Hematopoietic Cell Transplantation for B-Cell Lymphoma: An Update

Ernesto Ayala, MD

Background: B-cell lymphoma comprises the majority of non-Hodgkin lymphomas worldwide. Hematopoietic cell transplantation (HCT) is used for patients with high-risk, relapsed, or refractory B-cell lymphoma.

Methods: The current medical literature and the results of recently published trials were reviewed to provide an update on the most common indications for HCT in B-cell lymphoma.

Results: Autologous HCT has evolving and new roles in the treatment of patients with high-risk diffuse large B-cell lymphoma, mantle cell lymphoma, and HIV-related lymphoma. Reduced-intensity conditioning has largely replaced older myeloablative conditioning regimens, making allogeneic transplantation safer for more patients with lymphoma.

Conclusions: The indication and timing of HCT depend on the patient’s histology, age, and response to previous therapies. HCT is an essential component in the armamentarium to treat B-cell lymphoma.

Introduction

Non-Hodgkin lymphoma (NHL) is a heterogeneous group of hematologic malignancies with varied aggressiveness and many therapeutic options. An estimated 66,360 new cases of NHL were diagnosed in the United States in 2011.³ B-cell lymphoma comprises approximately 85% of these cases. Transplantation, both autologous and allogeneic, has a role in the management of B-cell lymphoma, and more than 5,000 hematopoietic cell transplantations (HCTs) are performed annually in North America for this indication.²

An article published in this journal in 2011 reviewed the current general indications for autologous and allogeneic transplantation in lymphoma.³ The current article provides an update regarding recent regimens and describes the results of recently published studies. The impact in the current application of transplantation in B-cell lymphoma is discussed. Sources for this review included PubMed and abstracts of clinical studies presented in major meetings in the field. Studies were selected according to relevance in the view of the author.

Diffuse Large B-Cell Lymphoma

Diffuse large B-cell lymphoma (DLBCL) is the most common type of lymphoma seen in developed countries, accounting for 30% of all newly diagnosed NHL. It is an aggressive lymphoma, and when treated with anthracycline and rituximab-based chemotherapy, approximately half of the patients are cured. Transplantation has been used in the treatment of high-risk, primary refractory, and relapsed disease.
Autologous Transplantation

High-Dose Therapy as Part of the Initial Treatment: The role of autologous transplantation (auto-HCT) as part of the initial therapy for DLBCL has been explored in several prospective randomized trials that targeted patients considered to be at high risk of relapse after conventional chemotherapy. Since the definition of high-risk patients preceded the development of the International Prognostic Index (IPI), the eligibility criteria varied from trial to trial according to investigator criteria. In addition, all were done before the rituximab era and thus the results may not be applicable to the current treatment of DLBCL.13 Thirteen trials have been completed with contradictory results. Nine studies showed no difference in overall survival (OS) or disease-free survival (DFS), while four studies showed improvement in DFS and/or OS in the high-dose therapy arm.

The Southwest Oncology Group embarked on a US/Canadian phase III multicenter prospective randomized trial, SWOG 9704, which was recently presented in abstract form.2 The trial investigated the benefit of auto-HCT in first-remission patients with bulky stage II, III, and IV disease and high-intermediate or high IPI score. After 5 courses of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), patients having at least a partial response (PR) were randomly assigned to 3 more courses of CHOP or 1 course of CHOP followed by auto-HCT, using total body irradiation (TBI) or carmustine-based conditioning regimens. The trial included 397 patients up to 65 years of age from 40 sites. CHOP was used in 215 patients, but the protocol was amended to add rituximab to CHOP in the last 182 patients. Primary endpoints were toxicity and 2-year progression-free survival (PFS) and OS for randomized patients. Of 370 induction-eligible patients, 253 were randomized to standard therapy (n = 128) or transplant (n = 125). The 2-year PFS rates were 56% and 69%, respectively, with a hazard ratio of 1.72 favoring the transplant arm. The 2-year OS rates were 74% and 71%, with a hazard ratio of 1.24. The difference in favor of transplantation was stronger in patients in the high-risk group and was seen in both the rituximab and non-rituximab arms.

In summary, early auto-HCT improved PFS in responders with high-intermediate or high IPI risk, with a stronger difference in the high-risk group. Based in this well-conducted study, auto-HCT should be offered as part of the initial therapy to all patients with a high IPI score at diagnosis. The data are less convincing in the intermediate high-risk group.

Treatment of Relapsed Disease: The role of auto-HCT in the treatment of relapsed disease was defined more than a decade ago by Philip et al6 in a multicenter prospective randomized trial that compared auto-HCT vs nontransplant salvage therapy. Based in the results of other phase II trials and this phase III trial, auto-HCT became the standard of care in patients less than 60 years of age with chemotherapy-sensitive relapsed or primary refractory aggressive NHL.

More recently, several retrospective studies have assessed the outcomes of auto-HCT in older patients with aggressive lymphoma. Three cohort studies and a multicenter retrospective analysis by the Center for International Bone Marrow Transplantation Research (CIBMTR) showed that age should not be a contraindication for auto-HCT as long as other eligibility criteria are met.7-10 The largest of these reports reviewed the outcomes of 805 patients more than 55 years of age who received a transplant at 176 different transplant centers in 10 countries. Disease and transplant-related outcomes, including OS, DFS, transplant-related mortality (TRM), and relapse, were analyzed and compared with a cohort of 1,949 patients younger than 55 years of age. Older patients with aggressive lymphoma were 1.86 times more likely to have TRM, and their risk of relapse was also greater. Consequently, OS and DFS were inferior (P < .001). The 149 patients over 65 years of age were more likely to have a worse performance status, more advanced stage, and more aggressive histologies, which could partially explain the difference.

In summary, patients older than 60 years of age should be considered for auto-HCT, but most disease-related outcomes in this population are statistically inferior to younger patients. Advances in supportive care in older patients may help to improve their outcome.

The Role of Rituximab: Rituximab, a chimeric monoclonal antibody against CD20, became an essential component of the initial therapy for DLBCL based on prospective studies that showed an improvement in DFS and OS with rituximab in younger and older patients when compared to chemotherapy alone.11-13 Subsequently, it was added to the salvage chemotherapy regimens used in relapsed or refractory disease and as a component of the high-dose chemotherapy regimens in transplantation.14-17 Vellenga et al18 reported on the impact of the addition of rituximab to the salvage therapy in relapsed/progressive aggressive lymphoma. In this trial, 225 patients were randomized to one of two regimens: (1) DHAP (cisplatin, cytarabine, dexamethasone)-VIM (etoposide, ifosfamide, methotrexate)-DHAP with rituximab followed by auto-HCT or (2) DHAP-VIM-DHAP without rituximab followed by auto-HCT. After the second course of chemotherapy, 75% of patients who received rituximab achieved either a complete response (CR) or a PR compared with 54% of those who received no rituximab (P = .01). The benefit noted after salvage therapy translated into a better outcome after transplant. With a median follow-up of 24 months, a significant difference was seen in failure-free survival (50% vs 24%, P < .001) in favor of the rituximab arm. Fenske et al19 completed a large retrospective analysis of patients who underwent auto-HCT for DLBCL between 1996
and 2003. Of 994 patients, 176 received rituximab with first-line and/or salvage chemotherapy, and 818 did not receive rituximab. Patients in the rituximab cohort were older and had received transplants more recently. The use of rituximab had no impact on engraftment or TRM. However, rituximab was associated with improved OS and DFS after HCT. A multicenter group in Italy used high-dose sequential salvage chemotherapy in preparation for auto-HCT in patients with relapsed follicular lymphoma (FL) and DLBCL. In 1998, rituximab was added to the high-dose phase immediately before peripheral blood stem cell collection, with 355 patients who did not receive rituximab and 355 who did. After a retrospective analysis, rituximab improved OS ($P < .001$) and EFS ($P < .001$) in patients who underwent auto-HCT for relapsed/refractory disease. Collectively, these data strongly support the addition of rituximab to salvage chemotherapy in relapsed B-cell lymphoma. Several centers (as well as my institute) have adopted rituximab as a component of the high-dose therapy regimen as well, based on the potential to eliminate CD20+ malignant cells in a setting of low tumor burden, and the concept of in vivo purging.

A multicenter international cooperative group conducted the Collaborative Trial in Relapsed Aggressive Lymphoma, which compared the efficacy of two commonly used chemotherapy regimens in salvage for aggressive B-cell lymphoma: rituximab, ifosfamide, carboplatin, and etoposide (R-ICE) and rituximab, cisplatin, cytarabine, and dexamethasone (R-DHAP). Following auto-HCT, patients had a second randomization to either no maintenance or maintenance with monthly doses of rituximab for 1 year. The trial enrolled 396 patients with a median age of 53 years. Similar response rates were observed after 3 courses of R-ICE (63.5%) or R-DHAP (62.8%), with worse responses in patients with refractory disease or with an IPI score > 1, in patients who relapsed within the first 12 months after initial therapy, and in those who had been previously exposed to rituximab. The 3-year PFS was 37% (95% confidence interval [CI], 31%-42%), and the R-ICE and R-DHAP arms were not significantly different (31% and 42%, respectively; $P = .97$). No differences in engraftment or other toxicities were apparent other than an increase in mucositis with the tositumomab/BEAM combination.

In summary, the addition of tositumomab to BEAM conditioning did not improve the outcomes in this population of patients with DLBCL. Despite promising phase II studies, this phase III trial does not support the routine use of RIT as part of the conditioning regimen for auto-HCT.

**Allogeneic Transplantation**

The number of patients treated and the number of published studies in allo-HCT for DLBCL are limited. Allo-HCT has been used as treatment of high-risk first relapse, refractory disease and in patients who have relapsed after auto-HCT. No prospective comparative studies have been completed in this setting.

For relapsed disease, Lazarus et al retrospectively analyzed the outcomes of DLBCL patients undergoing first autologous (n = 837) or HLA-identical sibling allo-HCT using myeloablative conditioning (n = 79) reported to the CIBMTR between 1995 and 2003. The allo-HCT group had more patients with an intermediate-high or high IPI score, extranodal involvement, B symptoms,
more prior chemotherapy regimens, and more resistant disease. Allo-HCT was associated with a higher TRM and treatment failure. Auto-HCT was associated with superior OS. Despite having several adverse risk features, patients in the allo-HCT group had a similar risk of relapse. The high TRM rate of myeloablative allo-HCT (45% at 5 years) greatly limited the potential benefit of this approach.

Given the high TRM associated with myeloablative conditioning, the use of reduced-intensity conditioning (RIC) and nonmyeloablative conditioning regimens has increased for allo-HCT in DLBCL. RIC and nonmyeloablative conditioning regimens rely more on graft-vs-lymphoma effect and less on the intensity of the chemotherapy to eradicate lymphoma. They are in general better tolerated and can be used for older patients or for patients with comorbidities. The French Society of Bone Marrow Transplant reported the collective experience on 68 patients undergoing RIC allo-HCT for DLBCL. Prior to transplant, 47% of the patients were on remission and 79% had received a prior auto-HCT. The donor was an HLA-identical sibling in 82% of the cases. With a median follow-up of 49 months, the estimated 2-year OS rate was 49%, the PFS rate was 44%, and cumulative incidence of relapse was 41%. The 1-year cumulative incidence of nonrelapse mortality was 23%.34

Bacher et al35 analyzed the outcomes of 396 adults who received allo-HCT for DLBCL following myeloablative conditioning (n = 165), RIC (n = 143), or nonmyeloablative conditioning (n = 88) regimens between 2000 and 2009, and they reported their findings to the CIBMTR. Significant baseline differences between the cohorts included the following: RIC and nonmyeloablative conditioning recipients were older (54% and 58% > 50 years vs 39% for myeloablative conditioning), and they were more likely to have received prior auto-HCT (36% and 51% vs 18%), prior radiation, and more prior chemotherapy regimens (55% and 70% vs 44% with > 3 regimens) than those with myeloablative conditioning recipients. The incidence of acute (43% to 44%) and chronic (37% to 42% at 5 years) graft-vs-host disease (GVHD) was similar across the groups. The TRM rate at 5 years was significantly higher in myeloablative conditioning recipients (56%) than in the RIC (47%) and nonmyeloablative conditioning (36%) recipients. Lymphoma relapse/progression at 5 years was significantly lower in the myeloablative conditioning group (26%) than in the RIC (38%) and nonmyeloablative conditioning (40%) groups, but the

<table>
<thead>
<tr>
<th>Study (yr)</th>
<th>Radioimmunotherapy</th>
<th>Regimen</th>
<th>No. of Patients</th>
<th>Histology</th>
<th>Overall Survival (yrs)</th>
<th>Progression-free Survival (yrs)</th>
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<td></td>
<td></td>
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<tr>
<td>Khouri et al 22 (2006)</td>
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<td>BEAM</td>
<td>26</td>
<td>Different</td>
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<tr>
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<td>BEAM</td>
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<td>BEAM</td>
<td>10</td>
<td>DLBCL and FL</td>
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<td>EFS 63% (2)</td>
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<tr>
<td>Vose et al 27 (2005)</td>
<td>131I</td>
<td>BEAM</td>
<td>23</td>
<td>Aggressive</td>
<td>55% (3)</td>
<td>39% (3)</td>
</tr>
<tr>
<td>Vose et al 28 (2007)</td>
<td>131I</td>
<td>BEAM</td>
<td>40</td>
<td>DLBCL</td>
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<td>70% (3)</td>
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<td>Nademanee et al 29 (2005)</td>
<td>90Y</td>
<td>Cy, VP16</td>
<td>42</td>
<td>Different</td>
<td>81% (4)</td>
<td>DFS 65% (4)</td>
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<td>Winter et al 30 (2009)</td>
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<td>BEAM</td>
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<td>60% (3)</td>
<td>43% (3)</td>
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<td>Press et al 31 (2000)</td>
<td>131I</td>
<td>Cy, VP16</td>
<td>52</td>
<td>Different</td>
<td>83% (2)</td>
<td>68% (2)</td>
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</table>

DLBCL = diffuse large B-cell lymphoma, FL = follicular lymphoma, BEAM = carmustine, etoposide, cytarabine, and melphalan, EFS = event-free survival, DFS = disease-free survival, Cy = cytarabine.
eventually many patients die of the disease. 38 

condition with conventional chemoimmunotherapy, and for more than 10 years. FL remains an incurable condition whereas other patients require minimal or no therapy for recurrence or transform to DLBCL within the first 2 years, variability in clinical behavior; some patients rapidly progress or transform to DLBCL within the first 2 years, whereas other patients require minimal or no therapy for more than 10 years. FL remains an incurable condition with conventional chemoimmunotherapy, and eventually many patients die of the disease.38

Allo-HCT can induce long-term PFS regardless of the intensity of conditioning, with a lower incidence of TRM with the RIC and nonmyeloablative conditioning regimens. The risk of relapse or progression is concordantly higher in the RIC and nonmyeloablative conditioning recipients so that survival does not differ significantly among conditioning regimens. However, the use of RIC or nonmyeloablative conditioning allowed older and sicker patients to proceed to transplant with a lower TRM. Figueroa et al36 recently reported experience at Moffitt Cancer Center using myeloablative doses of busulfan and fludarabine as conditioning for allo-HCT in 60 patients with lymphoma. The nonrelapse mortality rate was 25.3% at 3 years, which compares favorably with other published myeloablative conditioning regimens.

Allo-HCT has also been used as a salvage strategy with encouraging results for patients who failed a previous auto-HCT. In a retrospective analysis by the European Group for Blood and Marrow Transplantation (EBMT) registry that included 101 patients, approximately two-thirds received a RIC regimen and 70% had an identical sibling donor.37 Outcomes at 3 years were encouraging, with a nonrelapse mortality rate of 28.2%, a relapse rate of 30%, a PFS rate of 41%, and an OS rate of 53%. With a nonrelapse mortality incidence that can be considered acceptable in this heavily pretreated population, allo-HCT led to a long-term survival in this poor-risk group. Patients with a long remission after auto-HCT and with sensitive disease at allo-HCT appear to be the best candidates for this approach.

In summary, at this time it is not clear which conditioning intensity to use in allo-HCT for DLBCL. Myeloablative conditioning carries a higher mortality with a lower risk of relapse and may still be the preferred option for younger patients without comorbidities and for those considered to be at high risk for relapse (not in CR at transplant). RIC and nonmyeloablative conditioning regimens may be preferred for older patients or for those with multiple comorbid conditions and with a lower risk of relapse. Allo-HCT is effective salvage strategy in patients who have failed a previous auto-HCT for DLBCL.

**Follicular Lymphoma**

FL, the most common type of indolent lymphoma, accounts for 25% of all newly diagnosed NHL. While the median survival ranges from 8 to 10 years, there is wide variability in clinical behavior; some patients rapidly progress or transform to DLBCL within the first 2 years, whereas other patients require minimal or no therapy for more than 10 years. FL remains an incurable condition with conventional chemoimmunotherapy, and eventually many patients die of the disease.38

**Autologous Transplantation**

The role of auto-HCT as consolidation of the initial treatment in FL has been studied in four prospective multicenter randomized trials.39-42 Three of these were conducted before the rituximab era and compared the use of auto-HCT or interferon after induction chemotherapy. The last one compared induction with intensive vs conventional chemoimmunotherapy. In all trials, EFS and PFS improved in the intensive arm, but OS did not. In addition, morbidity was high in the intensive arm, with a significant increase in secondary malignancies. With this definitive data, auto-HCT should not be used as part of the initial therapy in FL.

In the setting of relapsed FL, some phase II trials suggested improvement in DFS and one phase III trial showed improvement in PFS and borderline improvement in OS. The EBMT group conducted the CUP trial (chemotherapy vs unpurged vs purged marrow), a prospective randomized study to address the value of auto-HCT in relapsed FL.43 In this study, 140 patients were randomly assigned to conventional chemotherapy, unpurged marrow, or purged marrow transplant. A significant improvement in PFS rates at 2 years was reported: conventional chemotherapy 26%, unpurged graft 58%, and purged graft 55% (P = .0037). At 4 years, OS rates were not statistically improved, but the data suggest benefit in the transplant arms: 46%, 71%, and 77%, respectively (P = .079). However, the trial closed early due to low accrual, and the role of ex vivo graft purging could not be ascertained.

In summary, the available data suggest a role for high-dose chemotherapy with auto-HCT in relapsed FL, particularly at the time of first relapse and also in those patients who do not have a suitable donor for allogeneic transplantation.

**Myeloablative Allogeneic Transplantation**

Until recently, the use of myeloablative allogeneic transplantation regimens using chemotherapy (busulfan, cyclophosphamide, etoposide) or chemoradiation (cyclophosphamide plus TBI) was common practice for allo-HCT in FL. Those regimens combined intensive anti-lymphoma therapy and a powerful graft-vs-lymphoma effect mediated by donor T cells. Accumulated experience consistently showed that the risk of relapse was substantially decreased compared with auto-HCT but at the cost of high nonrelapse mortality. The CIBMTR compared the outcomes of 176 patients with FL who underwent myeloablative conditioning allo-HCT with 131 patients who underwent purged auto-HCT and 597 who underwent unpurged auto-HCT.44 The respective 5-year TRM rates were 30%, 14%, and 8% (P < .001) and 5-year recurrence rates were 21%, 43%, and 58% (P < .001). The decrease in recurrence in the myeloablative conditioning group was offset by the increase in TRM incidence, so DFS and OS were similar. An important outcome was
that TRM decreased and OS increased in allo-HCT over the 10-year duration of the study (1990-1999).

The EBMT group assessed the outcomes of 1,185 patients with NHL, including 231 patients with low-grade NHL who underwent myeloablative conditioning allo-HCT and compared those with the outcomes of 14,687 patients who underwent auto-HCT.53 Again, relapse risk was significantly decreased in allo-HCT recipients; however, OS was comparable at 4 years due to a high nonrelapse mortality rate of 38%. Despite the low risk of relapse associated with myeloablative allo-HCT, less intensive and less toxic regimens have largely replaced intensive conditioning in FL.

**Reduced-Intensity Conditioning and Nonmyeloablative Allogeneic Transplantation**

Given the high mortality associated with myeloablative conditioning, less intensive preparative regimens have been increasingly used. These regimens induce profound immunosuppression to facilitate engraftment, and they rely on a graft-vs-lymphoma effect to eradicate the malignancy. Such regimens are associated with a lower nonrelapse mortality and can be offered to older and heavily treated patients. Among all NHL histologies, FL appears to be particularly sensitive to a graft-vs-malignancy effect.

The CIBMTR embarked in a retrospective analysis comparing myeloablative conditioning (n = 120) and RIC (n = 88) for allo-HCT patients in relapsed FL.46 Those in the RIC group were older and had more comorbidities. At 3 years following transplant, the OS (P = .15) and PFS (P = .07) rates were similar in both groups; however, a higher risk of progression was seen in the RIC group (17% vs 3%). Chemosensitivity and recipient performance status were better predictors of outcome than the intensity of the conditioning. This analysis showed that the practice of allo-HCT in FL has shifted in favor of RIC, which by 2002 represented 80% of allogeneic transplants for this disease.

Table 2 lists several published trials that used RIC or nonmyeloablative conditioning in FL.47-51 The largest series was published by Thompson et al48 and included 82 patients with FL. Conditioning included fludarabine, melphalan, and alemtuzumab. The use of alemtuzumab greatly decreased the incidence of acute and chronic GVHD but at the expense of a higher risk of relapse. Donor lymphocyte infusions were used in patients with mixed chimerism and relapsed disease. Other series have shown a lower nonrelapse mortality, a low risk of relapse, and excellent DFS/EFS, even in patients who had received a previous auto-HCT.

Khouri et al51 presented updated results of a phase II trial using a nonmyeloablative conditioning regimen for FL. The regimen included fludarabine, cyclophosphamide, and high-dose rituximab (1,000 mg/m² in 3 out of 4 doses). With a median follow-up of 60 months, the OS and PFS rates were 85% and 83%, respectively, and the TRM rate was 14%. The incidence of acute GVHD was only 11% and chronic GVHD was 60%. These impressive results were the basis for the ongoing prospective phase II BMT CTN Protocol 0701 aimed at reproducing these outcomes in a multicenter setting.

Rezvani et al50 recently updated the results of a nonmyeloablative conditioning regimen using low-dose TBI with or without fludarabine and postgrafting immunosuppression with cyclosporine and mycophenolate mofetil. Sixty-two patients with indolent or transformed NHL were included. The cumulative nonrelapse mortality incidence at 3 years was 42%. The OS and PFS rates were 62% and 43%, respectively. Patients with transformed disease had a worse OS and PFS and a much higher risk of relapse.

The only attempt at comparing a RIC allo-HCT with auto-HCT was completed by the BMT CTN using biological assignment.52 However, the trial closed early due to poor accrual. A total of 30 patients were included, 8 in the allo-HCT group and 22 in the auto-HCT group. With a median follow-up of 36 months, the OS rates were 73% in the allo-HCT group and 100% in the auto-HCT group, and the respective PFS rates were 63% and 86%. Due to the small sample, no valid comparisons can be made.

The use of alternative donors has increased in recent years, and early experience suggested worse outcomes with unrelated donors in FL. In the largest publication available, the Lymphoma Working Party of the EBMT reported the results of allo-HCT on 131 patients with FL.

### Table 2. — Prospective Series of Reduced-Intensity Conditioning for Follicular Lymphoma

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>Median Age (yrs)</th>
<th>Regimen</th>
<th>DFS/PFS (%)</th>
<th>OS (%)</th>
<th>Median Follow-up (mos)</th>
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<td>CALGB47</td>
<td>44 (16 FL)</td>
<td>53</td>
<td>Fludarabine/cyclophosphamide</td>
<td>75</td>
<td>81</td>
<td>55</td>
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<tr>
<td>United Kingdom49</td>
<td>82</td>
<td>45</td>
<td>Fludarabine/melphalan/alemtuzumab</td>
<td>76</td>
<td>76</td>
<td>43</td>
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<tr>
<td>GELTAMO49</td>
<td>37</td>
<td>50</td>
<td>Fludarabine/melphalan</td>
<td>57</td>
<td>54</td>
<td>52</td>
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<tr>
<td>Fred Hutchinson50</td>
<td>62</td>
<td>54</td>
<td>Fludarabine/total body irradiation</td>
<td>43</td>
<td>52</td>
<td>36</td>
</tr>
<tr>
<td>MD Anderson51</td>
<td>47</td>
<td>53</td>
<td>Fludarabine/cyclophosphamide/rituximab</td>
<td>83</td>
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<td>60</td>
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</table>

FL = follicular lymphoma, DFS = disease-free survival, PFS = progression-free survival, OS = overall survival.
who received grafts from matched unrelated donors. Patients received myeloablative conditioning or RIC conditioning. The estimated OS and PFS rates were 51% and 47% at 3 years for the whole group. There was no difference in OS, PFS, and nonrelapse mortality when myeloablative conditioning and RIC groups were compared ($P = NS$ for all comparisons). This retrospective study demonstrated that matched unrelated donor HCT results in PFS and OS were comparable to those with sibling donors.

Allogeneic transplantation using myeloablative conditioning, RIC, or nonmyeloablative conditioning can induce durable remissions in many patients with relapsed FL, and it is likely curative in most of them. Given the toxicity of myeloablative conditioning and the promising results of published phase II trials with RIC and nonmyeloablative conditioning, the latter appears to be the better choice for this disease. The timing of the transplant remains an open question but, in general, it is recommended that patients with FL be referred for transplant at the time of first relapse. Patients with transformed disease carry a much higher risk of relapse and may require more intensive conditioning pretransplant. Finally, transplant from matched unrelated donors appear to have comparable outcomes with sibling donors in FL.

**Mantle Cell Lymphoma**

Mantle cell lymphoma (MCL) comprises 5% to 10% of all NHLs, affecting primarily older patients with a median age of 60 years at diagnosis. The disease carries the genetic hallmark t(11; 14)(q13;q32), which is thought to be central in the pathogenesis of the disease. It is considered incurable with conventional chemotherapy and is characterized by an aggressive course with a median survival of 3 years. Using intensified induction regimens and the addition of rituximab, a higher proportion of patients achieve complete remission and a longer DFS. However, after long follow-up, survival curves do not plateau and there is a continuous pattern of relapse, thus suggesting that no patients are cured. In addition, most patients are older and cannot tolerate intensive induction chemotherapy.

**Autologous Transplantation**

Several small single-center trials in the 1990s reported disappointing results when auto-HCT was used in relapsed MCL or after several lines of therapy. EBMT and the Autologous Bone Marrow Transplant (ABMT) registries collected data on 195 patients with MCL who underwent an auto-HCT between 1988 and 1998. After a median follow-up of 3.9 years, the OS rates were 76% and 50% at 2 and 5 years, respectively, and the respective PFS rates were 55% and 33%. Disease status at the time of the transplant was the most important factor affecting OS, PFS, and relapse risk, with the best results achieved in patients transplanted in CR1. These retrospective data suggested a significant role for auto-HCT consolidation in CR1. Based on these results, the European MCL network designed a prospective randomized trial comparing consolidation with myeloablative chemotherapy followed by auto-HCT to interferon alpha (IFN-α) maintenance in first remission patients. Most patients received CHOP induction as initial therapy for 4 to 6 courses. Those who achieved CR or PR were randomized to mobilization with DexaBEAM (dexamethasone, carmustine, etoposide, cytarabine, and melphalan) followed by auto-HCT using cyclophosphamide/TBI as conditioning or 2 additional courses of DexaBEAM consolidation. Of the 122 evaluable patients, 62 received auto-HCT and 60 received interferon maintenance. The median PFS time was significantly better in the transplant arm, 39 months vs 17 months ($P = .01$). However, OS was not different, and a continuous pattern of relapse was observed. This trial was completed before the rituximab era, thereby limiting the applicability of the results.

Rituximab has become part of the initial treatment, mobilization regimens, and auto-HCT conditioning regimens for MCL. Small single-center trials showed the feasibility of this approach and suggested improved outcomes after induction with CHOP chemotherapy or with cyclophosphamide, vincristine, doxorubicin (hyperCVAD), with the addition of rituximab, followed by auto-HCT. Vose et al reported in abstract form that the initial induction regimen may have an impact on the final results, with intensive induction having a better PFS.

The Nordic Lymphoma Group published the largest prospective multicenter trial using intensive induction with chemoimmunotherapy followed by consolidation with auto-HCT. In the second Nordic MCL-2 trial, 160 patients younger than 66 years received a dose-intensified induction with maxi-CHOP and rituximab alternating with high-dose cytarabine and rituximab for a total of 6 courses. Responders were intensified with high-dose BEAM or BEAC (consisting of the BEAM regimen but with cyclophosphamide instead of melphalan), with rituximab in vivo purging. The 6-year OS, EFS, and PFS rates were 70%, 56%, and 66%, respectively. When compared with the previous Nordic MCL-1 trial, the addition of rituximab and high-dose cytarabine appeared to improve dramatically the final outcomes. In a more recent publication, the same group used the Mantle Cell Lymphoma International Prognostic Index (MIPI) to analyze the same cohort of patients and found that those in the good- and intermediate-risk groups had similarly good outcomes. The poor-risk group had a disappointing survival despite this aggressive therapy, suggesting that these patients may be candidates for the early use of allo-HCT.

The Cancer and Leukemia Group B (CALGB) recently published the results of a prospective multicenter trial using 2 to 3 courses of induction with augmented CHOP and methotrexate, followed by intensification
with high doses of cytarabine and etoposide used to mobilize hematopoietic progenitor cells. This was followed by high-dose carmustine, etoposide, and cyclophosphamide followed by auto-HCT. Rituximab was added to induction, consolidation, and high-dose chemotherapy. The trial included 78 patients up to 69 years of age. With a median follow-up of 4.7 years, the 5-year PFS and OS rates were 56% and 64%, respectively. This group is planning to add bortezomib as maintenance therapy to reduce the risk of relapse after auto-HCT.

The MD Anderson Cancer Center reported a single-institution experience that included 86 patients who underwent auto-HCT, 50 of them in first remission. In similar fashion as the Nordic group, the addition of rituximab substantially improved the OS and PFS when used in CR1 but not in relapsed or refractory disease. At 6 years, the PFS rate was 39% and the OS rate was 61%. In contrast, in those patients not in CR at transplant, the PFS rate was 10% and the OS rate was 35%.

The National Comprehensive Cancer Network (NCCN) has prospectively collected data on the outcomes of younger MCL patients who were treated with four different induction regimens: (1) CHOP with rituximab (CHOP-R) followed by auto-HCT, (2) hyperCVAD-R with auto-HCT, (3) hyperCVAD-R without auto-HCT, or (4) CHOP-R alone. With the limitations of a retrospective analysis on a small sample of patients, no difference in OS was seen between patients receiving hyperCVAD-R and those receiving CHOP-R followed by auto-HCT. CHOP-R was inferior to hyperCVAD-R or CHOP-R followed by auto-HCT. Despite aggressive regimens, the median PFS was 3 to 4 years.

Studies regarding the feasibility and efficacy of auto-HCT in elderly patients with MCL are limited since this therapy has been offered only recently. EBMT performed a retrospective analysis of patients over 65 years of age who underwent auto-HCT for MCL. Seventy-nine patients over 65 years of age were compared with 633 younger patients. The older group had more commonly been in CR1 but not in relapsed or refractory disease. The high response and low relapse rates suggested that the MIPI score is more important than the intensity of induction before HCT. However, once adjusted for MIPI score, differences in intensity in induction did not affect OS or PFS. These results suggest that the MIPI score is more important than the intensity of induction to define outcome so long as auto-HCT is used as consolidation therapy.

In summary, auto-HCT appears to improve the outcomes of patients with MCL when used as part of the first-line therapy. The benefit is independent of patient age and the intensity of the initial induction regimen. The MIPI score strongly correlates with outcome, and patients with high-risk disease should be targeted for new approaches, including RIC allo-HCT.

**Allogeneic Transplantation**

Small numbers of patients with MCL have been treated with allo-HCT. Most MCL patients are older than 60 years at diagnosis and are typically excluded from this approach. Although myeloablative allo-HCT has been associated with a TRM in the range of 30% to 40%, long-term remissions and cures have been reported even in patients in whom a previous auto-HCT has failed. To reduce toxicity and mortality in these heavily pretreated and frequently older patients, RIC allo-HCT has been proposed with promising results. Maris et al published the results of a nonmyeloablative conditioning regimen with fludarabine and 2 Gy TBI followed by post-grafting immunosuppression with cyclosporine and mycophenolate mofetil. HLA-matched related (n = 16) and unrelated (n = 17) patients with relapsed and refractory MCL underwent transplantation. The rates for relapse and nonrelapse mortality were 9% and 24%, respectively, at 2 years. None of the patients transplanted in CR had relapsed after a median follow-up of 24.6 months. The OS and DFS rates at 2 years were 65% and 60%. The high response and low relapse rates suggested an active graft-vs-tumor response. Tam et al published mature results of RIC allo-HCT using fludarabine, cyclophosphamide, and high-dose rituximab as conditioning in 35 patients with relapsed or refractory MCL; most patients exhibited chemotherapy-sensitive disease. The TRM rate was 9% at 1 year. With a median follow-up of 56 months, median PFS duration was 60 months and median OS has not been reached. Importantly, a clear plateau was seen in both series, suggesting that a significant proportion of patients with relapsed and refractory MCL may be cured with this approach.

The British Society for Blood and Marrow Transplantation published the results of a retrospective analysis of 70 heavily pretreated patients with relapsed/refractory MCL who received RIC allo-HCT with or without alemtuzumab. Regimens included fludarabine-melphalan, BEAM, or fludarabine-busulfan. Approximately 60% of the patients had a sibling donor, 90% received periph-
treated patients to benefit from this promising therapy.

The 3-year OS rate for patients who received donor lymphocyte infusions for relapse was 79%, indicating a powerful graft-vs-malignancy effect.

Le Gouill et al reported a multicenter retrospective analysis of 70 heavily pretreated patients with MCL who received RIC allo-HCT in 12 centers in France and Germany. The median age at transplant was 56 years, and the median time from diagnosis to transplantation was 44 months. A previous auto-HCT had failed in 47 patients. The 2-year EFS and OS rates were 50% and 53%, respectively, and the 2-year TRM rate was 32%. This study showed that RIC allo-HCT is effective not only in patients with chemosensitive disease regardless of the number of prior lines of therapy, but also as salvage therapy for those patients in whom auto-HCT had failed.

Fenske et al studied the results of 640 patients with MCL who underwent a first auto-HCT (n = 433) or reduced-intensity allo-HCT (n = 207) between 1996 and 2007. Their findings were reported to the CIBMTR. For early MCL (ie, 1 or 2 lines of therapy prior to HCT), the auto-HCT group included 251 patients and the allo-HCT group included 50 patients. The 1-year TRM rate was significantly higher in the allo-HCT group (25% vs 4%, P = .001), while the 5-year progression/relapse rate was lower in the allo-HCT group (16% vs 32%, P = .012). The 5-year OS rates were similar (allo-HCT = 62%, auto-HCT = 61%, P = .941). For late MCL (ie, more than 2 lines of therapy before HCT), analysis was restricted to chemosensitive patients (auto-HCT = 159, allo-HCT = 99). The 1-year TRM was again significantly higher in the allo-HCT group (18% vs 9%, P = .036). Unlike early MCL, progression/relapse rates in late MCL were similar at 5 years for both groups (auto-HCT = 38%, allo-HCT = 49%, P = .148). The 5-year OS rates were also similar (allo-HCT = 32%, auto-HCT = 44%, P = .193).

In summary, when applied early in the disease course, both auto-HCT and allo-HCT result in favorable long-term survival, with RIC allo-HCT associated with higher TRM but lower relapse rates. When applied in advanced disease, both auto-HCT and allo-HCT result in inferior outcomes.

Based on the presented data, allo-HCT appears to be effective for relapsed and refractory MCL and the only approach associated with long-term survival. However, toxicity is a limiting factor, and some patients may be unable to tolerate this therapy. Early referral for discussion of transplantation is warranted since the safety and tolerability of RIC allo-HCT has allowed older and heavily pretreated patients to benefit from this promising therapy.

Lymphoma in Patients With HIV Infection

NHL is an AIDS-defining diagnosis. After active antiretroviral therapy (HAART) became widely available, the incidence of NHL in developed countries decreased dramatically in HIV-infected patients. However, it occurs 20 to 50 times more often in HIV-infected patients than in non-HIV-infected patients. B-cell lymphomas predominate in HIV-infected patients, with the most common types being DLBCL, Burkitt lymphoma, and Burkitt-like lymphoma. Treatment outcomes for HIV-related NHL in patients on HAART have improved substantially and are now similar to outcomes for patients without HIV infection.

**Autologous Transplantation**

Auto-HCT in patients with AIDS and lymphoma was initially presented in case reports and small series. One study reported on 20 patients with relapsed, induction-failure, or high-risk lymphoma (18 patients with NHL and 2 patients with Hodgkin disease) using conditioning therapy with cyclophosphamide, etoposide, and carmustine or TBI. At a median length of follow-up of 31.8 months, 17 of the 20 patients were free of disease, 1 died of transplant-related complications, and 2 died of relapsed lymphoma early following transplant. The AIDS Malignancy Consortium published the results of autologous transplant in high-risk HIV-associated lymphoma in 15 patients with NHL and 5 patients with Hodgkin disease using low-dose busulfan and cyclophosphamide as conditioning. Of the 20 patients, 10 were alive and event-free at a median of 23 weeks following autologous transplant.

The EBMT Lymphoma Working Party presented the results of a retrospective analysis on treatment outcomes of 68 patients with HIV lymphoma who underwent auto-HCT using predominantly BEAM conditioning (n = 65). The cumulative incidence of nonrelapse mortality was 7.5% at 12 months, mainly from bacterial infections. The cumulative incidence of relapse was 30.4% at 24 months. At a median follow-up of 32 months, PFS and OS rates were 56%. Status of disease at transplantation and chemotherapy sensitivity correlated well with outcomes.

Two recent case-control studies compared the survival of HIV-infected patients and uninfected patients undergoing auto-HCT for lymphoma and found similar outcomes. Taken together, these results confirm that auto-HCT in patients with lymphoma and HIV infection is feasible, safe, and effective. In most studies, the patients continued HAART therapy throughout the peritransplant period. Survival, relapse, and nonrelapse mortality were similar to those seen in patients without HIV infection; however, no formal comparative studies have been done. The BMT CTN is currently enrolling patients on a phase II multicenter trial (CTN 0803) using BEAM as the conditioning regimen followed by auto-HCT for chemotherapy-sensitive aggressive B-cell lymphomas.
lymphoma and Hodgkin lymphoma in patients with HIV infection. In addition to lymphoma and transplant-related outcomes, this trial will assess HIV biology, HIV lymphoma tumor markers, and other correlative studies.

In summary, auto-HCT in patients with well-controlled HIV infection has similar outcomes compared with patients without HIV infection. Therefore, HIV infection should not be a contraindication for auto-HCT. The indications for transplant are similar in HIV-positive or HIV-negative patients with lymphoma.

**Allogeneic Transplantation**

Before HAART was available, initial attempts to treat HIV-infected patients with allo-HCT led to extremely poor outcomes. After HAART became widely available, several case reports suggested a potential benefit of allo-HCT in this patient population. Allo-HCT in patients with malignancy and HIV infection has particular challenges, including the risk of opportunistic infection before and after transplantation, the high frequency of other concomitant viral infections, the potential impact of HIV in bone marrow environment and immune reconstitution posttransplant, and the potential for complex interactions between HAART, high-dose therapy, and immunosuppressive agents.

The CIBMTR retrospectively evaluated the results of allo-HCT in 23 HIV-infected patients undergoing transplant between 1987 and 2003, including patients receiving transplantation prior to the advent of HAART. Median age at transplant was 32 years. The indications for transplant included primarily malignant conditions, with lymphoma being the most common, followed by acute leukemia. Bone marrow was the graft in most patients, and the common donor sources were HLA-identical siblings. Median time to neutrophil engraftment was 16 days, cumulative incidence of grade II to IV acute GVHD was 30%, and cumulative incidence of chronic GVHD at 2 years was 28%. With a median follow-up of 6 months, 30% of the patients were alive at 2 years; the primary causes of death were organ toxicity and infection. Despite initial mortality due to organ damage and infection, several patients achieved long-lasting remission. With currently available therapy, development of AIDS can be prolonged for decades with minimal morbidity; therefore, HIV infection should not be considered a contraindication for allo-HCT. Prospective studies with modern HAART and transplant support are needed. The BMT CTN is conducting a prospective multicenter trial (CTN 0903) enrolling patients with HIV infection and malignancy or bone marrow failure to assess the day 100 mortality after allo-HSCT. This trial will also study OS, PFS, and the impact of HCT on HIV reservoirs.

**Conclusions**

The role of auto-HCT and allo-HCT in the management of B-cell lymphoma continues to evolve. The timing of transplantation and the type of transplantation are continually being refined. Early referral to a transplant center is warranted for patients with this disease. The low transplant-related mortality of auto-HCT, as well as the acceptable transplant-related mortality following reduced-intensity conditioning allo-HCT, should permit patients previously considered to be too old or unfit to receive these beneficial therapies. Table 3 summarizes current recommendations for HCT in B-cell lymphoma.

**References**

5. Stiff PJ, Unger JM, Cook J, et al. Randomized phase III US/Canadian intergroup trial (SWOG S9704) comparing CHOP ± R for eight cycles to CHOP ± R for six cycles followed by autotransplant for patients with

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**Table 3. — Summary of Current Recommendations for Hematopoietic Cell Transplantation in B-Cell Lymphoma**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Autologous HCT</th>
<th>Allogeneic HCT</th>
</tr>
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<tbody>
<tr>
<td>Diffuse large B-cell lymphoma</td>
<td>Relapsed disease, primary induction failure, high risk (IPI) first CR</td>
<td>Relapsed disease with bone marrow involvement, relapse after auto-HCT</td>
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<tr>
<td>Follicular lymphoma</td>
<td>First relapse</td>
<td>Beyond first CR</td>
</tr>
<tr>
<td>Mantle cell lymphoma</td>
<td>After initial induction, first relapse</td>
<td>First or subsequent relapse, relapse after auto-HCT, high risk by MIPI*</td>
</tr>
<tr>
<td>Lymphoma in HIV-positive patients</td>
<td>Relapsed disease, primary induction failure, high risk (IPI) first CR</td>
<td>No current indication outside a clinical trial</td>
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