Reduced-intensity conditioning (allo-HCT) regimens are an effective option for selected patients with chronic lymphocytic leukemia.

Hematopoietic Stem Cell Allografting for Chronic Lymphocytic Leukemia: A Focus on Reduced-Intensity Conditioning Regimens

Mohamed A. Kharfan-Dabaja, MD, FACP, and Ali Bazarbachi, MD, PhD

Background: Allogeneic hematopoietic cell transplantation (allo-HCT) remains the only known treatment modality that currently offers a potential cure to patients with chronic lymphocytic leukemia (CLL). A better understanding of the role of adoptive immunotherapy and its consequent bona fide graft-vs-leukemia (GVL) effect has resulted in a reduction of the ablative intensity and toxicity of preparative allo-HCT regimens.

Methods: The authors review the published data of reduced-intensity conditioning (RIC) allo-HCT in patients with CLL.

Results: RIC allo-HCT has reduced the transplant associated morbidity and mortality of the procedure and has consequently broadened applicability of allo-HCT to patients with CLL who are generally of more advanced age (> 60 years) and who often have associated comorbidities.

Conclusions: Published literature supports the use of RIC allo-HCT for these patients once a suitable donor is identified, provided they fulfill acceptable consensus criteria for hematopoietic stem cell allografting. Several studies have shown that T-cell-replete RIC allo-HCT is also capable of overcoming the adverse effect of poor prognostic factors in CLL such as del(17p), unmutated IgVH, or ZAP-70 expression. Continued clinical trials to identify the optimal regimen for RIC allo-HCT for patients with CLL are warranted.

Introduction

Chronic lymphocytic leukemia (CLL) is a complex clinical entity with a variable disease course. Approximately one-third of patients with CLL survive many years without requiring treatment, whereas others need multiple therapies early in the course of the disease. Molecular and genomic markers are helping to prognosticate outcomes in CLL; however, their presence in the absence of clinical symptomatology is not a sufficient criterion to initiate treatment for these patients. Novel treatment strategies that combine conventional chemotherapy plus targeted immunotherapy, in either the front-line therapy or relapsed/refractory setting, are yielding higher rates and better quality of responses in patients with CLL but have not yet resulted in an ultimate cure of this disease.

Allogeneic hematopoietic cell transplantation (allo-HCT) remains the only known treatment modality that can potentially offer a cure to patients with CLL. Earlier studies focused on administering myeloablative doses of chemotherapy, with or without radiation therapy, to improve disease control prior to an infusion of healthy...
donor hematopoietic stem cells. Unfortunately, over one-third of patients die during the first year of the procedure due to causes other than disease relapse, mostly related to direct toxicity of the conditioning regimen. A better understanding of the role of adoptive immunotherapy and also of its consequent graft-vs-leukemia (GVL) effect has allowed reduction of the ablative intensity (and toxicity) of preparative regimens. This has contributed significantly to reducing the short-term morbidity and overall mortality of the procedure. Accordingly, allo-HCT is currently offered to a higher number of patients with CLL, especially those of more advanced age who commonly suffer from associated clinical comorbidities. This review evaluates the available published literature supporting the role of reduced-intensity conditioning (RIC) allo-HCT for patients with CLL, and it summarizes current recommendations on when this treatment needs to be considered.

**Allo-HCT for CLL**

In recent years, allo-HCT has clearly emerged as the preferred treatment option for patients with relapsed CLL. Outcomes following high-dose chemotherapy and autologous HCT failed to show a plateau effect on survival curves and resulted in an unacceptably high incidence of secondary myelodysplastic syndromes (9% to 12%).

One clear advantage of hematopoietic cell allografting, vis-à-vis autologous HCT, comprises infusion of tumor-free hematopoietic progenitor and effector cells from healthy donors. Initial studies evaluating allo-HCT in patients with CLL emphasized the use of myeloablative doses of chemotherapy with or without radiation. The benefits and limitations of this approach are discussed below.

**Myeloablative Preparative Regimens**

The treatment goal for patients with relapsed CLL, particularly those with chemosensitive disease, has increas-

### Table 1. — Selected Studies Evaluating Allogeneic Hematopoietic Cell Transplantation for CLL Using Myeloablative Preparative Regimens

<table>
<thead>
<tr>
<th>Study</th>
<th>Publication Year</th>
<th>Study Type</th>
<th>No. of Patients</th>
<th>Preparative Regimen (%)</th>
<th>Transplant-Related Mortality (%)</th>
<th>GVHD (%)</th>
<th>Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Michallet et al(^{9,10}) (IBMTR/EBMT)</td>
<td>1996, 2003</td>
<td>Registry</td>
<td>54</td>
<td>TBI-CY = 94</td>
<td>46</td>
<td>Acute: II–IV = 37, Chronic: All = 49</td>
<td>DFS = 37, OS = 41.2 (10-yr)</td>
</tr>
<tr>
<td>Pavletic et al(^{11}) (IBMTR/NMDP)</td>
<td>2005</td>
<td>Registry</td>
<td>38</td>
<td>TBI-based = 92</td>
<td>38</td>
<td>Acute: II–IV = 45 (100-day), Chronic: All = 85 (5-yr)</td>
<td>OS = 33 (5-yr)</td>
</tr>
<tr>
<td>Pavletic et al(^{12})</td>
<td>2000</td>
<td>Case series</td>
<td>23</td>
<td>TBI-based = 96</td>
<td>30</td>
<td>Acute: II–IV = 54, Chronic: All = 68</td>
<td>EFS = 65, OS = 62 (5-yr)</td>
</tr>
<tr>
<td>Doney et al(^{13})</td>
<td>2002</td>
<td>Case series</td>
<td>25</td>
<td>TBI-CY = 68</td>
<td>48</td>
<td>Acute: II–IV = 56, Chronic: Extensive = 40</td>
<td>OS = 32 (5-yr)</td>
</tr>
<tr>
<td>Toze et al(^{14})</td>
<td>2005</td>
<td>Case series</td>
<td>30</td>
<td>TBI-CY = 50, BU-CY = 50</td>
<td>47</td>
<td>Acute: II–IV = 52, Chronic: All = 65</td>
<td>OS = 39 (5-yr)</td>
</tr>
<tr>
<td>Malhotra et al(^{15})</td>
<td>2008</td>
<td>Case series</td>
<td>12*</td>
<td>TBI-CY = 75</td>
<td>42</td>
<td>Acute: II–IV = 42, Chronic: All = 33</td>
<td>PFS = 42, OS = 50 (10-yr)</td>
</tr>
<tr>
<td>Peres et al(^{16})</td>
<td>2009</td>
<td>Case series</td>
<td>29</td>
<td>CY-VP16-BCNU = 69, BU-CY = 31</td>
<td>27</td>
<td>Acute: II–IV = 55, Chronic: Extensive = 48</td>
<td>OS = 18 (5-yr)</td>
</tr>
</tbody>
</table>

IBMTR = International Bone Marrow Transplant Research, EBMT = European Group for Blood and Marrow Transplantation, NMDP = National Marrow Donor Program, TBI = total body irradiation, CY = cyclophosphamide, BU = busulfan, VP16 = etoposide, BCNU = carmustine, DFS = disease-free survival, EFS = event-free survival, PFS = progression-free survival, OS = overall survival, All = both limited and extensive chronic GVHD.

* 11 of 12 received a myeloablative regimen.
ingly focused on therapies with curative potential, namely allo-HCT. The resultant GVL effect derived from alloreactive donor T cells is the key mechanism responsible for lowering relapse rates after allo-HCT. A major limitation, however, of using myeloablative doses of chemotherapy or chemoradiotherapy in these patients is the increased risk of transplant-associated morbidity and mortality, mostly from organ failure due to direct toxicity of the preparative regimen and/or development of graft-vs-host disease (GVHD). Registry data from the International Bone Marrow Transplant Research Group and the European Group for Blood and Marrow Transplantation (EBMT) reported a transplant-related mortality (TRM) of 46% in 54 recipients of matched-sibling hematopoietic cell allografts who received myeloablative conditioning regimens combining cyclophosphamide plus total body irradiation (n = 51, 94.4%) or busulfan (n = 3, 5.6%). This high TRM is a particular concern when considering that patients who received an allo-HCT in this study were at least 25 years younger (median = 41 years) than the median age of CLL patients at diagnosis. A 10-year follow-up demonstrated a leukemia-free survival of 36.6% and an overall survival (OS) of 41.2%, suggesting that allo-HCT offers long-term remission and the possibility of cure for these patients. Similar findings were reported by the EBMT/National Marrow Donor Program in 38 recipients of unrelated donor hematopoietic allografts, with a resultant TRM of 38% and a 5-year failure-free survival and OS of 30% and 33%, respectively.

Small case series have also shown a high TRM ranging from 27% to 48% and a 5-year OS ranging from 18% to 62% in patients with CLL, with median ages under 55 years. It is important to note that patients whose disease is responsive to pretransplant salvage chemotherapy/chemotherapies or chemoinmunotherapy have better post-allo-HCT outcomes compared to those with chemorefractory CLL. This suggests that allo-HCT should be offered earlier in the course of the disease, before the onset of chemoresistance.

A major drawback of myeloablative allo-HCT is the increased toxicity of the procedure, which has tempered broader applicability of this approach. These and other studies are summarized in Table 1.

Reduced-Intensity (and Toxicity) Preparative Regimens

A better understanding of the contributing role of adoptive immunotherapy in allo-HCT led to the development of lesser ablative preparative regimens aimed at reducing overall toxicity of the procedure. These regimens, now categorized as reduced-toxicity regimens, are associated with improved TRM, hence broadening the applicability of allo-HCT in patients with CLL.

In 2003, the EBMT reported outcomes of 77 patients with a median age of 54 years who received an allo-HCT for CLL across 29 transplant centers in Europe. The majority of patients (81%) received an allograft from a matched-sibling donor and 43 (56%) of 77 received a moderate intensity preparative regimen. The authors reported an encouraging TRM rate of 18%. Also, an impressive overall response rate of 91% was achieved, as well as a 69% complete response rate and a 22% partial response rate, despite reduction in the ablative intensity of the preparative regimen. This lower TRM of 18% compares favorably to the corresponding TRM of 46% reported with similar registry analyses of patients with CLL who received myeloablative conditioning. Other registry studies as well as single-arm prospective studies or single institution case series have further supported the efficacy of RIC allo-HCT with 5-year OS rates ranging from 39% to 70% and a lower incidence of TRM (Table 2).

Sorror et al reported encouraging long-term outcomes in 82 CLL patients (52 matched-sibling donors, 30 unrelated donors) with a median age of 56 years (range, 42–72 years) who received RIC allo-HCT. In this study, 84% of patients received a preparative regimen consisting of 2 Gy total body irradiation plus fludarabine. The overall response rate was 70% (complete response = 55%, partial response = 15%). At a median follow-up of 5 years, TRM, progression-free survival, and OS were 23%, 39%, and 50%, respectively. There were no statistically significant differences in these outcomes between matched-sibling donor recipients and unrelated donor allograft recipients. Interestingly, TRM and OS rates at 5 years were comparable among patients older than 60 years of age (P = .96) vs those younger than 60 years of age (P = .35). These findings support a curative potential for RIC allo-HCT in patients with relapsed CLL, with a more favorable toxicity profile particularly in older patients who would not have been eligible to receive myeloablative conditioning regimens in the past.

To date, no prospective randomized studies have been reported that compare myeloablative vs RIC allo-HCT regimens in patients with CLL. Most comparisons are limited to retrospective nonrandomized comparisons or population matched-analysis from registry databases. On behalf of the Chronic Leukemia Working Party of the EBMT, Dreger et al compared 73 CLL patients who received RIC allo-HCT with 82 patients from the EBMT database who underwent myeloablative allo-HCT for CLL during the same time period. The two groups were matched for age, gender, donor source, and pretransplant remission status. They were also evaluated for effect on TRM, incidence of relapse, event-free survival, and OS. RIC allo-HCT showed a significant reduction of TRM but a higher incidence of relapse. Overall, there was no significant difference in event-free survival or OS between the groups. This analysis has several limitations, including its retrospective nature and the use of pretransplant remission status without incorporating modern molecular and genetic prognostic markers to match the groups.
Table 2. — Selected Studies Evaluating Allogeneic Hematopoietic Cell Transplantation for CLL Using RIC Preparative Regimens

<table>
<thead>
<tr>
<th>Study</th>
<th>Publication Year</th>
<th>Study Type</th>
<th>No. of Patients</th>
<th>Preparative Regimen (%)</th>
<th>Transplant-Related Mortality (%)</th>
<th>GVHD (%)</th>
<th>Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dreger et al(^2) (EBMT)</td>
<td>2003</td>
<td>Registry</td>
<td>77</td>
<td>Moderate intensity = 56(^a)</td>
<td>18</td>
<td>Acute: II-IV = 34, Chronic: 57</td>
<td>OS = 72 (2-yr)</td>
</tr>
<tr>
<td>Schetelig et al(^2) (EBMT)</td>
<td>2008</td>
<td>Registry del(17p) only</td>
<td>44</td>
<td>Various reduced toxicity = 89</td>
<td>20</td>
<td>Acute: II-IV = 43, Chronic: Extensive = 57</td>
<td>PFS = 37 OS = 44 (3-yr)</td>
</tr>
<tr>
<td>Schetelig et al(^2)</td>
<td>2003</td>
<td>Prospective, single arm</td>
<td>30</td>
<td>FLU-BU-ATG = 100</td>
<td>15 (2-yr)</td>
<td>Acute: II-IV = 56, Chronic: Limited = 54, Extensive = 21</td>
<td>PFS = 67 OS = 72 (2-yr)</td>
</tr>
<tr>
<td>Caballero et al(^2)</td>
<td>2005</td>
<td>Retrospective, consecutive patients with del(11q) ± del(17p)</td>
<td>30</td>
<td>FLU-MEL = 67 FLU-BU-ATG or FLU-TBI 2 Gy ATG = 33</td>
<td>20 (1-yr)</td>
<td>Acute: II-IV = 40, Chronic: 76</td>
<td>OS = 70 (6-yr)</td>
</tr>
<tr>
<td>Brown et al(^2)</td>
<td>2006</td>
<td>Retrospective</td>
<td>46</td>
<td>FLU-BU = 100</td>
<td>17 (2-yr)</td>
<td>Acute: II-IV = 34, Chronic: Limited = 15, Extensive = 38</td>
<td>PFS = 34 OS = 54 (2-yr)</td>
</tr>
<tr>
<td>Khouri et al(^2)</td>
<td>2007</td>
<td>Prospective(^b)</td>
<td>39</td>
<td>FLU-CY-RIT = 100</td>
<td>26</td>
<td>Acute: II-IV = 45, Chronic: Extensive = 58</td>
<td>OS = 48 (4-yr)(^c)</td>
</tr>
<tr>
<td>Sorr et al(^2)</td>
<td>2008</td>
<td>Prospective, single arm</td>
<td>82</td>
<td>FLU-TBI 2 Gy = 84</td>
<td>23 (5-yr)</td>
<td>Acute: II-IV = 55 (MRD), II-VI = 66 (URD), Chronic: Extensive = 49 (MRD), Extensive = 53 (URD)</td>
<td>PFS = 39 OS = 50 (6-yr)</td>
</tr>
<tr>
<td>Delgado et al(^2)</td>
<td>2009</td>
<td>Retrospective</td>
<td>37</td>
<td>FLU-MEL = 100</td>
<td>34 (1-yr)(^d)</td>
<td>19%(^e)</td>
<td>PFS = 22 OS = 39 (3-yr)(^f)</td>
</tr>
<tr>
<td>Peres et al(^1)</td>
<td>2009</td>
<td>Case series</td>
<td>21</td>
<td>FLU-BU-TLI 2 Gy = 100</td>
<td>14</td>
<td>Acute: II-IV = 39, Chronic: Extensive = 38</td>
<td>OS = 63 (5-yr)</td>
</tr>
<tr>
<td>Dreger et al(^2) (GCLLSG CLL3X)</td>
<td>2010</td>
<td>Multicenter, single arm, prospective</td>
<td>90</td>
<td>FLU-CY = 100 (± ATG for URD)</td>
<td>23 (4-yr)</td>
<td>Acute: II-IV = 45, Chronic: Extensive = 53</td>
<td>OS = 65 (4-yr)</td>
</tr>
</tbody>
</table>

EBMT = European Group for Blood and Marrow Transplantation, FLU = fludarabine, BU = busulfan, CY = cyclophosphamide, RIT = rituximab, MEL = melphalan, TLI = total lymph node irradiation, PFS = progression-free survival, OS = overall survival, MRD = matched-related donor, URD = unrelated donor, ATG = antithymocyte globulin.

\(^a\) FLU 150 mg/m\(^2\) plus CY 1–4 g/m\(^2\) (with anti-thymocyte globulin = 2) = 17, TBI 2 Gy plus FLU 90 mg/m\(^2\) to 180 mg/m\(^2\) = 10, TBI 2 Gy = 7, FLU 60 mg/m\(^2\) plus CY 2.5 g/m\(^2\) plus thiotepa 10 mg/kg = 4, regimen not specified = 5.

\(^b\) ZAP-70–positive in 64% of cases.

\(^c\) Provided through personal communication with authors.

\(^d\) OS at 4-yrs = 56% for ZAP-70–positive patients.

\(^e\) Does not specify if acute or chronic.
Conceptually, RIC allo-HCT is thought to result in a lower incidence of GVHD due to reduced organ damage with the use of less ablative therapies, among other reasons. However, as shown in Tables 1 and 2, this does not appear to be the case thus far because of several reasons known to cause higher rates of GVHD: (1) the use of granulocyte colony-stimulating factor (G-CSF)-mobilized peripheral blood stem cells (PBSCs) has increased in recent years,\(^{30}\) (2) the number of RIC allo-HCTs being performed currently using HLA-mismatched or unrelated donor cells is growing, and (3) RIC allo-HCT is currently being offered to older patients who generally receive stem cell allografts from older siblings.

**Efficacy of RIC Allo-HCT in Poor-Risk CLL**

Advances in the understanding of the prognostic significance of biologic and genetic markers in CLL are helping to better predict responses, disease progression, and survival in this disease.\(^{31-34}\) Several studies have shown that T-cell–replete RIC allo-HCT is capable of overcoming the adverse effects of poor prognostic factors in patients with CLL. For instance, Ritgen et al\(^{35}\) showed that 7 of 9 patients (78%) with unmutated IgVH CLL achieved durable molecular remission following RIC allo-HCT. Similarly, Caballero et al\(^{36}\) demonstrated that RIC allo-HCT induces an encouraging 5-year OS rate of 70% in CLL patients with adverse chromosomal aberrations such as del(17p) or del(11q), unmutated IgVH, or fludarabine-refractory disease.

Khouri et al\(^{37}\) reported post-allo HCT outcomes in 39 CLL patients (25 with ZAP-70–positive expression). In this series, the estimated 4-year progression-free survival and OS rates were 53% and 56%, respectively. This shows that CLL patients whose disease overexpresses ZAP-70 are responsive to RIC allo-HCT. Interestingly, a multivariable analysis showed that mixed T-cell chimerism at day 90 post-allograft and chemorefractory disease, but not ZAP-70 overexpression, were predictors of worse post-transplant risk of CLL progression.

Dreger et al\(^{38}\) reported long-term results of the German CLL Study Group (GCLLSG) CLL3X trial, which evaluated the efficacy of RIC allo-HCT in 90 patients with poor-risk CLL. The definition of poor risk consisted of refractoriness or early relapse within 12 months after receiving a purine analog-containing treatment regimen, relapse following high-dose chemotherapy and autologous HCT; or progressive disease associated with poor-risk genetic abnormalities such as del(17p) or del(11q) or unmutated IgVH. Conditioning therapy consisted of intravenous fludarabine plus cyclophosphamide for 5 days. Anti-thymocyte globulin (ATG) was added in cases where unrelated donors were the source of hematopoietic cells. Sixteen of 100 patients (16%) died of progressive CLL following RIC allo-HCT. The overall response rate was 94% (complete response = 73% in evaluable cases). Minimal residual disease (MRD) kinetics to assess for molecular remission was performed using flow cytometry or allele-specific oligonucleotide primer IgH RQ-PCR. Data regarding MRD were reported in only 52 cases. After 1 year, 39 of 52 patients (75%) were event-free and 27 of 52 (52%) were MRD-negative. Only 2 patients who were MRD-negative after 1 year became MRD-positive. Specific analysis of patients with del(17p) showed that 7 of 13 allograft recipients (54%) remain in complete response at a median follow-up of 43 months (range, 18–75 months). Six of 7 were MRD-negative and had complete donor chimerism. The 4-year OS rate was 65% for the entire group of patients. These findings confirm that RIC allo-HCT can overcome the adverse prognostic effect of genomic aberrations such as del(17p) in patients with CLL and result in durable long-term remissions.

**Evidence of Graft-vs-Leukemia Effect in CLL**

In contrast to autologous, syngeneic, or T-cell–depleted allogeneic HCT, which are solely dependent on the ablative intensity of the preparative regimen (chemotherapy with or without radiation) to eradicate disease, the efficacy of T-cell–replete allo-HCT — RIC or myeloablative — is derived in large part from the adoptive immunotherapy mediated by donor lymphocytes. Genetic disparities between donors and recipients appear to be largely responsible for the development of GVHD and its consequent GVL effect that contributes to CLL eradication. However, separating the beneficial GVL effect from the more deleterious GVHD has not been easy to achieve clinically thus far and represents the holy grail of allo-HCT. Evidence supporting the GVL effect following T-cell–replete RIC or myeloablative allo-HCT includes (1) a relatively low incidence of relapse, which continues to decrease with longer follow-up, (2) an increased risk of relapse following T-cell–depleted allo-HCT,\(^{39}\) (3) the ability of donor lymphocyte infusions to induce responses, even molecular remissions (MRD-negative), in cases of persistent or recurring disease (for instance, in the CLL3X trial reported by the GCLLSG, 15 patients received 32 fractions of donor lymphocyte infusions for recurring MRD [n = 6] or evidence of clinical relapse [n = 8] or incomplete chimerism [n = 1]; interestingly, 5 of the 15 patients [3 recurring MRD, 2 clinical relapse] responded by achieving a MRD-negative remission),\(^{28}\) and (4) MRD-negative remission is achieved in the majority of patients who develop chronic GVHD or through immunomodulation by tapering of immunosuppression.\(^{57}\) This supports alloreactivity as the principal mechanism responsible for GVL; it also demonstrates that GVL is effective in CLL.

Nishida et al\(^{38}\) recently demonstrated that CLL-specific T cells develop, albeit with variable kinetics, in all patients who achieve a complete remission but not in those who fail to achieve clinical responses after allo-HCT. These CLL-reactive T cells appear to be specific against minor histocompatibility antigens expressed by CLL and other host cells and also to antigens solely expressed by the ma-
lignant B-cell population. Not surprisingly, acute and/or chronic GVHD was reported in all patients who achieved a complete response, highlighting the difficulty to effectively separate GVL from GVHD with current allo-HCT approaches. These findings provide the scientific basis to continue to identify additional tumor-specific targets for alloreactive T cells in order to achieve a more specific GVL effect.

**Incorporation of Monoclonal Antibodies in RIC Allo-HCT Strategies**

Monoclonal antibodies (MoAbs) with recognized clinical activity against CLL, namely alemtuzumab and rituximab, have also been used as part of RIC allo-HCT preparative regimens for the main purpose of reducing the incidence and severity of GVHD. Alemtuzumab is a humanized anti-CD52 IgG1 MoAb that has been evaluated as part of an in vivo T-cell depletion strategy in patients undergoing RIC allo-HCT for CLL. Delgado et al evaluated outcomes of 41 patients with CLL who received RIC allo-HCT preparative regimens combining alemtuzumab with fludarabine plus melphalan. In this series, 32% of patients achieved an allo-HCT from an HLA-matched unrelated donor and 10% from an HLA-mismatched unrelated donor. The reported incidence of acute and chronic GVHD was 41% and 33%, respectively. TRM was 26%, resulting primarily from opportunistic infections (bacterial, fungal, viral). The 2-year relapse-risk rate was 29% and the OS rate was 51%. This study shows that in vivo T-cell depletion using alemtuzumab is effective in reducing the incidence of GVHD but at the expense of increased risk of death from opportunistic infections.

Rituximab, a genetically engineered chimeric murine/human IgG1x anti-CD20 MoAb, has been shown to be feasible in combining with RIC preparative regimens and resulting in a relatively low incidence of acute GVHD in patients undergoing allo-HCT for lymphoid malignancies. Khouri et al reported an incidence of acute GVHD of 45% in 39 patients with CLL who received RIC allo-HCT preparative regimens that combined rituximab with fludarabine plus cyclophosphamide. Death due to nonrelapse causes was reported in 18% of patients (10% chronic GVHD, 8% infection plus chronic GVHD). The higher incidence of acute GVHD of 45% in this study vs that reported in the initial study (acute GVHD = 20%), in which 90% of patients were transplanted for follicular non-Hodgkin lymphoma using the same preparative regimen and GVHD prophylaxis, is noteworthy. The authors suggest that this discrepancy is likely due to the fact that 14 of 39 patients (36%) in the CLL study required immunomodulation for progressive disease consisting of rituximab plus donor lymphocyte infusion, whereas only 2% of patients in the follicular non-Hodgkin lymphoma study required such type of intervention.

The use of MoAbs as part of RIC allo-HCT preparative regimens should include a consideration of the benefits of reducing the incidence of GVHD against the risk of developing deadly opportunistic infections or increasing the risk of relapse as a result of T-cell depletion.

**Relapse After Allogeneic HCT in Patients With CLL**

Despite improved outcomes following RIC allo-HCT for patients with CLL, over one-third of cases are at risk of relapse, posing a major impediment to further advancing the role of hematopoietic cell allografting in this disease at the present time. In this regard, Sorror et al reported a cumulative incidence of relapse or progression of 38% at 5 years following allografting in 82 cases of CLL, where the majority received a nonmyeloablative conditioning regimen consisting of fludarabine plus 2 Gy total body irradiation. Importantly, the presence of bulky lymphadenopathy (defined as ≥5 cm) at the time of allo-HCT strongly predicted for an increased risk of relapse in these cases (5-year relapse rates = 71% vs 27%; P = .0004). In this study, the quality of remission achieved prior to allografting (complete vs partial response), CD38 expression (>30% vs ≤30%), and the presence of adverse cytogenetics did not appear to correlate adversely with risk of relapse, in conformity with other published series. Dreger et al showed, in multivariate analyses, that previous purine analog refractoriness at the time of allografting is also an important predictor of worse OS and event-free survival. Late relapses following allo-HCT for CLL have been described in registry studies.

Attempts to improve outcome in patients with known adverse risk factors, such as bulky lymphadenopathy (≥5 cm) among others, should weigh the benefit of a cyoreductive approach by using more aggressive salvage chemoimmunotherapy against the increased risk of organ damage and impairment in performance status resulting from such intervention.

Identifying subclinical relapses by detecting MRD before overt disease ensues is a logical approach to consider in order to further improve outcomes in these patients. This is particularly important when taking into account that the efficacy of immunotherapy, whether through adoptive immunity mediated by donor effector T cells or therapeutic monoclonal antibodies, is generally inversely proportional to the bulk of disease present. In the CLL3X trial, administration of donor lymphocyte infusions to 15 patients with persistent/increasing/recurring MRD (n = 6, 40%), clinical relapse (n = 8, 53%), or incomplete chimerism (n = 1, 7%) resulted in molecular remissions (MRD-negative complete response) in 5 cases (33%). These encouraging results suggest that an MRD-guided preemptive immunomodulation approach could provide potential benefit in some patients. Failure to respond to immune modulating strategies, eg, by withdrawal of immunosuppressants or by administration of donor lymphocyte infusion, generally entails a poor prognosis in patients with CLL relapsing after allo-HCT.
Recommendations for Allo-HCT in Patients With CLL

In 2007, the EBMT published a consensus on indications for allo-HCT in patients with CLL. Accordingly, allo-HCT is a reasonable treatment option to consider for eligible patients with previously treated poor-risk CLL. The criteria for poor-risk disease consist of (1) lack of response or early relapse within 1 year of receiving a purine analog-containing treatment regimen, (2) disease relapse within 2 years of receiving a purine analog combination therapy or after other therapies such as autologous HCT, and (3) CLL associated with p53 mutations or deletions and/or del(17p) requiring first-line treatment. It is important that patients demonstrate evidence of a chemosensitive response prior to proceeding with allo-HCT.

Conclusions

There is no clear consensus concerning the optimal conditioning regimen (RIC or myeloablative) to be used prior to allo-HCT. However, since more than two-thirds of patients with CLL are greater than 60 years of age and often have associated comorbidities, it appears logical to offer RIC allo-HCT to these patients once a suitable donor is identified. On the other hand, younger patients with good performance status could be offered RIC allo-HCT or myeloablative allo-HCT, provided they are well informed about the benefits and risks associated with either approach. Patients should be referred to transplant centers as early as possible to assess their candidacy for allo-HCT, to initiate the search for a suitable donor, to avoid excessive organ toxicity resulting from multiple treatments of recurrent disease, and ultimately to facilitate a timely intervention with an allo-HCT. Proper screening of donors, predominantly when selecting matched-sibling donors, is vital in light of the high incidence of familial CLL, which is 5- to 8.5-fold higher in these cases. In such cases, use of these donors should be discouraged and a search for an HLA-compatible unrelated donor would be the favored approach. RIC allo-HCT is a reasonable option to consider in eligible patients with relapsed and/or poor-risk CLL who are otherwise incurable with conventional chemotherapy or chemoinmunotherapy approaches.

References


