before becoming eligible to receive maintenance chemotherapy.

In the same population of patients, there was no significant difference in the outcome of those getting no maintenance chemotherapy and those getting any maintenance chemotherapy (data not shown). There was no obvious relationship between the amount of chemotherapy given and outcome (data not shown).
Cox analysis

Table 5 shows the results of the multivariable analysis adjusted by survival on day 120 post-transplant. Standard-risk disease, longer CR-autograft intervals, and more intense maintenance chemotherapy were associated with lower relapse and higher DFS. OS was beneficially impacted by standard-risk disease and more intense maintenance chemotherapy.

The effect of maintenance chemotherapy by risk group

Table 6 shows that receiving more intensive maintenance chemotherapy made a significant difference to outcome in the standard-risk group and a less-marked difference to patients in the intermediate-risk group. On the other hand, it made no difference to patients in the high-risk group at all.

Discussion

Our data suggest that standard ALL-type maintenance chemotherapy can be administered safely after autotransplantation in patients with ALL. While only a randomized study can answer the question of its benefit, if any, there are 2 observations in this series of patients that suggest that maintenance chemotherapy may contribute to an improved outcome in terms of reduced relapse and increased survival. The first is that higher intensity of maintenance
therapy was clearly associated with better outcome. The second is that the results reported here are better than most reported using the more conventional approach of autograft without any post-transplant intervention.

An obvious shortcoming of the first observation here is that autografted patients with compromised myeloid reserve have a higher risk of disease recurrence. These are also the patients that are likely to be unable to start chemotherapy post-transplant. This obstacle was partially overcome by excluding patients relapsing early. However, even after excluding the 3 patients relapsing within 4 months, 4 additional patients continued to have poor counts and eventually relapsed without being able to start any maintenance therapy at all.

Another indirect observation which may support using post-transplant therapy in ALL comes from the International Bone Marrow Transplant Registry which showed that the use of methotrexate post-transplant as graft-versus-host disease prophylaxis decreased relapse in patients allografted for ALL independently of clinically obvious GVHD; perhaps secondary to a direct anti-leukemic effect [27].

In a French cooperative group study that showed no impact of ABMT on survival compared to chemotherapy alone, late relapses were significantly less common amongst autografted patients [12], and relapse relatively early after the transplant was an important cause of treatment failure. It is conceivable that post-transplant maintenance chemotherapy in a setting like this may reduce the incidence of
early post-transplant relapse and improve DFS by eliminating clonogenic leukemic cells reinfused with the graft, or more likely, have remained viable in the patient despite the conditioning regimen.

Other post-transplant treatments which have been employed to decrease relapse rates after autotransplantation in ALL have included intensive chemotherapy [28], interleukin-2 infusions [11], and cell-mediated immunotherapy with haploidentical T lymphocytes [29]. Reports describing these approaches have suffered from small patient numbers and inadequate follow-up; making any assessment difficult.

Patients with HLA-identical siblings in the ABMT era were allografted at the Royal Marsden Hospital. Those with HLA-identical siblings in the PBSCT era were autografted – and the allograft was reserved for salvage therapy of relapse. The reasoning behind this was avoidance of toxic therapy (allograft) unless absolutely essential. While treatment-related mortality was indeed reduced with the elimination of TBI and the use of blood-derived stem cells, this did not necessarily make the outcome of subsequent salvage therapy any easier or more successful: only 2 of 11 allografted patients survive; with high treatment-related mortality rates that were no different from we had observed in the past [30]. These patients were conditioned using conventional-intensity regimens. It is possible that the outcome may have been better if reduced-intensity regimens had been used. In any case, we feel that an allograft from an HLA-identical
sibling is probably the best treatment option in adult patients with ALL who requires a transplant in first CR – especially with the possibility of augmented graft-versus-leukemia reactions from the use of blood-derived stem cells [31,32] and limited TRM with the use of an adequate number of CD34+ cells for the transplant [33].

What is the role of the pre-transplant conventional chemotherapy administered for induction and intensification/consolidation? It was disappointing to see that there was no difference in the outcome of patients receiving less intensive therapy initially (UKALL X and similar) compared with those getting more intensive therapy (UKALL XII). This is unlike in acute myeloid leukemia (AML) where in vivo purging pre-transplant – achieved by administering at least 2 cycles of consolidation chemotherapy – makes a significant impact on outcome [34]. Because graft source and conditioning regimen were changed simultaneously, and there was a strong association between these and the initial induction therapy, the relative contribution of each to outcome cannot be assessed. A beneficial effect of TBI of reduction of relapse cannot be ruled out because the higher-intensity induction chemotherapy that non-TBI patients received could have offset the disadvantage of not having received TBI. It is also possible that the difference between less and more intensive initial therapy is negated to some extent by by post-transplant maintenance therapy.
There has been a strong trend towards the use of alternative donor transplants rather than autografts in ALL because of poor results of autotransplantation in ALL. However, high-risk allografts may not be the right approach for all patients. A recent registry comparison of unrelated donor transplants and autografts in first and second remission ALL found that while relapse rates were lower with allografts, the benefits of this were negated by significantly higher TRM. Because of this, survival was comparable with the 2 modalities of transplantation [35]. In view of this, it is clearly important to identify patients who are likely to do poorly with an autograft and offer them alternative-donor transplantation. Those without features that increase the risk of relapse to prohibitive levels may be better off with an autograft. Our data provide some clues towards who these patients may be.

The data in Table 6 suffer from very small patient numbers in the various subgroups and must be interpreted with caution. They suggest that the outcome of patients with high-risk disease is dismal with autotransplantation whether post-transplant chemotherapy is administered or not. This is the group of patients most likely to benefit from high-risk allograft approaches [35]. What should be done for patients with standard-risk disease? It is tempting to suggest an autograft as the first approach even in patients who have an HLA-identical sibling donor because of the excellent outcome seen here. Relapsing patients can then be salvaged by an allograft in the second remission. However, we do not have adequate data to suggest an optimum approach in this situation; especially
because of the poor outcome of allografted patients in this series (vide supra).

Patients with intermediate-risk disease ought to be allografted if an HLA-identical sibling is available. In the absence of a sibling donor, an autograft should be the preferred mode of therapy – to be followed by a salvage, high-risk, alternative-donor allograft in case of relapse.

Within the limitations of the data in Table 6 (small patient numbers), the suggestion that patients with the best disease also respond further to the maximum extent with post-transplant therapy is interesting - and is in keeping with observations in AML that patients with good-risk karyotypes gain the most from further intensification of therapy; either with chemotherapy [36] or with autotransplantation [37].

We conclude that autotransplantation followed by maintenance chemotherapy is an excellent way of intensifying therapy in adult patients with ALL unless the disease is high-risk. This is a strategy that should ideally be explored in a randomized trial. In the absence of such a study, it appears safe enough to use routinely in practice to improve outcome of autografted ALL patients.

Acknowledgments
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Table 1: Patient characteristics

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<th>All</th>
<th>Marrow</th>
<th>Blood</th>
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<tr>
<td>n</td>
<td>77</td>
<td>35 *</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>30 (39%)</td>
<td>10 (29%)</td>
<td>20 (48%)</td>
<td>0.089</td>
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<tr>
<td>Age (years)</td>
<td>26 (16-59)</td>
<td>25 (17-53)</td>
<td>32 (16-59)</td>
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<td>Presentation leukocyte count</td>
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<td>12.2 (0.9-900)</td>
<td>4.4 (0.7-602)</td>
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<td>t(4;11)</td>
<td>3 (4%)</td>
<td>1 (3%)</td>
<td>2 (5%)</td>
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<tr>
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<td>26 (34%)</td>
<td>9 (26%)</td>
<td>17 (40%)</td>
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<tr>
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<td>27 (35%)</td>
<td>11 (31%)</td>
<td>16 (38%)</td>
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<tr>
<td>MRC UKALL X (or similar)</td>
<td>49 (63%)</td>
<td>34 (97%)</td>
<td>15 (36%)</td>
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<tr>
<td>MRC UKALL XII (or similar)</td>
<td>28 (37%)</td>
<td>1 (3%)</td>
<td>27 (64%)</td>
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<td>CR-transplant interval (weeks)</td>
<td>16 (1-90)</td>
<td>15 (5-69)</td>
<td>18 (1-90)</td>
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<tr>
<td>Melphalan-TBI</td>
<td>35 (45%)</td>
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<td>Melphalan alone</td>
<td>42 (55%)</td>
<td>42 (100%)</td>
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</table>

* 3 patients with lymphoblastic lymphoma and bone marrow involvement who were included in our prior report have been excluded here.

# Six patients had Ph+ disease detected on conventional cytogenetic studies (G-banding). RT-PCR was not performed routinely. It is therefore possible that the actual proportion of patients with Ph+ disease may be higher.
Table 2: Adverse disease factors and risk stratification

<table>
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<th>Adverse factor</th>
<th>n</th>
<th>%</th>
<th>Marrow (n=35)</th>
<th>Blood (n=42)</th>
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<td>Age &gt;30 years</td>
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<td>47</td>
<td>14 (40%)</td>
<td>22 (52%)</td>
<td>0.28</td>
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<td>t(4;11) or t(9;22)</td>
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<td>12</td>
<td>5 (14%)</td>
<td>4 (10%)</td>
<td>0.52</td>
</tr>
<tr>
<td>Time to CR &gt;4 weeks</td>
<td>9</td>
<td>12</td>
<td>5 (14%)</td>
<td>4 (10%)</td>
<td>0.52</td>
</tr>
<tr>
<td>Risk stratification</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard (0 adverse factors)</td>
<td>36</td>
<td>47</td>
<td>19 (54%)</td>
<td>17 (40%)</td>
<td>0.39</td>
</tr>
<tr>
<td>Intermediate (1 adverse factor)</td>
<td>28</td>
<td>36</td>
<td>10 (29%)</td>
<td>18 (43%)</td>
<td></td>
</tr>
<tr>
<td>High (2 adverse factors)</td>
<td>13</td>
<td>17</td>
<td>6 (17%)</td>
<td>7 (17%)</td>
<td></td>
</tr>
</tbody>
</table>
Table 3: Outcome of patients with adverse features. The relapse and treatment-related mortality figures represent cumulative incidences at 10 years, and the disease-free and overall survival figures, actuarial 10-year probabilities.

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>%</th>
<th>TRM</th>
<th>Relapse</th>
<th>DFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;30 years</td>
<td>36</td>
<td>47</td>
<td>3%</td>
<td>63%</td>
<td>34%</td>
<td>38%</td>
</tr>
<tr>
<td>≤30 years</td>
<td>41</td>
<td>53</td>
<td>12%</td>
<td>23%</td>
<td>64%</td>
<td>66%</td>
</tr>
<tr>
<td>P</td>
<td></td>
<td></td>
<td>0.18</td>
<td>0.0007</td>
<td>0.007</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Karyotype</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t(4;11) or t(9;22)</td>
<td>9</td>
<td>12</td>
<td>0%</td>
<td>89%</td>
<td>11%</td>
<td>22%</td>
</tr>
<tr>
<td>Other</td>
<td>68</td>
<td>88</td>
<td>9%</td>
<td>35%</td>
<td>55%</td>
<td>57%</td>
</tr>
<tr>
<td>P</td>
<td></td>
<td></td>
<td>0.99</td>
<td>0.0003</td>
<td>0.002</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Time to CR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;4 weeks</td>
<td>9</td>
<td>12</td>
<td>22%</td>
<td>56%</td>
<td>14%</td>
<td>14%</td>
</tr>
<tr>
<td>≤4 weeks</td>
<td>68</td>
<td>88</td>
<td>6%</td>
<td>39%</td>
<td>55%</td>
<td>59%</td>
</tr>
<tr>
<td>P</td>
<td></td>
<td></td>
<td>0.11</td>
<td>0.17</td>
<td>0.05</td>
<td>0.04</td>
</tr>
</tbody>
</table>
## Table 4: Time to starting maintenance chemotherapy

<table>
<thead>
<tr>
<th>Drug</th>
<th>n</th>
<th>Marrow</th>
<th>Blood</th>
<th>P</th>
<th>Time to starting drug</th>
<th>Probability of being on drug 1 year post-transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>All (15-678)</td>
<td>All (34-891) Marrow (24-692) Blood (84)</td>
</tr>
<tr>
<td>6-mercaptopurine</td>
<td>55</td>
<td>25 (71%)</td>
<td>30 (71%)</td>
<td>1</td>
<td>61</td>
<td>74% 84% 67%</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>44</td>
<td>18 (51%)</td>
<td>26 (62%)</td>
<td>0.36</td>
<td>114</td>
<td>51% 60% 46%</td>
</tr>
<tr>
<td>Vincristine-prednisolone</td>
<td>29</td>
<td>8 (23%)</td>
<td>21 (50%)</td>
<td>0.015</td>
<td>83</td>
<td>38% 28% 47%</td>
</tr>
</tbody>
</table>
Table 5: Cox analysis of factors affecting outcome independently amongst patients alive and disease-free on day 120

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Covariate</th>
<th>Favorable</th>
<th>Adverse</th>
<th>Risk ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapse</td>
<td>Disease risk</td>
<td>Standard</td>
<td>Intermediate</td>
<td>3.3 (1.1-9.8)</td>
<td>0.034</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>High</td>
<td>11.1 (3.5-35.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CR-transplant interval</td>
<td>&gt;120 days</td>
<td>Standard</td>
<td>&lt;120 days</td>
<td>2.6 (1.1-6.2)</td>
<td>0.031</td>
</tr>
<tr>
<td>Maintenance therapy</td>
<td>2-3 agents</td>
<td>Intermediate</td>
<td></td>
<td>2.7 (1.0-7.2)</td>
<td>0.049</td>
</tr>
<tr>
<td>Disease-free survival</td>
<td>Disease risk</td>
<td>Standard</td>
<td>Intermediate</td>
<td>3.1 (1.2-7.9)</td>
<td>0.018</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>High</td>
<td>7.2 (2.5-20.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CR-transplant interval</td>
<td>&gt;120 days</td>
<td>Standard</td>
<td>&lt;120 days</td>
<td>2.3 (1.0-5.1)</td>
<td>0.038</td>
</tr>
<tr>
<td>Maintenance therapy</td>
<td>2-3 agents</td>
<td>Intermediate</td>
<td></td>
<td>2.5 (1.0-6.0)</td>
<td>0.046</td>
</tr>
<tr>
<td>Overall survival</td>
<td>Disease risk</td>
<td>Standard</td>
<td>Intermediate</td>
<td>3.0 (1.2-7.7)</td>
<td>0.024</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>High</td>
<td>3.5 (1.2-10.5)</td>
<td>0.024</td>
</tr>
<tr>
<td>Maintenance therapy</td>
<td>2-3 agents</td>
<td>Intermediate</td>
<td></td>
<td>2.9 (1.2-7.1)</td>
<td>0.022</td>
</tr>
</tbody>
</table>
Table 6: The effect of maintenance chemotherapy by risk group. The figures represent 10-year cumulative incidence of relapse and the 10-year probabilities of DFS and OS.

<table>
<thead>
<tr>
<th>Risk</th>
<th>Number of maintenance chemotherapy agents</th>
<th>n</th>
<th>Relapse (%)</th>
<th>DFS (%)</th>
<th>OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard</td>
<td>0-1</td>
<td>7</td>
<td>29 (9-92)</td>
<td>43 (6-80)</td>
<td>36 (0-75)</td>
</tr>
<tr>
<td></td>
<td>2-3</td>
<td>29</td>
<td>17 (7-44)</td>
<td>79 (62-96)</td>
<td>83 (67-99)</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td></td>
<td>0.07</td>
<td>0.002</td>
<td>0.0007</td>
</tr>
<tr>
<td>Intermediate</td>
<td>0-1</td>
<td>12</td>
<td>50 (28-88)</td>
<td>25 (5-50)</td>
<td>33 (7-60)</td>
</tr>
<tr>
<td></td>
<td>2-3</td>
<td>16</td>
<td>45 (26-79)</td>
<td>55 (29-80)</td>
<td>52 (25-78)</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td></td>
<td>0.09</td>
<td>0.008</td>
<td>0.03</td>
</tr>
<tr>
<td>High</td>
<td>0-1</td>
<td>7</td>
<td>86 (63-100)</td>
<td>14 (0-40)</td>
<td>14 (0-40)</td>
</tr>
<tr>
<td></td>
<td>2-3</td>
<td>6</td>
<td>83 (58-100)</td>
<td>0</td>
<td>25 (0-65)</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td></td>
<td>0.75</td>
<td>0.75</td>
<td>0.45</td>
</tr>
</tbody>
</table>
Figure 1: Relapse with 95% confidence limits

30 relapses
Figure 2: Disease-free survival with 95% confidence limits

41 alive in continuous first remission
Figure 3: Overall survival with 95% confidence limits
Figure 4: Relapse: effect of the number of adverse factors (P<0.0001)

- No adverse factor (standard risk): 6 of 36 relapsed
- 1 adverse factor (intermediate risk): 13 of 28 relapsed
- 2 adverse factors (high risk): 11 of 13 relapsed
Figure 5: Disease-free survival: effect of the number of adverse factors (P=0.0003)

- No adverse factor (standard risk): 27 of 36 disease-free
- 1 adverse factor (intermediate risk): 12 of 28 disease-free
- 2 adverse factors (high risk): 2 of 13 disease-free
Figure 6: The effect of maintenance chemotherapy on relapse in patients alive and well on day 120 following the autograft (P=0.004)

0-1 agent; 11 of 20 relapsed

2-3 agents; 16 of 51 relapsed
Figure 7: The effect of maintenance chemotherapy on disease-free survival in patients alive and well on day 120 following the autograft (P=0.0005)

- 2-3 agents: 34 of 51 alive in continuous remission
- 0-1 agent: 7 of 20 alive in continuous remission
The role of post-transplant maintenance chemotherapy in improving the outcome of autotransplantation in adult acute lymphoblastic leukemia

Ray Powles, Bhawna Sirohi, Jennie Treleaven, Samar Kulkarni, Diana Tait, Seema Singhal and Jayesh Mehta