

## REVIEW

# Allogeneic transplantation for ALL in adults

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**Allogeneic transplantation is an effective treatment for adult patients with high-risk ALL, including patients in first or second remission. Although only a few studies have evaluated the optimal transplant regimens, the data would suggest that a TBI-based regimen results in better disease control. Although not as potent as it is in other hematologic malignancies, the GVL effect is an important component of achieving cure of ALL. Because of the toxicity of the fully ablative regimen, reduced-intensity transplants are being explored in older patients with ALL when the prognosis is especially poor with standard chemotherapy.**

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## Prognostic features in the treatment of ALL in the adult

Cytogenetic abnormalities found in patients with ALL are important predictors of treatment outcome. In many instances, results of cytogenetic studies can help to direct treatment, highlighting where more aggressive treatment, such as allogeneic transplantation, should be considered. Chromosomal changes are found in 60–85% of all cases of ALL.<sup>5,6</sup> Numerical chromosome abnormalities, either alone or in association with structural changes, are found in about half of ALL cases. Although more than 30 distinct nonrandomly occurring rearrangements are presently known in ALL, a few particular cytogenetic anomalies are significantly more common than others and determine the prognosis for the patient. The Third International Workshop on Chromosomes in Leukemia (TIWCL) identified several significant differences between groups of patients, based on results of cytogenetic studies. Translocations t(8;14), t(4;11) and 14q+ correlate with a higher risk of central nervous system involvement, while t(4;11) and t(9;22) were associated with a higher leukocyte and blast count and risk for relapse. Recently, karyotype complexity has been identified as a predictor of treatment failure and can be used to risk stratify patients in future trials.<sup>7</sup>

The most common cytogenetic abnormality in adult ALL is the Ph+ chromosome. The Ph+ chromosome appears in about 95% of patients with CML, in about 1–2% of patients with AML as well as in up to 5% of children and 15–30% of adults with ALL<sup>8</sup> and increases with age. In contrast to CML, in which the bcr-abl hybrid protein in patients almost always measures 210 kDa (the p210 protein), about half of the patients with ALL and the Ph+ chromosome have a 190 kDa protein (p195). The development of bcr-abl-specific tyrosine kinase inhibitors has changed the treatment of ALL to include these drugs in the initial induction treatment, leading to an improved remission success and potentially improved disease-free survival (DFS).<sup>8–10</sup>

As with any other hematologic malignancy, the decision of whether and when to proceed to allogeneic transplant is often dictated by prognostic features identified at diagnosis and response to treatment. Initial treatment of adult patients with ALL has evolved over the past few decades, with an increase in the intensity of treatment and with the addition of consolidation and maintenance arms of treatment. Overall, CR rates have risen to as high as 80–90% of those patients under the age of 60.<sup>4,10–16</sup> However,

## Introduction

ALL is characterized by clonal proliferation, accumulation and tissue infiltration of immature lymphoid cells of the bone marrow. Although ALL accounts for approximately 80% of childhood leukemias in the United States, a second peak occurs around age 50, and there is an increase in incidence with increasing age. Age greater than 60 years, leukocyte count greater than 30 000, non T-cell phenotype, lack of mediastinal adenopathy, poor performance status at diagnosis, Philadelphia chromosome positive (Ph+) at cytogenetic analysis as well as the finding of other chromosomal translocations such as t(4;11), t(1;19) or t(8;14) all predict for a poor long-term outcome even with aggressive chemotherapy. Those patients requiring more than 4 weeks of induction therapy to achieve remission or who have detectable molecular or immunophenotypic evidence of disease while in remission also have a poorer prognosis.<sup>1–4</sup>

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the higher dose regimens do select for disease that is more chemotherapy resistant when relapses do occur. Second remissions occur with lower frequency than in previous years and, when achieved, tend to be shorter lasting. New treatment protocols incorporating monoclonal antibodies (anti-CD22, anti-CD20, anti-CD52) into the early treatment of patients with ALL are being tested for their impact on improving DFS.<sup>17</sup>

Currently, the overall DFS for adult patients with ALL is 35%, with those patients with T-cell ALL having the better treatment outcomes compared to all other subtypes of ALL in the adult.<sup>4,10-16</sup> Some recent studies suggest that, for young adult patients, a chemotherapy treatment program used for high-risk pediatric patients may improve prognosis for this subgroup of patients with adult ALL.<sup>18</sup>

### **Evolving prognostic role of minimal residual disease in ALL**

In addition to age and cytogenetic analysis at the time of diagnosis, the most important prognostic factor, and a direct reflection of sensitivity to chemotherapy, is the achievement of a CR. Thus, a slower time to achieving a remission is an indicator of relative chemoresistance, similar to what has been observed in pediatric patients. Those patients who take more than one cycle of induction chemotherapy have a poor long-term prognosis and a shorter remission duration.<sup>4,12,13</sup>

A more quantitative approach to assess the response of an individual to chemotherapy is the measurement of minimal residual disease (MRD) at various time points after therapy. This is emerging as an independent prognostic factor that reflects the resistance of the cells to chemotherapy and allows potential individualization of treatment.<sup>19,20</sup> The assessment allows the identification of patients at high risk for relapse, despite achieving a morphologic remission, and who may benefit from early transplantation. Studies are being performed to determine the most predictive time point for its measurement. It appears that after consolidation, a high level of MRD at  $10^{-4}$  is associated with a high risk of relapse, with a rising level of MRD on treatment also portending relapse.<sup>19,20</sup> In some studies, a high level of MRD after induction and consolidation has been identified as a high-risk feature, despite the achievement of a morphologic remission and the absence of high-risk cytogenetics.<sup>19-21</sup> Conversely, the identification of patients who are sensitive to chemotherapy and achieve a low level of MRD (non-detectable) may identify a group of patients who do not need transplantation or can wait until there is clear evidence of relapse.<sup>19-22</sup> It also remains to be determined what the benefit of transplant may be in patients who are in first remission but have evidence of a new factor defining high-risk disease, that is high MRD. Thus, the future of treatment of adult patients with ALL in first remission may be refined to determine those patients who are unlikely to benefit from further chemotherapy and should be considered for transplantation during first remission.

### **Allogeneic transplantation in first CR using a myeloablative transplant regimen**

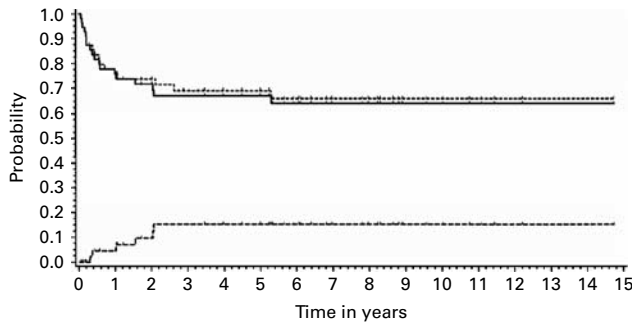
Allogeneic transplantation in first CR (CR1) is generally reserved for those patients who present with poor risk features, such as those described earlier. In several phase 2 studies, patients with high-risk disease treated with allogeneic transplantation had a DFS longer than would have been predicted. Depending on the risk factors present at diagnosis in an individual patient, standard chemotherapy leads to continued remissions ranging from less than 10% to more than 50%.<sup>12</sup> Studies have been conducted to indicate that transplant offers some groups of high-risk patients long-term disease survival rates of between 40 and 60%, with most patients being treated with a TBI-based transplant regimen.<sup>23-25</sup> At the City of Hope and Stanford, two series of patients with high-risk features who were transplanted in CR1 have been recently updated. Selection criteria included WBC >25 000; chromosomal translocations t(9;22), t(4;11), t(8;14); age older than 30; extramedullary disease at the time of diagnosis; and/or requiring more than 4 weeks to achieve a CR. Two-thirds of the patients had at least one risk factor and the remaining patients had two or more high-risk features at presentation. The majority of these patients underwent hematopoietic cell transplantation (HCT) in the first 4 months after achieving a CR. HCT during first remission led to prolonged DFS in this patient population who would otherwise have been expected to fare poorly. At a median follow-up of more than 5 years, the probability of event-free survival was 64% with a relapse rate of 15%<sup>25</sup> (Figure 1).

The French Group on Therapy for Adult ALL conducted a study comparing chemotherapy to autologous SCT and allogeneic BMT.<sup>16</sup> Although the overall results of treatment did not show a treatment advantage for the allogeneic transplant group, subgroup analysis revealed that those patients with high-risk disease had a higher 5-year survival of 44% as opposed to 20% in the other two groups (Figure 2). The recently completed UK ALL XII/ECOG 2993 trial showed that an allogeneic transplant resulted in better disease control compared to chemotherapy or autologous transplant, with survival benefit seen mostly in younger patients.<sup>26</sup> In some centers, allogeneic transplantation is offered to all patients with a sibling donor with ALL in CR1 as the most effective means to cure the disease. A recent economic analysis of transplantation for patients with ALL in first remission suggested that this therapeutic approach also had an acceptable cost-effectiveness profile.<sup>27</sup>

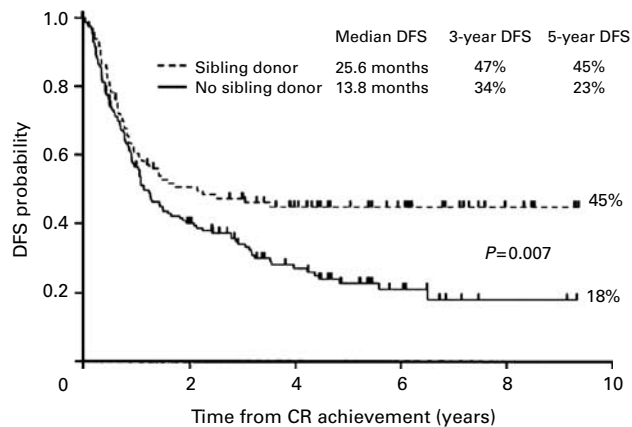
### **Hematopoietic stem cell transplantation for Ph + ALL**

Historically, the dismal outcome with chemotherapy has led to trials focusing on the use of allogeneic transplantation for treatment of adult Ph + ALL. Most have been single-institution studies using a variety of regimens, and the cure rate varies from 30 to 65%, dependent upon age and remission status.<sup>28</sup> Investigators from City of Hope and Stanford have analyzed their experience in 44 patients

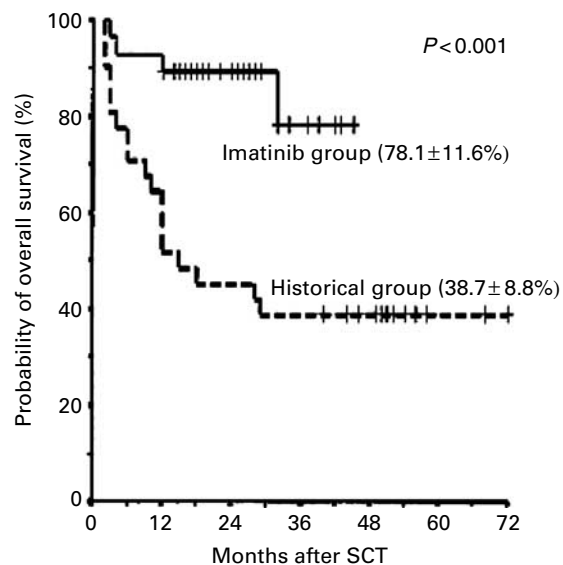
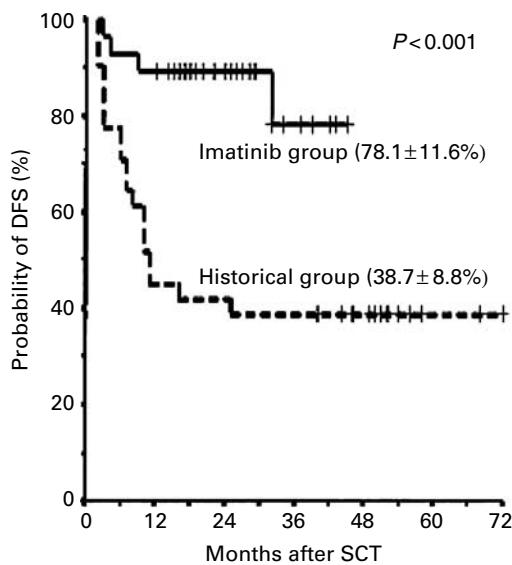
with Ph + ALL transplanted from HLA-identical siblings while in CR1 between 1984 and 1997, with all patients having 10-year follow-up. All patients but two were conditioned with FTBI (1320 cGy) and high-dose etoposide



**Figure 1** Probability of event-free survival (EFS), overall survival and relapse for 55 adult patients with high-risk ALL transplanted in first remission. Updated with permission.<sup>24</sup>



**Figure 2** DFS according to genetic randomization. The group with a sibling donor comprised 100 patients, whereas that with no sibling donor included 159 patients.<sup>15</sup> DFS, disease-free survival.



**Figure 3** Probabilities of DFS and overall survival in the imatinib group versus the historical group. Solid line indicates imatinib group; dotted line, historical group.<sup>28</sup> DFS, disease-free survival.

(60 mg/kg). The 3-year probability of DFS and relapse was 55 and 18%, respectively. Beyond first remission, stem cell transplantation is curative in a much smaller minority of patients but remains the treatment of choice.

The development of imatinib and other tyrosine kinase inhibitors for the treatment of bcr-abl-positive hematopoietic malignancy has changed the upfront treatment paradigm and also may affect the outcome after transplantation. Recently, the feasibility of performing allogeneic stem cell transplant after first-line imatinib plus chemotherapy has been reported.<sup>29</sup> In this series, 29 adult patients who completed induction therapy were treated with allogeneic transplantation, and the authors compared their results with 31 patients who had received transplantation in their unit prior to the availability of imatinib treatment. The data suggest that the risk of relapse was significantly less in the imatinib group (3.5 versus 47.3%) ( $P=0.02$ ), potentially reflecting a lower burden of MRD at the time of transplant and allowing a higher percentage of patients to come to transplant in a good first remission. The results also indicated a superiority in DFS (76 versus 38%) ( $P=0.01$ ) without much difference in the transplant-related toxicities (Figure 3). Thus, in the same way that imatinib may be able to improve the upfront success of induction therapy and potential long-term outcome of patients with Ph + ALL, entering transplant with lower burden of disease may improve the cure rate for such patients. In addition, recent studies have demonstrated the feasibility of giving imatinib following allogeneic transplant for bcr-abl-positive hematologic malignancy and can be used either preemptively or to treat any MRD detected after transplant prior to relapse instead of using a donor lymphocyte infusion.<sup>30</sup>

### Relapsed or refractory ALL

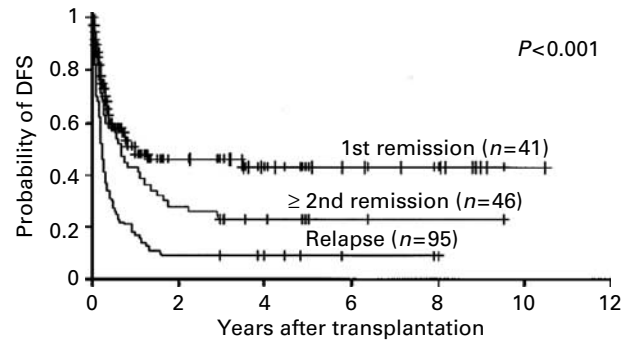
ALL is refractory to primary chemotherapy in approximately 10–15% of patients, and transplant can be

successfully used to achieve both a remission and long-term control in approximately 20% of patients.<sup>23</sup> Of all those patients who achieve a CR1 to primary therapy, approximately 50–70% will relapse. On the basis of risk of relapse in most patients, HLA typing should be performed when treatment is initiated to know the transplant options early in treatment. Relapsed ALL in an adult is not curable, but remissions are sometimes achieved with re-induction with either a standard vincristine, prednisone and anthracycline or with a cytarabine-based regimen, particularly high-dose Ara-C combined with an anthracycline or clofarabine.<sup>31–33</sup> Available data from the IBMTR show that patients transplanted from an HLA-identical sibling for ALL in second CR (CR2) have approximately a 35–40% chance of long-term DFS, while those transplanted with disease not in remission have a DFS of only 10–20%.<sup>34</sup> Figure 4 shows the overall DFS for patients with ALL, depending on their remission status, who underwent allogeneic transplantation.<sup>35</sup> Comparable results can now be achieved for patients receiving a transplant from an unrelated donor. This is an option for those patients with very high risk disease in first remission or in any patient with relapsed disease, but who lack a sibling donor.<sup>36,37</sup>

#### Regimen development for allogeneic HCT for ALL

The most commonly used regimen for transplantation of patients with ALL is CY plus TBI. Several different preparative regimens have been developed, each based on substituting a different chemotherapeutic agent for CY in combination with TBI for patients with ALL. High-dose fractionated TBI in combination with high-dose Ara-C has been employed by several centers and, with the exception of a small series of pediatric patients at Case Western Reserve, there has been no significant improvement in DFS with this regimen in recipients of allogeneic HCT from sibling donors.<sup>38,39</sup>

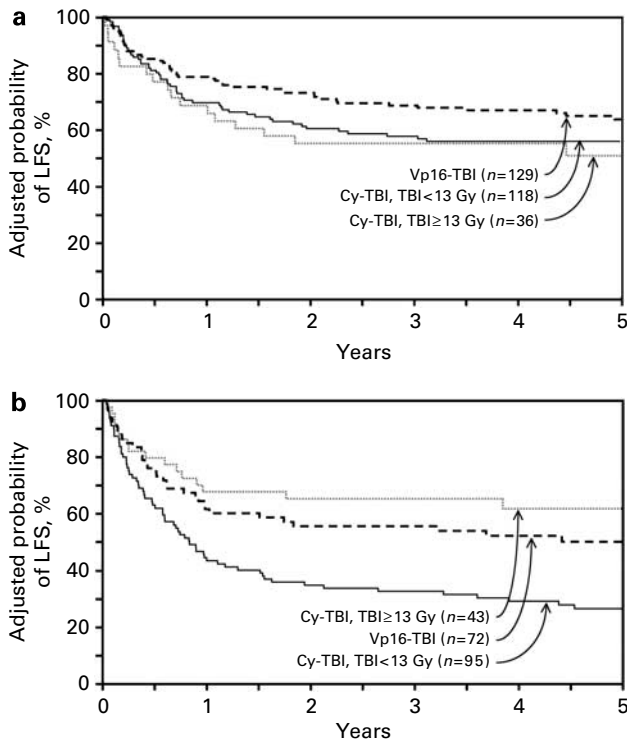
Investigators at Johns Hopkins University approached the problem by substituting BU for TBI in order to decrease the long-term side effects of TBI and determine the efficacy of high-dose combined alkylating therapy in eliminating leukemic cells.<sup>40,41</sup> These nonradiation-dependent regimens have shown activity in the treatment of advanced ALL, suggesting that TBI is not an absolute requirement for successful treatment of ALL by HCT. A retrospective analysis from the IBMTR found that a conventional CY/TBI regimen was superior to a non-TBI-containing regimen of BU plus CY, with a 3-year survival of 55 versus 40% for BU/CY.<sup>42</sup> However, despite these differences in survival, the risk of relapse was similar. A recent study of BU, Fludarabine and 400 cGy of TBI, which would be considered a myeloablative regimen, showed a low transplant-related mortality of 3% and a projected DFS of 65%.<sup>43</sup> The group at the City of Hope National Medical Center studied the substitution of etoposide (VP16) for CY in combination with fractionated TBI (13.2 Gy) followed by allogeneic HCT.<sup>44</sup> A phase 1–2 trial indicated that a VP16 dose of 60 mg/kg is the maximum tolerated dose when combined with TBI. In that study, 36 patients with ALL were treated, 20 of whom were



**Figure 4** Long-term survival in patients with ALL demonstrating the impact of remission status on the outcome of transplant.

in relapse. The actual DFS was 57% with a 32% relapse rate, suggesting that the regimen had significant activity in patients with advanced ALL, a result confirmed in a subsequent trial from the Southwest Oncology Group.<sup>45</sup> A subsequent study from City of Hope/Stanford showed a 64% DFS for adult patients undergoing transplantation with this regimen in CR1 (see section on Allogeneic transplant for ALL in first remission). The recently completed UK ALL XII/ECOG 2993 Trial, a comparative study of chemotherapy, autologous and allogeneic stem cell transplantation, utilized this regimen for patients in CR1. An interim report of overall event-free survival for the allogeneic stem cell transplantation group was 58 versus 39% for the chemotherapy or autologous stem cell transplantation group.<sup>26</sup>

A comparative analysis of TBI combined with either CY or etoposide chemotherapy was conducted to determine the relative efficacy of the chemotherapy in the transplant regimen.<sup>24</sup> The outcomes of 298 patients with ALL in CR1 or CR2 receiving HLA-matched sibling allografts after CY–TBI conditioning, with 204 patients receiving etoposide and TBI, were compared. In this analysis, four groups were compared based on the radiation dose: CY–TBI < 13 Gy ( $n = 217$ ), CY–TBI > 13 Gy ( $n = 81$ ), etoposide–TBI < 13 Gy ( $n = 53$ ) and etoposide–TBI > 13 Gy ( $n = 151$ ). Analyses of relapse, leukemia-free survival, and survival were performed separately for CR1 and CR2 transplantations. Transplant-related mortality did not differ by conditioning regimen. In CR1, there were no significant differences also in relapse, leukemia-free survival or survival by conditioning regimen. In CR2, the outcomes differed among conditioning groups. In comparison with CY–TBI < 13 Gy, the risks of relapse, treatment failure (inverse of leukemia-free survival) and mortality tended to be lower with etoposide (regardless of TBI dose) or with TBI doses > 13 Gy. For both CR1 and CR2 transplantations, causes of death were similar among the groups; disease recurrence accounted for 47% of deaths. Those data indicate that for HLA-identical sibling allografts for patients with ALL in CR2, there is an advantage in substituting etoposide for CY or, when CY is used, in increasing the TBI dose to > 13 Gy (Figure 5).



**Figure 5** Adjusted probability (derived from multivariate regression models) of LFS after HLA-identical sibling transplantations for ALL in CR1 (a) or CR2 (b), according to the pretransplantation conditioning regimen (pointwise *P*-value at 5 years for CR1 patients: etoposide-TBI versus CY-TBI  $P < 13$  Gy,  $P = 0.21$ ; etoposide-TBI versus CY-TBI  $\geq 13$  Gy,  $P = 0.17$ ; CY-TBI  $P < 13$  Gy versus CY-TBI  $\geq 13$  Gy,  $P = 0.59$ ; pointwise *P*-value at 5 years for CR2 patients: etoposide-TBI versus CY-TBI  $P < 13$  Gy,  $P = 0.002$ ; etoposide-TBI versus CY-TBI  $\geq 13$  Gy,  $P = 0.23$ ; CY-TBI  $P < 13$  Gy versus CY-TBI  $\geq 13$  Gy,  $P < 0.001$ ). Vp16 indicates etoposide. CR1, first CR; CR2, second CR; LFS, leukemia-free survival.

### Radioimmunotherapy for ALL

Studies in AML have shown lower relapse rates with higher doses of TBI, suggesting that methods that can selectively deliver radiation to sites of leukemia without increasing systemic toxicity might be of benefit to the patient. The use of tumor-reactive monoclonal antibody (MAB) conjugated with local acting radionuclides such as iodine-131 ( $^{131}\text{I}$ ) or yttrium-90 ( $^{90}\text{Y}$ ) is being explored to accomplish the goal of decreased relapse. Initial studies conducted in Seattle in an animal model showed the feasibility of this novel approach, and subsequent phase 1 and phase 2 studies in patients have been initiated. These studies have demonstrated that initial targeting of marrow and other sites of leukemia could be accomplished using  $^{131}\text{I}$ -conjugated MABs. The most recent studies have focused on an MAB reactive with CD45, an antigen that is found in leukemic cells as well as hematopoietic tissue and, unlike CD33, does not internalize after antibody binding. A phase 1 trial of  $^{131}\text{I}$  anti-CD45 MAB plus CY and TBI for advanced leukemia was completed.<sup>46</sup> This study focused on the biodistribution and toxicity of escalating doses of targeted radiation combined with 120 mg/kg CY and 12 Gy TBI followed by matched related HCT or autologous BMT.

Among 44 patients, 5 had ALL in relapse or refractory disease and 5 were in CR2 or third CR of ALL. Eighty-four percent of the patients had a favorable biodistribution of antibody with a higher estimated radiation absorbed dose to marrow and spleen than in normal tissues. Thirty-four patients received a therapeutic dose of  $^{131}\text{I}$  labeled with 76–612 mg  $^{131}\text{I}$  designed to deliver an estimated radiation absorbed dose to liver of 3.5–12.25 Gy. In the group of nine patients treated for ALL, six of whom underwent allogeneic and three autologous HCT, two died of infection, four relapsed and three survived 10, 45 and 57 months after transplantation. This study demonstrated that  $^{131}\text{I}$  anti-CD45 antibody can deliver appreciable supplemental doses of radiation to the marrow (approximately 24 Gy) and spleen when combined with conventional fractionated TBI. Estimation of the ultimate benefit to DFS and improved safety of the regimen will await larger phase 2 studies in patients with ALL undergoing transplantation either in remission or in relapse.

Given the efficacy of radiation-based regimens and a dose-response effect of radiation on leukemia, newer approaches to the delivery of marrow are also being evaluated to increase the safety and the dose of radiation. Helical tomotherapy, used to focus and intensify local radiation treatment, can be utilized to treat the major marrow containing bones and offers a potential means to augment the dose of radiation to the marrow without increasing toxicity to other organs. This approach is now being combined with chemotherapy evaluated in phase 1/2 trials.<sup>47</sup>

### Role of GVL effect in patients with ALL

The low response rate in patients with ALL following donor lymphocyte infusion(s) (DLI) has led to questions about the significance of the GVL effect in preventing relapse in this disease. The GVL effect is derived from observations of a higher relapse after autologous or syngeneic HCT compared to allogeneic HCT, lower incidence of relapse in patients who had GVHD, as well as increased relapse rates in recipients of T-cell-depleted marrow grafts. The most compelling argument for a strong GVL effect in ALL comes from both single institution and registry data.<sup>48,49</sup> These studies show consistent decrease in relapse rates in patients who develop GVHD compared to those patients who do not. Table 1 shows the rate of relapse after HCT for ALL in CR1 and the correlation with GVHD. The occurrence of acute, chronic or both forms of GVHD correlated with the best DFS. A study of 192 patients with ALL, most of whom were transplanted in second remission,<sup>50</sup> evaluated the probability of relapse among patients without or with GVHD. Relapse was significantly higher in the group that had less grade II GVHD. In fact, in patients without significant GVHD, the actuarial risk of relapse approached 80 versus 40% in those who developed grade II or more. A subsequent study<sup>49</sup> confirmed this observation for both relapse and overall DFS. An evaluation of 1132 patients with T- or B-lineage ALL supports the observation that both acute and chronic GVHD are associated with a

**Table 1** Relapse after transplantation for all in CR1

Group	Relapse probability at 3 years (%)
Allogeneic, non-T-depleted	
No GVHD	44 ± 17
Acute only	17 ± 9
Chronic only	20 ± 19
Both	15 ± 10
Syngeneic	41 ± 32
Allogeneic, T-depleted	34 ± 13

decreased risk of relapse in both of the major immunophenotypes of adult ALL.<sup>51</sup>

Although the data support the importance of GVL effect in mediating a clinically useful antileukemic response in patients with ALL, the reasons for the limited beneficial effect for patients with relapsed ALL treated with DLI is not clear. The different outcomes may reflect differences in the ability of ALL cells to present antigen targets, the low frequency of T-cell precursors reactive with minor antigens presented by ALL cells, the susceptibility of ALL targets to lysis or kinetic differences in the way leukemic cells grow after HCT. Thus, cyto-reduction with chemotherapy prior to infusion of DLI is a better strategy for patients with relapsed ALL. It is for these reasons that reduced-intensity transplants are of limited effectiveness in patients with ALL not in remission. Studies focused on developing antigen-specific T-cell immunotherapy for ALL may help augment the GVL activity of donor T cells.<sup>52–56</sup>

### Reduced-intensity transplant for treatment of ALL

Although there has been a large number of studies performed in evaluating the role of allogeneic reduced-intensity transplant in patients with myeloid malignancies, multiple myeloma and low-grade lymphoma, there have been fewer studies conducted in ALL. In general, the consensus has been that, for patients with ALL, high-dose chemoradiotherapy was required for an improved cure rate, but this approach is of limited use in patients over the age of 50. In addition, an evaluation of outcome suggests that the graft-versus-tumor effect is more effective against myeloid malignancy such as AML and CML and B-cell malignancies of mature B cells such as low-grade lymphoma and myeloma, but less so with a more undifferentiated B-cell disease such as pre-B ALL, especially if not in remission.<sup>57–59</sup> Nevertheless, a few small studies have been conducted, which suggest that there may be a role for reduced-intensity allogeneic transplant even in this disease, particularly in older patients, with 34% achieving long-term remission in a report from the EBMT.<sup>57</sup> A recent report of patients undergoing a transplant using related, unrelated or cord blood donor and a fludarabine/melphalan regimen showed an optimistic outcome in a group of patients either at high risk during first remission or who were transplanted after achieving a second and subsequent remission.<sup>60</sup> Given the results of the recent UK ALL XII ECOG 2993 study of adult ALL showing surprisingly high toxicity and limited improvement in DFS, despite better

disease control in older patients, there is increased interest in the development of clinical trials exploring these approaches in patients with ALL in remission over the age of 35–40 who would otherwise be candidates for transplantation based on age, cytogenetics, MRD and response to initial treatment.<sup>61</sup>

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