

## Tendências / Trends

## The role of allogeneic stem cell transplantation in the therapy of adult acute lymphoblastic leukemia

### *O papel do transplante alogênico de células progenitoras na terapia de leucemia linfoblástica aguda em adultos*

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While adult patients with acute lymphoblastic leukemia (ALL) can now achieve complete remission (CR) rates of up to 90% with intensive chemotherapy regimens, only 25-50% of these patients remain in long-term remission. Current research efforts are focused on innovative post-remission strategies with the goal of improving disease-free (DFS) and overall survival (OS). The identification of different prognostic groups based on the biology of the malignant clone and clinical patterns of disease presentation allows for risk-adapted therapy. Multiple randomized trials have demonstrated that hematopoietic stem cell transplantation (SCT) improves the outcome of patients with high-risk ALL. Among high-risk patients, the presence of disease at time of stem cell transplantation, and the source of stem cells used have great impact on survival. The incorporation of monoclonal antibodies into the transplant preparative regimen may improve transplant efficacy. The use of donor lymphocyte infusions (DLI) is still under investigation in this patient population. Rev. bras. hematol. hemoter. 2005;27(1):61-69.

**Key words:** Acute lymphoblastic leukemia; allogeneic stem cell transplantation; prognostic factors.

### Introduction

Adult patients with acute lymphoblastic leukemia (ALL) can now achieve complete remission (CR) rates of 80-90%.<sup>1-3</sup> However, only 25-50% of these patients remain in remission. Current research efforts are focused on innovative post-remission strategies with the goal of improving disease-free (DFS) and overall survival (OS). The identification of different prognostic groups based on the biology of the malignant clone and prognostic factors allows for risk-adapted therapy. Multiple randomized trials have demonstrated that hematopoietic stem cell transplantation (SCT) improves the outcome of patients with high-risk ALL. In this review, we will define the different disease risk groups, the clinical outcomes of major transplant trials for ALL, and the therapeutic factors that affect outcome after SCT.

### Prognostic factors in adult ALL

Several biologic features and specific clinical characteristics have been consistently noted to influence the outcome of adult ALL and impact on risk-stratification (Figure 1). Older age, an elevated white blood cell count (WBC) at presentation, and failure to achieve a clinical remission within the first four weeks of treatment are generally

Figure 1. Adverse prognostic features in adult ALL

- Age greater than 60 years\*
- WBC count greater than 30,000/uL
- Cytogenetics: t(9;22)(q34;q11), trisomy 8, t(4;11)(q21;q23), monosomy 7, a hypodiploid karyotype, t(1;19)(q23;p13)
- Delayed time to complete remission, greater than 4 weeks

\*Established in US series; German series use age 30-, 35-, or 50-years as cut-off.

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accepted adverse clinical features. The detection of specific recurring cytogenetic abnormalities has emerged as the most important prognostic factor for risk stratification of adults with ALL.<sup>4</sup> Clonal chromosomal aberrations can be detected in cells from 62% to 85% of adult ALL patients, and numerous studies have shown their significance as predictors of outcome.<sup>5-8</sup>

In addition to the adverse prognostic factors listed in Figure 1, the detection of minimal residual disease (MRD) using qualitative or semi-quantitative polymerase chain reaction (PCR) or flow cytometric techniques also provides important prognostic information.<sup>9</sup> Persistent MRD positivity post induction appears to be associated with an increased risk of relapse.<sup>10</sup> In addition, MRD positivity after transplant is associated with an increased risk of relapse. In 28 Ph+ ALL patients, Radich et al found that the relative risk (RR) for relapse was significantly higher for patients with a detectable BCR/ABL transcript following transplantation than for those without detectable BCR/ABL (RR = 5.7, p = 0.025).<sup>11</sup> Furthermore, the risk of relapse was greater for patients with a p190 fusion transcript than for those with p210 BCR/ABL. The median time from detection of a positive PCR result to relapse was 94 days. Other investigators have found similar results.<sup>12-15</sup>

### Results with Allogeneic Transplantation for High-risk ALL

#### First complete remission

Review of a number of small, phase II trials in high-risk adult ALL who have undergone ASCT in CR1 suggest a higher DFS when compared with historic controls based on conventional chemotherapy.<sup>16-22</sup> High-risk in these studies was defined as patients having at least one or more of the following: age greater than 30 years, WBC greater than 30x10<sup>9</sup>/L at presentation, extramedullary disease, unfavorable

cytogenetic abnormalities, and requiring more than four weeks to achieve CR. As shown in Table 1, DFS ranges broadly from 21% -71%, with a 3 to 8 year follow-up. The large difference in the outcome of these phase II studies is influenced by multiple variables, including differences in patient selection, type of graft versus host disease (GVHD) prophylaxis, and different supportive care regimens. The choice of preparative regimen may have played a smaller role since all received a total body irradiation (TBI)-based conditioning regimen.

Two large, prospective controlled trials have directly compared transplant with chemotherapy in patients in CR1. The French Leucemie Aigue Lymphoblastique de l'Adulte LALA 87 protocol was a cooperative study that examined the role of chemotherapy and SCT for adult ALL patients. This was a prospective, randomized study, initiated in November 1986 and completed in July 1991, which enrolled 634 newly diagnosed patients (572 patients after exclusions) and reported 10 year follow-up results. The median age of patients entered onto this trial was 33 years. All patients received standard induction therapy and CNS prophylaxis. Among those patients who achieved CR (76%), patients greater than 50 years-old received post-remission chemotherapy, those up to the age of 40 continued to a TBI-based allogeneic SCT if they had a histocompatible donor, and all others were further randomized to consolidation chemotherapy followed by long-term maintenance therapy, or autologous SCT. Survival at 10 years was significantly greater for the allogeneic SCT group compared to consolidation chemotherapy (46% SCT vs. 31% chemotherapy, p=0.04). Furthermore, when these groups were stratified into high and standard risk, there was a highly significant benefit for allogeneic SCT in the high risk subset (high-risk: 44% SCT, 11% chemotherapy, p=0.009; standard-risk: 49% SCT, 43% chemotherapy, p=0.6).<sup>23,24</sup> There was no statistically significant difference in outcome between

patients who received autologous SCT vs. consolidation chemotherapy (34% SCT, 29% chemotherapy, p=0.6). Risk stratification did not change these findings.

The United Kingdom Medical Research Council's (MRC) UKALL XII/Eastern Cooperative Oncology Group (ECOG) E2993 is also conducting a prospective trial to define the role of allogeneic SCT, autologous SCT, and conventional dose chemotherapy in adult patients with ALL in CR1. Initiated in 1993, over 1200 patients have been enrolled to date. All patients received two phases of induction therapy, and continued to allogeneic SCT if they

Table 1. Allogeneic Transplantation for ALL in CR1

Study	No.Pt	Med. Age (Yr.)	Prep. Regimen	GVHD Proph	II-IV GVHD	3-Yr.DFS%
Wingard, 1990 <sup>23</sup>	18	24 (5-36)	CY/TBI	CSA +/- MP	8	42
Blaise, 1990 <sup>17</sup>	25	22 (4-36)	CY/ftBI, ML/ftBI CY/ML/ftBI	MR	7	71
Chao, 1991 <sup>18</sup>	53	28 (1-45)	Ara-C/CY/TBI CY/TBI VP-16/TBI	CSA +/- MP MTX +/- MP	6	61
Doney, 1991 <sup>20</sup>	41	22 (18-50)	CY/ftBI or single dose TBI	MR	7	21 (5 yr)
Sutton, 1993 <sup>21</sup> (retrospective review)	184	25 (15-44)	CY/TBI (majority)	MR	15 deaths	49.5 (6 yr)
Vey, 1994 <sup>22</sup>	29	24 (16-41)	CY/TBI	CSA/MTX	7	62 (8 yr)
DeWitte, 1994 <sup>19</sup>	22	15-51	CY/TBI	CSA	NR	58

CY, cyclophosphamide; TBI, total body irradiation; ftBI, fractionated TBI; VP-16, etoposide; MR, multiple regimens; NR, not reported; CSA, cyclosporine; MTX, methotrexate; MP, methylprednisolone

achieved CR and had a histocompatible donor. The remaining patients were randomized to standard consolidation/maintenance therapy for 2.5 years vs. a single autologous SCT. The conditioning regimen for both allogeneic and autologous transplants was fractionated TBI (1320 cGy) and VP-16 (60 mg/kg). Based on the data presented in an abstract in 2001,<sup>25</sup> 239 patients received an allogeneic SCT (170 Ph-) and 291 patients received chemotherapy or autologous SCT. The overall event free survival (EFS) for the allogeneic SCT group was 54% vs. 34% ( $p=.04$ ) for the chemotherapy or autologous BMT group. Excluding the t(9;22) karyotype, when patients were stratified into high or standard risk, the difference in EFS becomes more dramatic in the high risk subset (allogeneic BMT 44% vs. chemo./autologous BMT 26%,  $p=.06$ ). In conclusion, both of these large prospective controlled studies determined that allogeneic SCT improved the outcome for adults with high-risk ALL in CR1.

### Beyond CR1

There are no data suggesting that durable remissions can be achieved with standard chemotherapy for adults with ALL who fail to achieve an initial complete remission or have recurrent disease. Second complete remissions can often be achieved, but are typically of shorter duration than the initial response. Patients who undergo an allogeneic SCT in CR2 have achieved long-term leukemia-free survival (LFS) rates between 14% to 43%, as illustrated in Table 2.<sup>19,22,26-29</sup> Therefore, if patients are in remission, allogeneic SCT results in greater LFS when compared to chemotherapy. The primary cause of failure is relapse (>50%).

### Primary refractory ALL

With current induction regimens, only 5-10% of adults with newly diagnosed ALL fail to achieve remission with initial induction chemotherapy. These patients often have poor prognostic factors at presentation, and additional attempts at induction chemotherapy are usually of limited benefit. Several studies suggest that patients with an HLA identical sibling benefit by receiving allogeneic transplantation without undergoing a second attempt at induction therapy.<sup>30-32</sup> In the largest of these studies, 38 patients with ALL failing to achieve remission received HLA identical sibling transplants.

Approximately 35% of these patients with refractory disease became long-term disease-free survivors. In a retrospective review of patients with primary refractory and relapsed ALL, the records of 314 adults were reviewed for disease outcome at MD Anderson Cancer Center between 1980 and 1997. Allogeneic SCT was performed in 29 patients (13 in salvage and 16 in CR2). The rates for durable CR post transplant were comparable between the two groups; 5/13 (38%) in the salvage group and 5/16 (31%) in the remission group. Although patient numbers are small and a variety of transplant conditioning regimens were used, these results corroborate the findings of earlier studies, and suggest that allogeneic transplant should be considered for these patients with an otherwise dismal chance of long-term survival.<sup>33,34</sup>

### Philadelphia Chromosome Positive All

Ph+ acute lymphoblastic leukemia is well established to have a very poor prognosis. The recent incorporation of imatinib mesylate into combination chemotherapy has been a major development. Imatinib is a highly effective, targeted therapy directed against the *BCR/ABL* tyrosine kinase that is over-expressed as a result of the t(9;22) (q34;q11) in chronic myeloid leukemia and Ph+ ALL.<sup>33</sup> The rapid initial response to therapy and minimal side effects make imatinib an ideal drug for incorporation into clinical trials for treatment of newly diagnosed Ph+ ALL. In a study by Thomas et al, 20 patients with newly diagnosed Ph+ ALL received concurrent hyper-CVAD (cyclophosphamide, vincristine, Adriamycin, dexamethasone) and imatinib at the 400mg dose. All patients achieved CR. Ten patients received allogeneic SCT in first CR within a median of 3.5 months, with 9 remaining alive in CR with a median follow-up of 12 months.<sup>35</sup> Although this is an early study with very short follow-up, these results are very encouraging for a subset of patients with a traditionally very poor prognosis.

Data from the MRC UKALL XII/ECOG E2993 study described earlier revealed similar poor results for Ph+ patients treated with chemotherapy only. In this on-going, prospective, randomized study, 167 Ph+ patients were treated on the MRC UKALL XII/ECOG E2993 protocol between 1993 and 2000. Seventy-two patients received a matched-related or unrelated donor transplant in CR1, while 7 received an autologous transplant and 88 received chemotherapy due to lack of donors. As expected, the 5-year EFS and OS were significantly higher for the allogeneic transplant group, 36% and 42%, respectively, compared to 17% and 19% for the nonallogeneic transplant groups.<sup>36</sup> These results suggest that the presence of the Ph chromosome is most detrimental to maintaining long-term remission, and underscore the need for long-term follow-up of ongoing studies with imatinib. Until long-term results are obtained, all Ph+ patients should still receive an allogeneic SCT in CR1 if a donor is available.

Table 2. Allogeneic Transplantation for ALL in CR2

Study	No.Pt.	LFS (%)	Risk of Relapse
IBMTR, 1989 <sup>27</sup>	208 (high risk)	22 (4 yr)	56
	97 (standard ris)	36 (4 yr)	49
Barrett, 1989 <sup>28</sup>	391	26 (5yr)	52
Wingard, 1990 <sup>23</sup>	36	43 (5 yr)	26
Doney, 1991 <sup>20</sup>	48	15 (5 yr)	64
Greinix, 1998 <sup>29</sup>	27	14 (3 yr)	78
Michallet, 2000 <sup>30</sup>	47	44+/-12%	44+/-12%

Table 3. Allogeneic Transplantation for Ph+ ALL

Study	No. Pt.	Med. Age (Yr.)	Prep. Regimen	3-Yr.DFS%
Stockschlader, 1995 <sup>39</sup>	10	31	VP-16/CY/TBI	46
Dunlop, 1996 <sup>40</sup>	11	27	TBI-based	21.8
Snyder, 1999 <sup>38</sup>	23	30	VP-16/fTBI	65 (SCT before 1992) 81 (SCT after 1992)

CY, cyclophosphamide; TBI, total body irradiation; fTBI, fractionated TBI; VP-16, etoposide

Disease outcome from a series of single-center retrospective studies are listed in Table 3.<sup>18,37-39</sup> It is difficult to draw conclusions from these small series that vary considerably with respect to type of patient (CR1 or beyond), type of preparative regimen, GVHD prophylaxis, and supportive care. The reported DFS rate varies widely between 20% to 80%, and it is difficult to determine if a particular preparative regimen is superior. Generally, data from most series suggest that Ph+ patients fare best when transplanted in CR1. Follow-up from the prospective MRC UKALL XII/ECOG E2993 study is eagerly anticipated. Trials incorporating novel agents such as imatinib mesylate, or using reduced intensity preparative regimens, are currently in progress, and these results are also anticipated.

The feasibility of alternative donor transplants has been investigated in Ph+ ALL patients in efforts to provide allogeneic transplantation to patients who lack a matched sibling. At the Fred Hutchinson Cancer Research Center, matched unrelated donor (MUD) transplantation was investigated in 18 patients with Ph+ ALL between 1988 and 1995, and the probability of LFS at 2 years was 49%, similar to rates reported for matched sibling-SCT.<sup>40</sup> However, it must be emphasized that this was a highly selected population of relatively young patients. Too few adults with Ph+ ALL have received cord blood or haploidentical donor transplants to comment on results.

Donor lymphocyte infusion (DLI) has also been investigated in patients with Ph+ ALL, and shows very limited efficacy,<sup>41,42</sup> in contrast to Ph+ CML. It is not known whether this disparity in efficacy stems from differences in the immunogenicity of the p190 *BCR/ABL* (most Ph+ ALL) vs. the p210 *BCR/ABL* (most CML), differences in growth kinetics of Ph+ ALL relapse (high tumor burden) vs. those in CML (lower tumor burden), or other disease specific factors.

## Factors Influencing Transplant Outcome

### Preparative Regimens

#### Radiation-based

Several different preparative regimens for allogeneic SCT have been described in attempts to decrease transplant related mortality (TRM) and improve DFS. The most widely

used regimen is the combination of total body irradiation (TBI) and cyclophosphamide developed by Thomas and colleagues. TBI can be administered as single dose, or fractionated over 3-5 days. A comparative analysis of fractionated-dose vs. single-dose TBI in adult ALL patients showed a significantly higher TRM in the single-dose group ( $p=0.017$ ), but an increase in the relapse rate of the fractionated-dose group; consequently, there were no differences in the overall LFS between the 2 groups.<sup>20</sup> The Minnesota Group compared TBI/cyclophosphamide with TBI/Ara-C in a study including both adults and children, and found no outcome difference in regards to toxicity or outcome.<sup>43</sup> The City of Hope group studied fractionated TBI with etoposide followed by SCT in patients with advanced leukemia. A Phase I/II trial indicated that etoposide at 60 mg/kg is the maximum tolerated dose when combined with TBI. In that study, 36 ALL patients were treated; 20 had relapsed disease. The DFS was 57%, with a 32% relapse rate suggesting that the regimen has significant activity in advanced ALL.<sup>44</sup>

Novel methods to allow selective delivery of radiation to sites of leukemia without increasing systemic toxicity are currently under investigation. One method with great potential is the incorporation of radiolabeled monoclonal antibodies (MoAb) into the conditioning regimen. Preliminary results from Phase I trials are intriguing.<sup>45,46</sup> The ultimate benefits of this approach with respect to safety and improvements in survival will be defined by Phase II studies.

#### Non-radiation based preparative regimens

Non-radiation containing regimens, most commonly busulfan and cyclophosphamide have been investigated in hopes of decreasing radiation-related complications. Fractionated TBI/etoposide was compared with busulfan/cyclophosphamide in a prospective, randomized study conducted by the Southwest Oncology Group (SWOG 8612). There was no significant difference with respect to toxicity, incidence of acute GVHD, OS or DFS between the two groups. The leading cause for treatment failure was leukemia relapse (39%).<sup>56</sup> Furthermore, retrospective analysis of registry data from the International Bone Marrow Transplant Registry (IBMTR) shows similar rates for LFS and relapse when busulfan/cyclophosphamide is compared to TBI/cyclophosphamide.<sup>47</sup>

The addition of monoclonal antibodies to the transplant conditioning regimen is another method of developing potentially more effective, and less toxic, regimens. Antibody therapy is generally considered to be an option when the target antigen is expressed on at least 30% of the targeted cells.<sup>48</sup> ALL blasts express a variety of B- or T-cell differentiation antigens, such as CD19, CD20, CD22, CD33, and CD52, which can serve as targets for directed therapy.<sup>48</sup>

Phase I data are available for antibody therapy directed against CD19, CD20, and CD52, and suggest that antibodies should be used as an adjunct to chemotherapy. The efficacy for Moabs as monotherapy is limited, especially in the setting of overt relapse or rapidly progressive disease.<sup>49,50</sup> Definitive data from Phase II and III trials are pending.

Campath-1H, a humanized MoAb developed against the CD52 antigen, is particularly interesting since it targets a subset of ALL for disease eradication, as well as provides a novel method of T-cell depletion to prevent GVHD in the allogeneic transplant setting. Novitzky et al evaluated 13 patients with ALL (8 in CR1) and 37 patients with AML (33 in CR1), who had undergone HLA-identical sibling transplants. The conditioning regimen consisted of TBI/cyclophosphamide. Bone marrow or PBSC were exposed to CAMPATH-1H ex-vivo. Patients received no post-transplant immunosuppression. All but 1 patient engrafted, and only 22% of all patients developed grade I or II GVHD; there was no severe GVHD. There is concern that the immunosuppressive effect of Campath-1H may inhibit the immune graft-vs-malignancy effect and 54% (7/13) of the ALL patients on this study relapsed.<sup>51</sup> Large, randomized studies will be required to determine whether inclusion of Campath-1H will improve the overall outcome for patients undergoing transplantation for ALL.

#### **Non-myeloablative SCT (NMSCT)**

Numerous studies have now demonstrated successful donor stem cell engraftment with NMSCT for hematologic and solid organ malignancies. These regimens use reduced doses of chemotherapy +/- low dose TBI as immune suppression to prevent graft rejection and allow development of an immune graft-vs-malignancy (GVM) effect. GVM appears to be operative against ALL; the major evidence being a reduced rate of relapse in patients who have GVHD. However, ALL appears less effected by GVM than the other major forms of leukemia and the role of NMSCT requires further evaluation. The major benefit of NMSCT is a lower risk of drug toxicity and treatment related morbidity and mortality, which is most relevant to older or debilitated patients unable to tolerate ablative preparative regimens. This option would be particularly attractive for patients with Ph+ ALL where the majority of patients are older than 50 years.

Martino et al reported on the largest published cohort of adult ALL patients receiving NMSCT.<sup>52</sup> He analyzed the results of 27 patients with high-risk ALL that were included in 4 prospective studies. Similar to other reduced-intensity transplant series, these were older patients with advanced disease. The median age was 50 years; 23 (85%) patients were beyond CR1, 44% were chemorefractory, and 41% were Ph+. Donors were mismatched related donors or volunteer unrelated donors in 12 cases (44%). The incidence of grades II-IV acute GVHD was 48%, and 13 of 18 evaluable patients (72%) developed chronic GVHD. With a median follow-up of

809 days, the incidence of TRM was 23%, the probability of OS was 31%, and the incidence of disease progression was 49% at 2 years. The incidence of disease progression in patients with and without GVHD, 35% and 47%, respectively, approached statistical significance ( $p=0.05$ ). The incidence of disease relapse was 33% in patients transplanted in CR compared to 60% in those with overt disease.

These observations for NMSCT must be validated in well-defined prospective trials. NMSCT, as an immunotherapeutic approach, is probably most appropriate in patients with low bulk disease. In this study, and others, a higher relapse rate was observed for patients transplanted with overt disease.<sup>53</sup> Thus, NMSCT does not appear indicated for patients with overt relapsed or resistant ALL. The initial studies appear most promising for older patients transplanted in remission, and the reported OS and TRM rates were quite favorable considering the advanced disease state of the patients and the number of unrelated transplants included in this series. Thus, it is reasonable to enroll older patients (age >50 years) and those with a high risk of TRM onto prospective studies of NMSCT. Younger allogeneic transplant candidates without major comorbidities, should still receive high dose therapy with ablative preparative regimens, as established effective treatment for ALL.

#### **Source of Stem Cells**

##### **Bone marrow vs. peripheral blood stem cells**

Bensinger et al published a prospective, randomized trial comparing bone marrow (BM) to peripheral blood as the source of stem cells. It was concluded from this study that allogeneic PBSC result in faster engraftment without an increased risk of GVHD (median day to neutrophil recovery defined as  $>500/\text{mm}^3$ , 16 vs. 21,  $p\text{-value} < 0.001$ ; median day to platelet recovery defined as  $>20,000/\text{mm}^3$ , 13 vs. 19,  $p\text{-value} < 0.001$ ). It was also observed that patients who received PBSC had a lower incidence of relapse at 2 years, and higher OS and DFS.<sup>51</sup> While similar subsequent series have confirmed that PBSC result in faster engraftment, a large retrospective analysis from the IBMTR and EBMT showed that the incidence of chronic GVHD was significantly higher with the use of PBSC (65% vs. 53%,  $p=0.02$ ). In addition, the risk of relapse was not significantly different between these two groups.<sup>54</sup> Thus, a large, multicenter, prospective study was developed to help define the role of PBSC in allogeneic SCT. In this collaborative effort by the BMT-CTN, adult leukemia patients requiring MUD transplantation will be randomized to BM or PBSC donors. Results of this trial are eagerly anticipated.

##### **Umbilical Cord Blood (UCB)**

Recently, UCB transplantation (UCBT) is beginning to emerge as a viable, alternative hematopoietic stem cell source for patients who lack an HLA-matched donor. UCBT is less likely to produce severe GVHD compared to bone marrow

transplantation, and thus has the advantage of allowing for greater HLA disparity between donor and recipient. Its disadvantage, however, is the significantly lower cell dose in UCB when compared to PBSC or BM (the cell dose in one average UCB unit is 1/10 of a typical BM allograft and 1/100 of a PBSC allograft), predictably resulting in a longer time to engraftment, and potentially greater early post-transplant complications. UCB transplants have had the best results in children where a relatively high cell dose/kg can be administered. There has been a greater risk of complications in adult recipients.

More than 500 adults have undergone UCBT worldwide,<sup>55-60</sup> mainly for hematologic malignancies. Similar to the pediatric series, the majority of patients received HLA-mismatched grafts and myeloablative regimens. The largest series was reported by Eurocord, and contains 108 adults, with 32 cases of ALL, with a mean follow up of 20 months. The mean age was 26 years (range 15-53 years), mean weight 60 kg (range 35-110 kg), and mean number of nucleated cells infused  $1.7 \times 10^7/\text{kg}$ . The overall one-year survival was 27%. Survival for early disease stage patients was 39% vs. 17% for those transplanted with more advanced disease. The 60-day probability of neutrophil engraftment was 81% at a mean time of 32 days (range 13-60 days). The incidence of acute GVHD  $\geq$  II was 38%. Most deaths were due to infection or GVHD. These findings were corroborated by other series. The TRM at 100 days approached 43-54% for the myeloablative regimens, and 28-48% using non-myeloablative regimens,<sup>55</sup> with main reasons for TRM being regimen-related toxicity, infection, and relapse. Nucleate cell dose was a significant variable, conferring better outcome when the cell dose was  $>2 \times 10^7/\text{kg}$  and/or CD34 cells  $> 1.2 \times 10^5/\text{kg}$ .<sup>56,58</sup> HLA disparity had less influence on EFS.<sup>56</sup> In summary, despite cell dose limitations, UCBT on clinical protocols for may be a viable option for selected adult patients with limited treatment options. Current research in UCB expansion may help to overcome the cell dose limitations and contribute toward reducing the TRM.

#### **Source of Donor Cells: Partially matched related or matched unrelated donors**

The majority of studies indicate that the best chance for cure for refractory or high-risk ALL is allogeneic SCT with a matched related donor. Unfortunately, less than 30% of these patients have a matched sibling donor. Thus, much work continues to be done in making partially matched related donor (PMRD) and matched unrelated donor (MUD) transplantation safe and more feasible as curative therapy. Typically these transplants have been associated with a higher risk of graft rejection, GVHD, and infection. However, more precise HLA matching of donor and recipient via the use of high resolution allele-based typing for class I and II HLA molecules, has allowed selection of better matched donors; this has resulted in a progressive improvement in

the incidence of severe GVHD, and survival in patients undergoing MUD transplantation.<sup>61</sup>

Two large, retrospective series compared the outcome of MUD SCT with autologous SCT. Weisdorf et al. reported the results of 517 ALL patients (median age 14 years, range 1-50) who received MUD-SCT and compared them to 195 patients (median age 18 years, range 1-50) who underwent autologous SCT between 1989 and 1998. The proportion of patients in CR1 vs. CR2 was similar for both groups. However, patients receiving MUD transplants had a greater frequency of high-risk karyotypes and elevated WBC count at presentation. TRM was higher in the MUD-SCT vs. the autologous SCT group (42% vs. 20%,  $p=0.004$ ). Conversely, relapse was more frequent after autologous SCT (49% vs. 14% in CR1, 64% vs. 25% in CR2), resulting in net similar outcomes with either transplant approach. Three-year survival rates were 45-50% for patients transplanted in CR1 and 30-40% for patients in CR2.<sup>62</sup> The Acute Leukemia Working Party of the European Cooperative Group for Blood and Marrow Transplantation (EBMT) reported very similar outcomes. A significantly higher TRM, from GVHD and graft failure, in the MUD-SCT group was offset by a significantly higher risk of relapse in the autologous SCT group, resulting in similar 2-year LFS for both groups (39% MUD, 32% auto).<sup>63</sup>

Due to the small numbers of patients and differing approaches to partially matched related donor (PMRD) transplantation, little data exists for this investigational approach. Most studies suggest a higher rate of rejection and acute GVHD, but similar overall survival for patients with donors matched for 5 of the 6 HLA A, B and DR antigens as with fully matched sibling donors.<sup>64</sup> Greater degrees of mismatch are associated for higher risks of rejection, GVHD and treatment related mortality, and an autologous SCT may become preferable in the absence of an HLA-matched donor.<sup>65</sup> In summary, the decision to proceed with MUD or autologous transplantation, or to proceed with other "Phase I" approaches for these high-risk patients currently remains very complex, and should be based on the specific situation of each individual patient.

#### **The Role of T-cell Depletion**

Studies have shown consistently that a major therapeutic effect of allogeneic SCT is derived from the GVM effect, with a reduced risk of relapse noted in patients with GVHD. The major difficulty lies in separating the beneficial GVM effect from the adverse consequences of GVHD. GVHD is primarily mediated by donor derived T-lymphocytes. One approach to prevent acute GVHD, is to deplete T-cells from the donor marrow or PBSC. After initial immune reconstitution, donor T-lymphocytes (DLI) can be administered with a lower risk of GVHD to enhance the GVM anti-leukemic effect. As described previously, Campath-1H, directed against the CD52 antigen, provides a novel approach for both ex vivo and in vivo T-cell purging.

The role of T-cell depleted SCT remains controversial. While T-cell depleted SCT are associated with a lower incidence of acute and chronic GVHD, GVM effects may be reduced and leukemia free survival has not been improved in controlled trials for either matched sibling or unrelated donor transplants. Several groups have reported a decreased risk of relapse with T-cell depleted SCT by manipulating the preparative regimen to compensate for potential lack of a GVM effect, reporting EFS rates up to 64%, which compare very favorably with non T-cell depleted transplants.<sup>66,67</sup>

### Immunomodulation with DLI

Table 4 summarizes results obtained from both single institution and registry data, and demonstrates a consistent decrease in relapse rates for patients who develop GVHD vs. those who do not.<sup>19,68,69</sup> A GVM effect that is associated with the presence of GVHD has been described in ALL, AML, and CML; interestingly this effect appears most potent in ALL and is reflected by the data in Table 4.<sup>70</sup> However, in distinct contrast to observations of the benefit of GVHD in reducing the relapse rate, there is a marked absence of a significant GVM effect in ALL following DLI. In contrast to CML and AML where DLI often results in complete remissions in patients with relapsed disease following allogeneic transplant, DLI does not appear to be effective for ALL with relapse following an allogeneic transplant.<sup>71</sup>

Study	Number of Patients	Risk of Relapse	(%)
Doney, 1991 <sup>20</sup>	192 (SCT in CR2)	No GVHD	80
		Grade II-IV GVHD	40
Sullivan, 1989 <sup>72</sup>	200 (SCT in CR)  (SCT in relapse)	No GVHD	56
		acute GVHD	27
		acute & chronic GVHD	22
		No GVHD	81
Horowitz, 1990 <sup>73</sup> (IBMTR)	349 (SCT in CR1)	acute GVHD	39
		acute & chronic GVHD	43
		No GVHD	44
		chronic GVHD	17
		acute & chronic GVHD	20
			15

### Long-term Complications of Allogeneic SCT

Socie et al analyzed the characteristics of 6691 patients listed in the IBMTR who underwent allogeneic SCT for hematologic malignancies between January 1980 and December 1993.<sup>72</sup> The median duration of follow-up was 80 months. Mortality rates in this cohort were compared with those of an age-, sex-, and nationality-matched general population. For ALL patients, the relative mortality rate was 20.1 two years after transplantation, 25.9 five years after transplantation, and 15.4 ten years after transplantation. Not

surprisingly, recurrent leukemia was the chief cause of death with older age associated with an increased risk of relapse in the ALL group (48% vs. 11% relapses in the overall group). Chronic GVHD was the second leading cause of death overall, with 23% observed in the ALL cohort. The incidence of secondary cancers was 10% in the ALL group.

Quality of life and psychosocial functioning are major issues following allogeneic SCT. Broers et al evaluated quality of life in a prospective study of 125 consecutive patients who underwent BMT between 1987 and 1992.<sup>73</sup> Patients were evaluated with questionnaires measuring quality of life, functional limitations, psychological distress, anxiety, depression, and self-esteem. Nearly 90% of patients reported a good to excellent quality of life at 3 years. Changes in quality of life and psychological distress could be explained entirely by changes in functional limitations and somatic symptoms. One such limitation is the late neurotoxic effects of BMT on cognitive functioning. Harder et al investigated this phenomenon in a consecutively treated cohort of long-term adult survivors.<sup>74</sup> All received total body irradiation up to 12 Gy. Assessment took place 22-82 months after BMT. Mild to moderate cognitive impairment was found in 60% of patients. Compared with healthy population norms, selective attention and executive function, information processing speed, verbal learning, and verbal and visual memory were most likely to be affected. Therefore, cognitive functioning should be used as an outcome parameter in BMT studies, and emphasis should be placed on interventions that help patients cope with their physical limitations.

### Conclusion

In conclusion, allogeneic SCT has been demonstrated to have a major therapeutic benefit for selected patients with high-risk ALL. However, much work remains to be done to improve survival for patients with this challenging disease. Results of trials of novel strategies are eagerly awaited including the incorporation of molecularly targeted chemotherapy, targeted immunotherapy using monoclonal antibodies or adoptive cellular therapy, and novel non-myeloablative preparative regimens with promise to decrease treatment-related morbidity and improve survival.

### Resumo

*Enquanto pacientes adultos com leucemia linfoblástica aguda (LLA) podem alcançar taxas de remissão completa (RC) de até 90% com regimes quimioterápicos intensivos, somente 25-50% destes pacientes mantêm remissão em prazos longos. Esforços de pesquisas atuais focam estratégias inovadoras pós-remissão com o objetivo de melhorar a sobrevida livre de doença e sobrevida global. A identificação dos grupos prognósticos diferentes com base na biologia da mutação maligna e os padrões clínicos da apresentação da*

doença permitem terapia adaptada ao risco. Ensaios múltiplos randomizados têm mostrado que transplante das células hematopoiéticas melhora os resultados dos pacientes com LLA de alto risco. Entre os pacientes de alto risco, a presença da doença na hora do transplante das células progenitoras e a fonte destas células utilizadas, têm um grande impacto em sobrevivência. A incorporação de anticorpos monoclonais no regime preparativo pode melhorar a eficácia do procedimento. O uso das infusões de linfócitos do doador está ainda sobre investigação nestes pacientes. *Rev. bras. hematol. hemoter.* 2005;27(1):61-69.

**Palavras-chave:** Leucemia linfoblástica aguda; transplante alogênico de células progenitoras; fatores prognósticos.

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