Symposium article

The role of bone marrow transplantation in adult acute lymphocytic leukemia


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Introduction

Adult acute lymphocytic leukemia (ALL) is a hematologic malignancy characterized by an uncontrolled proliferation and accumulation of immature lymphocytes and their progenitors. ALL is most common in children, however a substantial proportion of cases occur in adolescents and adults. Approximately 25% of the acute leukemia cases in adults are ALL. This review is limited to adult ALL.

ALL is a heterogeneous disease. Morphologic and immunologic features are useful in classifying patients with ALL. A French-American-British (FAB) morphologic classification of ALL has been established. This system recognizes 3 types of lymphoblasts termed L1, L2 and L3 [1]. The FAB classification is based on a spectrum of cell properties such as the size ratio of nucleus to cytoplasm, the number and size of nucleoli, and the degree of cytoplasmic basophilia. Adults with ALL have a predominance of L2 morphology. L2 cells are typically large with an irregular nuclear outline. The nucleus may be cleft and it contains one or more large nucleoli. The cytoplasm is deeply basophilic and may be abundant. The L3 morphology, resembling that in Burkitt's lymphoma, is occasionally present in adult ALL. In addition, cytochemical reactions such as periodic acid Schiff reaction (PAS) and acid phosphatase are useful for confirmation.

A second approach in the classification of adult ALL is based on the immune features of leukemic cells [2, 3]. Subtypes of ALL include the common, T, B and null phenotypes. The nomenclature is based on detection on the cell surface of one of the following: the common ALL antigen, a glycoprotein, Mw 100 Kd; receptors for sheep red blood cells (RBCs) or T cell antigens; and immunoglobulin molecules. Null cells lack these surface features. Recent data indicate that most cases of common ALL are committed to the B lymphocyte lineage based on the detection of intracytoplasmic immunoglobulin and immunoglobulin gene rearrangements [4–6]. In adults, 50% of the cases are of the common phenotype, T-ALL account for 20% and B-ALL comprises 20%–70% of the cases. Over 20% of the cases are null-ALL. Using monoclonal antibodies it is now possible to further classify null-ALL; most cases appear to be B-ALL. By the use of monoclonal antibodies, B-ALL can be subdivided into pre-pre-B, pre-B and B and T-ALL into pre-pre-T, pre-T and T-ALL.

Treatment with chemotherapy

The results of chemotherapy in ALL is determined by risk factors. Factors have been identified predicting an adverse effect on outcome of treatment. Therefore in this review these factors will be discussed and correlated with outcome of treatment of the various subgroups of ALL patients.

Treatment dependent variables

There are two treatment dependent variables often evaluated, the initial response to a single cytostatic drug and the time to achieve complete remission after an induction treatment.
In recent childhood ALL studies the initial response to single cytostatic drugs, particularly prednisone and an anthracycline, has been investigated. In two consecutive ALL-BFM trials with 1579 patients [7] and also in an EORTC trial [8] the exposure to pre-induction prednisone was the most predictive factor for event free survival. Similarly, early response to daunorubicin was predictive for better survival. These results indicate that there is probably not a specific 'prednisone response' but that in general a patient population with sensitive leukemic blast cells is selected.

The other treatment dependent variable investigated in several adult studies is the time to achieve complete remission (CR) after induction therapy, at 4–5 weeks or later. This treatment response is one of the most independent prognostic factors in adult ALL. As evident from Table 1, a fast initial response is correlated with a significantly superior outcome compared to late response. It shows the proportion of children and adults achieving CR within or after 8 days or 4 weeks respectively and the correlation to leukemia free survival.

**Table 1. Time to achieve CR and outcome in ALL.**

<table>
<thead>
<tr>
<th></th>
<th>No. of studies</th>
<th>CR Response early/late</th>
<th>LFS Outcome early/late</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adults</strong></td>
<td>5</td>
<td>77%/63% 14%</td>
<td>46%/25%</td>
</tr>
<tr>
<td><strong>Children</strong></td>
<td>4</td>
<td>95%/89% 6%</td>
<td>65%/33%</td>
</tr>
</tbody>
</table>

**Pre-treatment variables**

A great number of pre-treatment variables have been found to have an adverse prognosis in ALL but in recent adult ALL studies with intensive chemotherapy regimens only few similar risk factors for LFS have emerged which are age, initial WBC, karyotype and immunophenotype.

**Age**

Increasing age is the most adverse factor for the CR rate. Whereas in children the CR rate approaches 95%, there is a continuous decline in CR rate from 80%–90% for adolescents down to CR rates of 35%–55% or even less for patients above 60 years. Older age is also prognostic for a poorer remission duration and survival in most adult ALL series and the survival rate at 5 years for patients above 60 years might be even <10% [9]. Reasons for the poor outcome of elderly patients might be a higher treatment toxicity, probably not hematotoxicity since regeneration after chemotherapy is not significantly delayed but mainly other organ toxicity such as liver or cardiotoxicity. This toxicity may lead to incomplete application of a proposed treatment schedule which additionally worsens the outcome. The major reason seems, however, the higher incidence of biologically adverse risk features, particularly the increasing frequency of Ph' + ALL with age.

**Immunological subtype**

**T-ALL.** T-ALL, which constitutes about 20%–25% of adult ALL, formerly had a very poor outcome, particularly for patients with mediastinal mass, with a LFS of 10% (Table 2). Now the CR rate is 80%–85% and LFS has increased to >45% [10]. Although there are no randomized data available, sufficient evidence has accumulated that cyclophosphamide (C) and cytosine arabinoside (AraC), originally selected because of their synergistic action on leukemic cells, are mainly responsible for this improvement. The epipodophyllotoxins and anthracyclines may also contribute.

T-ALL patients can be subclassified according to their thymic or pre-thymic stage. The pre-T-ALL phenotype is characterized by expression of CD7 and TdT activity, lack of a receptor for sheep erythrocytes (E-R-) and negativity for CD1, CD4 and CD8. In a large series of adults with T-ALL (217 patients) those 45 patients (21% of T-ALL) classified as pre-T-ALL had an inferior prognosis with a shorter median remission duration (MRD) 17 mo. vs. 34 mo.) and lower probability of survival [11].

In patients with T-ALL and mediastinal mass, mediastinal irradiation after initial cell reduction by chemotherapy, given either after complete disappearance of, or to the residual tumor, was of benefit in two German multicenter trials in a retrospective analysis [10]. However, the benefit of such an additional mediastinal irradiation in T-ALL is not yet confirmed.

**B-ALL.** There has been a dramatic change in the outcome of B-ALL and Burkitt's lymphomas in several childhood and adult studies. In childhood B-ALL the outcome was significantly improved to CR rates of 81%–96% and LFS rates of up to 76% [12–14]. The essential drugs responsible for this improvement are cyclophosphamide in higher doses, high dose methotrexate and probably high dose AraC. In addition the regimens contain adriamycin or daunorubicin, teniposide or etoposide, vincristine, prednisone, and AraC in conventional doses.

In earlier adult ALL trials results for patients with

**Table 2. Subtype and outcome in adult ALL.**

<table>
<thead>
<tr>
<th>Subtype</th>
<th>N pts.</th>
<th>CR rate</th>
<th>MRD mo.</th>
<th>CCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-ALL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>'ALL'-therapy</td>
<td>63</td>
<td>44%</td>
<td>&lt;10%</td>
<td></td>
</tr>
<tr>
<td>'NHL'-therapy</td>
<td>40</td>
<td>68%</td>
<td>49%</td>
<td></td>
</tr>
<tr>
<td>T-ALL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AraC/C</td>
<td>47</td>
<td>72%</td>
<td>&lt;10%</td>
<td></td>
</tr>
<tr>
<td>AraC/C/T-ALL</td>
<td>253</td>
<td>85%</td>
<td>46%</td>
<td></td>
</tr>
<tr>
<td>Ph/bcr-abl</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ph/bcr-abl</td>
<td>83</td>
<td>80%</td>
<td>n.r.</td>
<td>8%</td>
</tr>
<tr>
<td>Ph/bcr-abl'</td>
<td>59</td>
<td>61%</td>
<td>6–8</td>
<td></td>
</tr>
</tbody>
</table>
B-ALL were very poor (Table 2) with a weighted mean CR rate of 44%, a MRD of 11 months and LFS of <10%. When the recent childhood B-ALL protocols were transferred to adult patients with B-ALL, results were substantially improved giving a weighted mean CR rate of 68% and LFS of 49% [15, 16].

Mixed or hybrid leukemia. Whether ALL patients with expression of myeloid antigens have a poorer outcome is still controversial in different studies. In a recent large analysis of 633 children with ALL, the 43 patients with B-cell precursor ALL being My+ achieved a high CR rate (98%) and also their LFS of 70% was not inferior to 63% in My- ALL patients [17]. However, lower remission rates in My+ ALL (45% vs. 78%) and shorter survival duration are also reported for adult ALL [18].

Cytogenetics
Ph/bcr-abl+ is the subgroup of ALL with the worst prognosis in children as well as in adults. In 11 studies with a total of 213 patients the weighted mean for CR rate is 60%. The MRD in all series is short (5–10 months) and the survival, of 0%–15% at 3 to 5 years, is extremely poor in all reports. This unsatisfactory outcome for Ph+ ALL increases with age from 2%–5% in children up to >44% in patients over 50 years [19].

A new diagnostic approach for Ph+ ALL is the detection of bcr-abl rearrangements by molecular analysis. In ongoing multicenter studies with adequate cytogenetic and molecular analysis the high incidence of about 30% Ph+/bcr-abl+ ALL in adults has been confirmed [20, 21]. The bcr-abl detection is of high prognostic significance since bcr-abl+ patients had a LFS of only 8% compared to 59% for the bcr-abl- group in the German trial. Similarly in a CALGB study the MRD was only 8 months for the bcr-abl+ patients but not reached for bcr-abl- patients.

(4; 11), (8; 14). Adult patients with the cytogenetic translocation (4; 11) have a similar poor prognosis to those with (9; 22) [22, 23]. Most patients with (4; 11) have the immunological subtype pre-pre-B-ALL. The adverse prediction of the 5(8; 14) translocation has lost its prognostic impact with the improved results for patients with B-ALL and Burkitt's lymphoma.

Other prognostic factors
In addition to the above prognostic factors a variety of other adverse prognostic factors have been observed: LDH >300 U/l, low serum IgM or IgG levels, low cholesterol level, low Hbs, high % peripheral blast cells, platelet count >500,000/ul, fibrinogen <100 mg/dl, spleno-, hepato- or hepatosplenomegaly and, in children, kidney enlargement, an abnormal CT brain scan, DAN index <1.16.

### Table 3. Major adverse prognostic factors in adult ALL.

- **Delayed time to reach CR** (>4 or 5 weeks)
- **Immunological subtype**: pre-T-ALL?
  - pre-pre-B-ALL?
  - My+ ALL?
- **Karyotype**: t(9; 22) or bcr-abl+
  - t(4; 11)
- **Higher age**: >35, >50, >60 years
- **High WBC**: >20,000, >35,000, >100,000

### Stratification into risk groups
Whereas in childhood ALL studies stratification into risk groups according to prognostic risk factors is common, it has become feasible in only a few adult ALL trials. Low risk patients (defined as having none or only one of the factors WBC >20,000/30,000/ul, null-ALL or B-ALL, age >35/60 years, Ph+, delayed time to CR >4/5 weeks), had a LFS of 48%–54% at 5 years. Poor risk patients (defined as having at least two of the above factors) had a LFS of 14%–33%.

Clearly the different risk features are associated: in B-ALL, L3 morphology, (4; 18) translocation; in pre-pre-B-ALL, t(4; 11) translocation; but for others such as bcr-abl+ ALL the associated risk factors e.g. time to response, WBC, have to be more precisely defined.

If in studies the stratification is carried out according to the number of risk factors, other correlations have to be considered. Some are evident: in B-ALL L3 morphology, Slg+, the karyotype (18; 14); in pre-pre-B-ALL, the karyotype t(4; 11), in Ph+, B-lineage. Other correlations, e.g. the above with late response to therapy, WBC, age, have to be more precisely defined in larger patient groups.

The better definition of risk groups in ALL may lead to a more specific therapy with regard to the selection of cytostatic drugs, more precise indications for allogeneic, autologous or unrelated bone marrow transplantation and the use of biological response modifiers.

### Treatment with allogeneic bone marrow transplantation

This review focuses on data presented to the International Bone Marrow Transplantation Registry (IBMTR), an international consortium of more than 200 transplant centers. This data set includes about one-half of transplants performed worldwide.

### HLA-identical sibling transplants

Over 3,000 transplants from HLA-identical siblings bone marrow transplants are reported in children and adults with ALL [24–31].

Transplants in advanced ALL result in about 20% 5-year leukemia-free survival; these results are clearly superior to those reported with chemotherapy where
there are no cures. Similarly favorable results are also reported in adults failing to achieve remission despite intensive induction chemotherapy [32, 33]. Treatment failure post transplant results from leukemia relapse, GVHD, interstitial pneumonia, immune deficiency, infection and toxicity. Actuarial relapse risk is about 60% after transplants for advanced ALL.

Results are better after transplants for ALL in second (and sometimes third) remission because of fewer relapse, about 40%. Five-year disease-free survival is about 30%. Survival after second remission transplants is higher in children than adults [31, 34–37]. In most studies, length of first remission typically correlates with relapse risk following second remission transplants [38, 39]. This trend is similar to chemotherapy in second remission. Also, as with chemotherapy, prognostic factors at diagnosis are inoperative once relapse occurs. Variables correlated with relapse and treatment failure after transplants in second remission are summarized in Table 4.

Transplant results are best in persons with ALL in first remission [26, 27, 31, 40, 41]. Typically these are adolescents or young adults or are children with extremely high-risk features at diagnosis. Relapse risk in first remission is about 20%. Risk factors for relapse for persons transplanted in first remission are similar to those predicting relapse after chemotherapy. Five-year leukemia-free survival is about 60% in children and 40% in adults. Risk factors for transplant outcome are indicated in Table 4 [42–48].

A recent IBMTR study in adults compared chemotherapy and transplants in first remission [46]. Relapses were less following transplants versus chemotherapy but leukemia-free survival was similar. Interestingly, decreased relapse risk was most evident in persons with favorable prognostic features rather than those with unfavorable risk factors for relapse. These data suggest delaying transplants until relapse in adults with ALL in first remission.

Another IBMTR study considered whether the timing of transplantation influences outcome in persons with comparable risk factors at diagnosis [47]. In this situation, transplants in first remission result in a superior outcome than when similar persons receive second remission transplants. Here the issue was transplant timing rather than comparing transplants and chemotherapy [48].

A third recent IBMTR study analyzed results of transplants in persons with the 5(9; 22) translocation and/or Ph1-chromosome [49]. These data indicate about 30% three-year leukemia-free survival, similar to other smaller series [50]. Although this result is worse than comparable persons receiving transplants for ALL but without the Ph1-Chromosome, they are widely believed to be superior to results of chemotherapy. Formal comparison of these alternative treatments is progressing. Interestingly, results of transplants in Ph1-chromosome positive ALL were similar in first and second remission and in relapse. Although these data suggest resolving transplants for persons who relapse after chemotherapy, this needs to be studied prospectively.

Recurrent leukemia is a major problem in persons with ALL receiving HLA-identical sibling transplants. Although new conditioning regimens using hyperfractionated total body radiation with cyclophosphamide [51], high doses of cytarabine [52], or etoposide [53] report relatively low relapse rates, none of these regimens is convincingly superior to cyclophosphamide and total body radiation in randomized trials.

Persons with ALL who develop GVHD have a decreased risk of relapse [54, 55]. In one study GVHD was intentionally induced by either decreasing post-transplant immune suppression or by adding T-cells to the graft. The object was to decrease relapse [56]. Unfortunately, this was unsuccessful.

The prognosis of persons who relapse after a bone marrow transplant is poor. Alternatives are chemo-

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**Table 4. Prognostic factors which determine outcome after allogeneic bone marrow transplantation.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Favorable</th>
<th>Unfavorable</th>
<th>First CR*</th>
<th>Second CR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR</td>
<td>P</td>
<td>RR</td>
<td>P</td>
</tr>
</tbody>
</table>

**A. Relapse**

<table>
<thead>
<tr>
<th></th>
<th>MTX</th>
<th>CxA or T-cell</th>
<th>5.2</th>
<th>&lt;0.0003</th>
</tr>
</thead>
<tbody>
<tr>
<td>GVHD prophylaxis</td>
<td>Acute and/or chronic</td>
<td>No acute or chronic</td>
<td>3.1</td>
<td>&lt;0.0004</td>
</tr>
<tr>
<td>WBC at diagnosis</td>
<td>&lt;50 x 109/l</td>
<td>&gt;50 x 109/l</td>
<td>2.5</td>
<td>&lt;0.03</td>
</tr>
<tr>
<td>Relapse occurred</td>
<td>Off chemotherapy</td>
<td>On chemotherapy</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

**B. Treatment failure**

<table>
<thead>
<tr>
<th></th>
<th>With steroids</th>
<th>Without steroids</th>
<th>2.8</th>
<th>&lt;0.0014</th>
</tr>
</thead>
<tbody>
<tr>
<td>GVHD prophylaxis</td>
<td>No acute or chronic</td>
<td>Acute and/or chronic</td>
<td>1.9</td>
<td>&lt;0.0012</td>
</tr>
<tr>
<td>Sex match</td>
<td>M-M, F-F, F-M</td>
<td>M-F</td>
<td>2.2</td>
<td>&lt;0.0012</td>
</tr>
<tr>
<td>Immune phenotype</td>
<td>T-cell</td>
<td>Not T-cell</td>
<td>1.7</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Patient age</td>
<td>&lt;16 yr</td>
<td>&gt;16 yr</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Relapse occurred</td>
<td>Off chemotherapy</td>
<td>On chemotherapy</td>
<td>NA</td>
<td>1.6</td>
</tr>
</tbody>
</table>

* Adults only.
therapy or a second transplant. Approximately one-fourth of these persons achieve remission with chemotherapy; some are long-term survivors [57–59]. Similar results are reported with transplants. In both instances results are best in younger persons and in those relapsing more than one year after the first transplant. There are no randomized trials comparing chemotherapy and transplants in this setting.

**Alternative Donors**

Only one-third of potential transplant recipients with ALL have an HLA-identical sibling donor. Recently, persons with diverse advanced leukemias received transplants from HLA-partially matched related donors or from HLA-matched or HLA-partially matched unrelated donors [60–63]. Compared to HLA-identical sibling transplant donors, alternative donor transplants are associated with increased risks of graft-failure and GVHD. Nevertheless, preliminary encouraging results are reported in persons seemingly otherwise incurable with chemotherapy. There are insufficient numbers of alternative donor transplants in persons with ALL to comment on their efficacy. Furthermore, controlled or randomized trials are not reported.

**Treatment with autologous bone marrow transplantation**

Autologous transplantation utilizes the patient’s own bone marrow for reconstitution after intensive chemotherapy and total body irradiation conditioning is delivered. Successful application of autologous transplantation, however, requires the collection and cryopreservation of suitable numbers of hematopoietic progenitor cells to allow prompt hematologic and immunologic reconstitution after the stem cells are thawed and rein fused. Additionally, however, measures to address potential contamination of the harvested marrow inoculum with viable leukemic progenitor cells must be undertaken. These have included ex vivo bone marrow purging after harvest and before cryopreservation using either leukemia-associated antigen directed immunologic purging techniques or ex vivo chemotherapy of the harvested autologous marrow. Additionally, successful leukemia control after autologous transplantation requires effective anti-leukemic pretransplant conditioning therapy and, in some recent approaches, post-transplant adjunct treatment to prevent leukemia relapse. Clinical studies to date have variably addressed all these elements in the search for optimal autologous marrow transplantation for ALL [64, 65].

**Clinical results of auto-BMT in CRI in adults**

The results of 11 major groups have been listed in Table 5. A total number of 400 patients were transplanted. The median disease-free survival (DFS) rate is 42±2 SE. It can be noted that the follow-up of patients differ between the groups so that the length of DFS per group is different. This makes comparison of data between the groups difficult. In many studies detailed descriptions of disease, age, cytogenetics, duration of remission induction and WBC at diagnosis have not been reported, which makes interpretation of results difficult. In 2 studies, Spinolo et al. [66] and Gilmore et al. [67], prognostic factors of the patient population were available. It appears that the same factors which determine outcome after chemotherapy influence the BMT results. Gorin analyzed the EBMTR data and found that the major prognostic factors were length of remission induction and time interval between onset of CR and BMT (Table 6). Cytogenetic data were not available in the EBMTR registry. It can be noted from Table 5 that the main stumbling block is re-

<table>
<thead>
<tr>
<th>Reference</th>
<th>N (total)</th>
<th>Conditioning</th>
<th>Purging</th>
<th>DFS %</th>
<th>Time post-BMT</th>
<th>Relapse %</th>
</tr>
</thead>
<tbody>
<tr>
<td>[61]</td>
<td>(22)</td>
<td>TBI + Cy or Melphalan</td>
<td>–</td>
<td>40%</td>
<td>3 years</td>
<td>52%</td>
</tr>
<tr>
<td>[79]</td>
<td>14 (37)</td>
<td>TBI + Cy</td>
<td>MoAb + C`</td>
<td>54%</td>
<td>2 years</td>
<td>36%</td>
</tr>
<tr>
<td>[87]</td>
<td>(15)</td>
<td>Melphalan + TBI</td>
<td>–</td>
<td>48%</td>
<td>3 years</td>
<td>N.R.</td>
</tr>
<tr>
<td>[67]</td>
<td>(27)</td>
<td>Cy + TBI + Ara-C</td>
<td>MoAb + C`</td>
<td>32%</td>
<td>&gt;5 years</td>
<td>67%</td>
</tr>
<tr>
<td>[68]</td>
<td>9 (30)</td>
<td>Busulfan + Cy</td>
<td>Asta-Z or mafosfamide</td>
<td>33%+</td>
<td>–</td>
<td>55%+</td>
</tr>
<tr>
<td>[64]</td>
<td>12 (31)</td>
<td>TBI + Cy</td>
<td>4HC</td>
<td>25%</td>
<td>2 years</td>
<td>71%</td>
</tr>
<tr>
<td>[72]</td>
<td>21 (54)</td>
<td>TBI + Cy ± multidrug</td>
<td>MoAb + C`</td>
<td>65%</td>
<td>&gt;2 years</td>
<td>40%+</td>
</tr>
<tr>
<td>[66]</td>
<td>(26)</td>
<td>Cy, RNCU, VP-16</td>
<td>–</td>
<td>54%</td>
<td>4 years</td>
<td>50%+</td>
</tr>
<tr>
<td>[89]</td>
<td>6 (12)</td>
<td>TBI ± Melphalan ± Cy</td>
<td>Immunomagnetic beads (CD10, 19)</td>
<td>50%+</td>
<td>1 year</td>
<td>50%+</td>
</tr>
<tr>
<td>[90]</td>
<td>14 (155)</td>
<td>rTBI + Cy or Ara-C</td>
<td>MoAb + C` or immunotoxin + 4HC</td>
<td>24%</td>
<td>&gt;5 years</td>
<td>60%</td>
</tr>
<tr>
<td>[80]</td>
<td>6 (15)</td>
<td>TBI + Cy</td>
<td>–</td>
<td>43%</td>
<td>2.5 years</td>
<td>54%</td>
</tr>
<tr>
<td>[85]</td>
<td>233 (438)</td>
<td>variable</td>
<td>variable</td>
<td>41%</td>
<td>&gt;3 years</td>
<td>~53%</td>
</tr>
</tbody>
</table>

**Survival, not disease free**

+ Not Kaplan-Meier projection

Abbreviations: MoAb = monoclonal antibody; Cy = cyclophosphamide; N.R. = not reported; C` = complement; EBMTR = European Bone Marrow Transplant Group.
Identification of factors influencing the outcome of auto-BMT in CR1 by the EBMTR database analysis

<table>
<thead>
<tr>
<th>Prognostic factors</th>
<th>DFS (5 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAB classification</td>
<td></td>
</tr>
<tr>
<td>L3</td>
<td>78</td>
</tr>
<tr>
<td>L1, L2</td>
<td>40</td>
</tr>
<tr>
<td>Interval diagnosis – CR</td>
<td></td>
</tr>
<tr>
<td>&lt;40 days</td>
<td>58</td>
</tr>
<tr>
<td>&gt;40 days</td>
<td>42</td>
</tr>
</tbody>
</table>

Table 6: Identification of factors influencing the outcome of auto-BMT in CR1 by the EBMTR database analysis

Clinical results of auto-BMT in CR2 in adults

The results of auto-BMT in CR2 have been outlined in Table 7. A total number of 182 patients were transplanted by 9 groups. The median disease-free survival rate is 28% ± 15%, which is less than the DFS in first remission. The relapse rate is 65% (36-88), the main factor of failure after BMT. Analysis of the EBMTR results revealed that time interval between initial diagnosis and BMT as well as the time between onset of CR and BMT were determining factors influencing outcome (Table 5).

Clinical results of randomized studies between auto-BMT and chemotherapy

The French group of Therapy of Adult ALL designed a study to evaluate the use of auto-BMT as intensification of remission in ALL [68]. After consolidation therapy, patients with ALL under 50 were randomized between a chemotherapy regimen and intensive consolidation with auto-BMT. With a median follow-up of 30 months, the projected 3-year DFS of the auto-BMT treated patients is 49% ± 5% and 42% ± 5% for the chemotherapy treated patients. The relapse rate in the auto-BMT arm is 57% versus 61% in the chemotherapy arm. These results are not statistically significant. In that study, patients with a related HLA-identical matched donor received an allogeneic transplant and the projected 3-year DFS is 55% ± 5%. In this arm the relapse rate was 33%, significantly less than the relapse rate in the chemotherapy and auto-BMT treated patient groups.

Purging of marrow in ALL

Leukemic blasts may differ in certain characteristics from the clonogenic leukemia progenitor cells capable of sustaining clinically active malignancy. During morphologically confirmed remission, marrow blasts are not recognizable microscopically, but it is generally accepted that viable clonogenic leukemia progenitor cells might proliferate and result in relapse in reinfused along with the cryopreserved autologous marrow [69]. Most clinical experience to date has, therefore, utilized ex vivo marrow purging to deplete or eliminate leukemic progenitors from the marrow inoculum.

Marrow purging techniques in ALL have used primarily immunologic methods directed towards leukemia-associated antigens expressed on the cell surface. Monoclonal antibodies against B lineage antigens (CD9, CD10, CD19, CD20, CD22, CD24) or % lineage antigens (CD5, CD7) have been used to opsonize cells and trigger the lytic capacity of exogenous complement. Alternatively, such antibodies have been combined with chemical toxins (e.g., ricin, pokeweed antiviral protein) as biochemico recombinant immunotoxins. These immunotoxins use the specificity of the monoclonal antibody and are able to selectively poison cells expressing the leukemia asso-

Table 7: Results of autologous BMT in ALL CR2

<table>
<thead>
<tr>
<th>Author</th>
<th>N (total)</th>
<th>Conditioning</th>
<th>Purging</th>
<th>DFS %</th>
<th>Time post-BMT</th>
<th>Relapse %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buckner</td>
<td>23</td>
<td>TBI + Cy</td>
<td>MoAb + C</td>
<td>17%</td>
<td>2 years</td>
<td>75%</td>
</tr>
<tr>
<td>Dicke</td>
<td>14</td>
<td>CBV</td>
<td>–</td>
<td>14%</td>
<td>8 years</td>
<td>70%</td>
</tr>
<tr>
<td>Meloni</td>
<td>16</td>
<td>Busulfan + Cy</td>
<td>Asta-Z or mafosfamide</td>
<td>40%</td>
<td>–</td>
<td>40%</td>
</tr>
<tr>
<td>Santos</td>
<td>19</td>
<td>TBI + Cy</td>
<td>HLC</td>
<td>10%</td>
<td>–</td>
<td>88%</td>
</tr>
<tr>
<td>Schroeder</td>
<td>7</td>
<td>Melphalan + TBI</td>
<td>Campath-1</td>
<td>50%*</td>
<td>25 months</td>
<td>N.R.</td>
</tr>
<tr>
<td>Simonsson</td>
<td>29</td>
<td>TBI + Cy ± multi drug</td>
<td>MoAb + C</td>
<td>31%</td>
<td>&gt;2 years</td>
<td>60%</td>
</tr>
<tr>
<td>Soiffer</td>
<td>48</td>
<td>Cy + TBI ± Ara-C</td>
<td>MoAb + C</td>
<td>34%</td>
<td>4 years</td>
<td>36%</td>
</tr>
<tr>
<td>Gorin (EBMTG Survey)</td>
<td>205</td>
<td>variable</td>
<td>variable</td>
<td>27%</td>
<td>&gt;3 years</td>
<td>~70%</td>
</tr>
</tbody>
</table>

* Survival, not disease free
b No Kaplan-Meier projection

Abbreviations: MoAb = monoclonal antibody, N.R. = not reported, Cy = cyclophosphamide, C = complement, EBMTG = European Bone Marrow Transplant Group
ciated antigen while sparing hematopoietic progenitors [69–71].

Ex vivo incubations of marrow with low dose chemotherapy designed to exploit the therapeutic window between leukemic cell sensitivity and hematopoietic progenitor sensitivity have been used as well. Most frequently, 4-hydroperoxycyclophosphamide (4HC) has been used either alone or in combination with immunologic purging techniques, but in some studies, combination ex vivo chemotherapy purging has been tested as well. Some reports have correlated the number of clonogenic leukemia progenitors present after purging with the clinical results of autologous transplantation [64, 72, 70, 73]. Such correlations have been interpreted as support for the efficacy of ex vivo marrow purging [74].

There are important conceptual limitations to these techniques [75]. First, these methods rarely eliminate more than 3 to 4 logs of leukemia cells. Second, leukemia cells are heterogeneous in cell surface antigen expression and drug sensitivity. Although antibodies or drugs may eliminate most leukemia cells, they may not affect putative leukemia progenitor cells [76, 77]. The efficacy of leukemia cell depletion is difficult to evaluate in vitro since assays of leukemia progenitor cells are imperfect and of unproven biologic import. The clinical value of ex vivo treatment of the graft to prevent leukemia relapse following an autotransplant is unproven so far and will be difficult to evaluate until more effective pretransplant antileukemia conditioning is developed.

Pretransplant conditioning

Autologous transplantation usually produces less transplant-related morbidity and mortality compared to allografting. In most studies, similar pretransplant conditioning has been employed for autologous and allogeneic transplants [78–83]. However, the additional safety of autologous transplantation might justify using more intensive and possible more effective conditioning regimens, but this approach has not been fully explored. Pretransplant conditioning has most often included total body irradiation (TBI) in single or multiple fractions delivered at varying dose rates, energies and total doses. Fractionated TBI is often used and reportedly induces less acute toxicity. Techniques to protect vulnerable tissues (lung shielding) and intensify antileukemic radiation (chest wall boosting) as well as high energy techniques designed to increment the marrow dose have also been evaluated. Imaginative delivery techniques including radioimmunoconjugates or radiochemicals which accumulate in the marrow cavity are being developed experimentally to more effectively deplete the body leukemia burden. Though high dose cyclophosphamide (100–200 mg/kg) has been the standard chemotherapy agent used with TBI before transplantation, some more recent reports have shown favorable results using cytarabine, etoposide, melphalan or combination drug chemoradiotherapy [74].

Adjunct antileukemia therapy after autologous BMT

The first reports of curative therapy childhood ALL emphasized that extended duration maintenance therapy is critical for long-term disease control. However, the compromised marrow reserve of autograft recipients has impaired attempts to test maintenance therapy after transplantation. In one small controlled trial at the University of Minnesota, post BMT maintenance (after allogeneic and autologous transplantation) was both difficult to deliver and ineffective at preventing or delaying leukemia relapse [84]. In the M.D. Anderson series, in adult ALL after transplantation with CBV in first remission with unmanipulated marrow cells, maintenance chemotherapy could be administered and even the extra cycle of first intensification could be repeated after BMT [65].

In the Powles’ study [85], thirty-eight patients with poor risk acute lymphoblastic leukemia in first remission (age 3–41 years, median 21 years) received maintenance chemotherapy following autologous bone marrow transplantation (ABMT). Patients were conditioned for ABMT with high dose melphalan and single fraction total body irradiation (TBI). Maintenance chemotherapy was commenced in a total of 26 patients, and was tolerated to a median daily dose of 40.5 mg/m² and a median weekly methotrexate dose of 8.3 mg/m². Twenty patients remain alive in first remission with a projected disease free survival of 50% and a median follow-up in survivors of 200 weeks (range, 48–387 weeks). Eleven patients have relapsed, at a median of 4.5 months from ABMT. This group of ABMT patients was compared with remission patients with ALL receiving conventional chemotherapy on the United Kingdom Medical Research Council trials UKALL X and XA. After stratifying for major risk factors and allowing for the delay from remission to transplant, a significant reduction in the risk of relapse after ABMT could be demonstrated (p = 0.04). Disease free survival was not significantly increased due to transplant related toxicity. This study strongly suggests that maintenance chemotherapy to prevent relapse after ABMT for ALL is well tolerated and warrants assessment in a formal controlled study [85].

Modern approaches to adjunct therapy have focused on non-specific immunotherapy or immunotoxins directed at leukemia associated antigens. Activation of cytotoxic T lymphocytes (CTL) or natural killer (NK) cells with recombinant Interleukin-2 (IL-2) has received considerable interest in recent years. IL-2 has been given in high doses, often in conjunction with exogenously cultured lymphokine-activated killer (LAK) cells and has demonstrated antineoplastic activity in various human tumors including some lymphoid neoplasms. However, the excess toxicity associated with high dose IL-2/LAK cell therapy has stimulated interest in more modest and hopefully less toxic applications of IL-2 after autologous transplantation. No re-
ports have yet demonstrated clinically useful antineoplastic activity of IL-2 given after autologous transplantation; however, immune activation (either CTL, NK or LAK) has been observed. A recent Minnesota trial of IL-2 given immediately post autologous transplantation for ALL resulted in enhancement of CTL activity against ALL targets [86]. In another report, low-dose, long-duration IL-2 therapy induced potent NK/LAK activation activity in autologous BMT recipients [87]. Ongoing studies will be required to test the clinical utility of immune effectors induced by IL-2 therapy.

Monoclonal antibodies or immunotoxins [70, 72] have also been considered for in vivo use in the post BMT setting. Because of their immune specificity in targeting leukemia associated antigens and because they are non-myelosuppressive, this therapy is well suited to the treatment of post transplant minimal residual disease.

These and other adjunct therapies offer great promise in enhancing the effectiveness of autologous transplantation in preventing leukemic relapse. They may substitute for the missing graft versus leukemia effect which accounts for some of the antileukemic potential of allogeneic transplantation. Because the toxicity of conventional chemotherapy conditioning is near maximal, these novel alternative therapies might be added to allogeneic transplantation as well. Future experimental and clinical studies have great potential to expand the applicability and effectiveness of autologous transplantation for ALL.

Conclusion

Bone marrow transplants are an effective treatment in ALL. HLA-identical transplants for family donors result in a significantly lower relapse rate but the higher treatment related mortality offsets the lower relapse rate so that the DFS is not significantly different for chemotherapy and auto-BMT. In advanced ALL allo-BMT is superior to chemotherapy since no or few disease-free surviving patients with chemotherapy after first relapse have been described.

The results with auto-BMT are not superior to chemotherapy although a trend of higher DFS rates is apparent and long term disease free survival with auto-BMT in disease after first relapse has been revealed by various groups. Although very promising, it needs to be seen if the DFS rate is significantly better than alternate treatment with chemotherapy alone.

Not only is there progress in transplants for ALL, but chemotherapy is also improving. Consequently, the greatest immediate challenge is to determine how to best use these modalities to cure persons with ALL.

Acknowledgement

The authors' thanks are due to Mrs. Kathy White for editing and typing the manuscript.

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