Diffuse Large B-Cell Lymphoma

Autologous Transplantation

High-Dose Therapy as Part of Initial Treatment for High-Risk Disease:

Thirteen prospective multicenter randomized studies have studied the role of high-dose therapy with autologous hematopoietic cell transplantation (autoHCT) as part of the first-line treatment for patients with diffuse large B-cell lymphoma (DLBCL). In those trials, patients received initial induction with conventional-dose chemotherapy and were then randomly assigned to consolidation with autoHCT or additional doses of conventional chemotherapy. Inclusion criteria and the intensity/number of courses of conventional therapy before autoHCT were varied, making comparisons difficult. Results are contradictory, with nine studies showing no difference in outcomes. Four studies showed improvement in disease-free survival (DFS) and/or overall survival (OS) for the high-dose therapy arm. Of note, all of these trials were completed before the rituximab era and thus the results may not be applicable to current practice.3-15

Many types of lymphoma benefit from autologous or allogeneic hematopoietic cell transplantation.

Introduction

The lymphomas are a heterogeneous group of hematologic malignancies with varied aggressiveness and many therapeutic options. In 2010 in the United States, approximately 8,490 new cases of Hodgkin lymphoma (HL) and 65,540 new cases of non-Hodgkin lymphoma (NHL) were diagnosed.1 Both autologous and allogeneic transplantations have roles in the management of these diseases; in 2008, approximately 5,500 transplants for these diseases were performed in North America.2

Hematopoietic Cell Transplantation for Lymphomas

Ernesto Ayala, MD, and Marcie Tomblyn, MD, MS

Background: The heterogeneity of lymphomas results in numerous treatment options, including both autologous and allogeneic hematopoietic cell transplantation. However, the type of transplantation, the timing the procedure, and the selection of suitable patients for transplant continue to evolve.

Methods: We reviewed the current medical literature to provide a succinct synthesis for the most common types of lymphoma and the indications for transplantation.

Results: This review discusses the outcomes of autologous and allogeneic transplantation for patients with diffuse large B-cell lymphoma, follicular lymphoma, HIV-associated lymphomas, mantle cell lymphoma, T-cell lymphoma, and Hodgkin lymphoma.

Conclusions: Each of these histologies differs in the indications and timing for transplantation. However, ongoing clinical trials support the continuing role of both autologous and allogeneic transplantation for lymphoma management.

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No significant relationship exists between the authors and the companies/organizations whose products or services may be referenced in this article.
The results of the US/Canadian phase III multicenter prospective randomized trial SWOG S9704 were recently presented in abstract format.

**Treatment of Relapsed Disease:** The role of autologous hematopoietic cell transplantation (auto-HCT) in the treatment of relapsed disease was defined in the late 1990s. Rituximab, a chimeric monoclonal antibody against CD20, has become part of the standard first-line treatment for DLBCL based on improvements in OS and PFS, when compared with chemotherapy alone. It has also been incorporated as part of the salvage for relapsed disease and as a component of high-dose therapy regimens. However, in contrast to the available data as part of first-line therapy, no prospective randomized studies have evaluated the impact on outcomes or defined the appropriate dose or schedule in the transplant setting. Despite this, many transplant centers (including ours) have adopted rituximab as a component of high-dose therapy regimens with the assumption that it might improve the outcome obtained with chemotherapy alone in a setting of low tumor burden and as an "in vivo purging" tool. Similarly, there are insufficient data to recommend routine maintenance with rituximab after auto-HCT outside of a clinical trial.

**The Role of Radioimmunotherapy:** Radioimmunotherapy is a novel type of immunotherapy that uses a linker to combine a monoclonal antibody with a certain specificity linked with a radioimmunoconjugate. The currently available agents used in lymphoma target the CD20 molecule. This potent combination has the independent effect of the monoclonal antibody through complement-mediated cytotoxicity, antibody-mediated cellular cytotoxicity, and apoptosis, in addition to the radioisotope emission that kills the cells bound to the antibody and other surrounding lymphoma cells. Two radiolabeled antibodies, iodine-131 tositumomab and yttrium-90 ibritumomab, have been approved by the US Food and Drug Administration (FDA) to treat relapsed lymphoma.

Radiation therapy has been a component of the conditioning regimens used to treat lymphoma in the past. Both antibodies have been used in phase I and phase II clinical trials, in conventional standard dose or escalated high dose, to potentiate the therapeutic effect of high-dose therapy or to substitute TBI, with the goal of decreasing relapse without adding toxicity to the conditioning regimens. Radioimmunotherapy delivers targeted radiation to lymphoma sites protecting other tissues; therefore, it limits toxicity and allows the use of auto-HCT in older patients or in patients with comorbidities and decreased organ function. Table 1 summarizes several trials that have incorporated radioimmunotherapy to the conditioning regimen. While no comparative trials against standard radiation therapy have been done, these phase I–II trials have shown this approach to be safe with low TRM.

The Blood and Marrow Transplant Clinical Trials Network (BMT CTN) conducted a prospective multicenter randomized phase III trial (04H1) comparing high-dose therapy with carmustine, etoposide, cytarabine, and melphalan (BEAM) plus rituximab vs BEAM plus conventional-dose tositumomab (Bexxar) followed by auto-HCT in patients with chemotherapy-sensitive relapsed DLBCL. The trial completed accrual and planned follow-up, and results will likely be available at the end of 2011. If the results
are positive, this trial may change the standard of care for relapsed chemotherapy-sensitive large B-cell lymphoma.29

**Allogeneic Transplantation**
In contrast to autoHCT, the number of patients and published studies using allogeneic transplantation (alloHCT) in DLBCL are small and do not allow definitive conclusions. AlloHCT has generally been used as treatment for relapsed high-risk or refractory disease or for patients who relapsed after autoHCT. No prospective comparative studies are available in this setting.

In a retrospective study, Lazarus et al30 compared the outcomes of DLBCL patients undergoing first autologous transplant (n = 837) or HLA-identical sibling alloHCT with myeloablative conditioning (n = 79) between 1995 and 2003 that were reported to the Center for International Blood and Marrow Transplant Research (CIBMTR). The alloHCT group had more patients with intermediate-high or high-risk IPI, extranodal involvement, marrow involvement, and B symptoms. AlloHCT was associated with higher TRM but with a similar risk of disease progression compared with lower-risk patients who received autoHCT.30

For patients who failed a previous autoHCT, encouraging results have been seen with alloHCT as a salvage strategy. The European Group for Blood and Marrow Transplantation (EBMT) registry published a retrospective analysis of 101 patients.31 Approximately two-thirds of the patients received a reduced-intensity conditioning (RIC) regimen and 70% had an identical sibling donor. Outcomes at 3 years were encouraging, with a non-relapse mortality (NRM) rate of 28.2%, a relapse rate of 30%, a PFS rate of 41%, and an OS rate of 53%. With an NRM that can be considered acceptable in this heavily pretreated population, alloHCT led to a long-term survival in this poor-risk group. Patients with a long remission after autoHCT and with sensitive disease at alloHCT appear to be the best candidates for this approach.31

As the morbidity and mortality of alloHCT continues to improve, the role of alloHCT in the treatment of DLBCL is likely to increase in the near future, and it may be realistic to contemplate a prospective comparison of autoHCT vs alloHCT for the treatment of relapsed disease, particularly in high-risk groups.

**Follicular Lymphoma**
Follicular lymphoma comprises approximately 25% of all newly diagnosed NHL cases. As an indolent lymphoma, the disease course is one of remissions and relapses with chemotherapy, followed inevitably by resistance and transformation to a more aggressive NHL histology. Generally, the goal of treatment is to provide durable remissions with intensification of therapy, including the use of radioimmunotherapy.32

**Autologous Transplantation**
Several studies have examined the benefit of autoHCT as consolidation after initial chemotherapy for follicular lymphoma, although only two of these trials incorporated rituximab.33-37 Early trials from the Groupe d’Etude des Lymphomes de l’Adulte, the German Low Grade Lymphoma Study Group, and the Groupe Ouest-Est des Leucémiés et Autres Maladies du Sang compared consolidative autoHCT to chemotherapy ± interferon alfa (IFN-α) maintenance therapy.35,53 In all trials, EFS and PFS were prolonged compared to maintenance; however,

<table>
<thead>
<tr>
<th>Study</th>
<th>RIT Regimen</th>
<th>No. of Patients</th>
<th>Histology</th>
<th>Overall Survival (yrs)</th>
<th>Progression-Free Survival (yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Standard-dose RIT + Chemotherapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Khouri et al105</td>
<td>90Y BEAM</td>
<td>26</td>
<td>Various</td>
<td>92% (3)</td>
<td>83% (3)</td>
</tr>
<tr>
<td>Shimoni et al106</td>
<td>90Y BEAM</td>
<td>23</td>
<td>Aggressive</td>
<td>67% (3)</td>
<td>52% (3)</td>
</tr>
<tr>
<td>Krishnan et al107</td>
<td>90Y BEAM</td>
<td>41</td>
<td>Most DLBCL</td>
<td>89% (2)</td>
<td>70% (2)</td>
</tr>
<tr>
<td>Shimabukuro-Vornhagen et al108</td>
<td>90Y BEAM</td>
<td>10</td>
<td>DLBCL and FL</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Decaudin et al109</td>
<td>90Y BEAM</td>
<td>77</td>
<td>Most FL</td>
<td>97% (2)</td>
<td>EFS 63% (2)</td>
</tr>
<tr>
<td>Vose et al110</td>
<td>131I BEAM</td>
<td>23</td>
<td>Aggressive</td>
<td>55% (3)</td>
<td>39% (3)</td>
</tr>
<tr>
<td>Vose et al111</td>
<td>131I BEAM</td>
<td>40</td>
<td>DLBCL</td>
<td>81% (3)</td>
<td>70% (3)</td>
</tr>
<tr>
<td><strong>High-dose RIT + Chemotherapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nademanee et al112</td>
<td>90Y Cy, VP16</td>
<td>42</td>
<td>Various</td>
<td>81% (4)</td>
<td>65%, DFS (4)</td>
</tr>
<tr>
<td>Winter et al113</td>
<td>90Y BEAM</td>
<td>44</td>
<td>Various</td>
<td>60% (3)</td>
<td>43% (3)</td>
</tr>
<tr>
<td>Press et al114</td>
<td>131I Cy, VP16</td>
<td>52</td>
<td>Various</td>
<td>83% (2)</td>
<td>68% (2)</td>
</tr>
</tbody>
</table>

RIT = radioimmunotherapy, BEAM = BCNU-etoposide-cytarabine-melphalan, DLBCL = diffuse large B-cell lymphoma, FL = follicular lymphoma, NR = not reported.

Table 1. — Radioimmunotherapy in Conventional or High Dose as Part of Conditioning Regimens for Autologous Transplantation in Lymphoma
there was no improvement in OS (Table 2). Similarly, there is evidence of improvement in PFS but not OS in the rituximab era. Consequently, in the absence of OS benefit, proceeding with autoHCT as consolidation is not recommended.

One prospective randomized trial and several retrospective analyses demonstrated improved EFS when autoHCT was used as consolidation after salvage chemotherapy for patients in first relapse. All three retrospective analyses demonstrated improved OS. The CUP trial compared standard chemotherapy to high-dose chemotherapy followed by autoHCT with either unpurged or ex vivo purged grafts. The trial closed early due to slow accrual, with only 70 patients evaluated. Despite this, the 2-year PFS rate was improved following autoHCT: chemotherapy, 26% (8% to 44%) vs unpurged grafts, 58% (37% to 79%) vs ex vivo purged grafts, 55% (34% to 75%) (P = .0037). While an improvement in OS was not statistically demonstrated, the respective OS rates at 4 years were 46% (25% to 67%), 71% (52% to 91%), and 77% (60% to 95%) (P = .79). Only one of these reports investigated the impact of rituximab on the outcomes at salvage and demonstrated a 5-year OS rate of 93% for 33 patients who received autoHCT following a rituximab-based salvage regimen compared to 63% for 65 patients who received autoHCT but did not have rituximab prior to transplant (P = .0071).

**Allogeneic Transplantation**

The graft-vs-lymphoma effect afforded by alloHCT is appealing as a potential curative approach. Unfortunately, several cohort analyses demonstrated similar outcomes in DFS and OS due to the higher TRM following myeloablative conditioning and alloHCT counterbalancing the higher relapse rate following autoHCT. Several studies using a RIC alloHCT suggest that the graft-vs-lymphoma effect may successfully control and potentially cure this disease with acceptable rates of TRM. In 2008, Khouri et al published the long-term results of their single institution trial of 43 patients with relapsed/refractory follicular lymphoma receiving a RIC alloHCT with high doses of rituximab during conditioning. At a median follow-up of 6 years, the PFS and OS rates were 83% (95% confidence interval [CI], 69%–91%) and 85% (95% CI, 71%–93%), respectively. With a shorter median follow-up, the Cancer and Leukemia Group B (CALGB) found similar excellent EFS and OS rates in its multicenter study that included a cohort of 16 patients with follicular lymphoma (3-year EFS = 75% [95% CI, 46%–90%], 3-year OS = 81% [95% CI, 51%–93%]). TRM was only 9% at 3 years. Currently, the BMT CTN is using the RIC conditioning regimen published by Khouri et al to assess the outcomes following an HLA-identical related or unrelated donor alloHCT.

As with any indolent disease, several therapeutic approaches may be beneficial. Progress in this area has been hampered by poor accrual to national clinical trials studying novel approaches.

**Table 2. — Autologous Transplantation vs Interferon Alfa (IFN-α) Maintenance Therapy as Initial Therapy for Follicular Lymphoma**

<table>
<thead>
<tr>
<th>Study</th>
<th>Induction</th>
<th>Treatment Arms</th>
<th>Progression-Free Survival/ Event-Free Survival</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLSG&lt;sup&gt;34&lt;/sup&gt;</td>
<td>CHOP ± R</td>
<td>AutoHCT (n = 195) IFN-α (n = 236)</td>
<td>At 5 yrs: 60.2% (51–69) 31.6% (25–39) P &lt; .001</td>
<td>Not reported</td>
</tr>
<tr>
<td>GELA&lt;sup&gt;33&lt;/sup&gt;</td>
<td>CHOP</td>
<td>AutoHCT (n = 167) IFN-α (n = 172)</td>
<td>At 7 yrs: 40% (33–48) 29% (21–36) P = .05</td>
<td>At 7 yrs: 76% (69–82) 71% (65–71) P = .53</td>
</tr>
<tr>
<td>GOELAMS&lt;sup&gt;37&lt;/sup&gt;</td>
<td>VCAP ± DHAP</td>
<td>AutoHCT (n = 86) IFN-α (n = 80)</td>
<td>At 9 yrs: 56% (45–67) 39% (28–50) P &lt; .03</td>
<td>At 9 yrs: 76% (67–85) 80% (72–89) P = .55</td>
</tr>
</tbody>
</table>

GLSG = German Low Grade Lymphoma Study Group, GELA = Group d’Etude des Lymphomes de l’Adulte, GOELAMS = Groupe Ouest-Est des Leucémies et Autres Maladies du Sang, CHOP(R) = cyclophosphamide/doxorubicin/vincristine/prednisone (rituximab), VCAP = vindesine/cyclophosphamide/doxorubicin/prednisone, DHAP = dexamethasone/cytarabine/cisplatin, AutoHCT = autologous hematopoietic cell transplantation.
Lymphoma in Patients With HIV Infection

NHL is an AIDS-defining diagnosis. After highly active antiretroviral therapy (HAART) became widely available, the incidence of NHL in developed countries decreased dramatically in HIV-infected patients. Yet, NHL occurs 20 to 50 times more often in this population than in non-HIV patients. The most common types of NHL in HIV patients are DLBCL, Burkitt lymphoma, and Burkitt-like lymphoma. The outcome of the treatment for HIV-related NHL in patients on HAART has improved substantially and is now similar to those patients without HIV infection.

Autologous Transplantation

AutoHCT in patients with AIDS and lymphoma was initially presented in case reports and small series. Krishnan et al published their experience of 20 patients (18 NHL and 2 HL) with relapsed, induction-failure, or high-risk lymphoma using a chemotherapy-based regimen of carmustine, etoposide, and cyclophosphamide or a radiation-based regimen of TBI, etoposide, and cyclophosphamide. At a median follow-up of 31 months, 17 of 20 patients were alive and free of disease. One patient died of transplant-related complications. The AIDS malignancy consortium published the results of autologous transplantation in high-risk HIV-associated lymphoma in 15 patients with NHL and in 5 patients with HL using low-dose busulfan and cyclophosphamide as the conditioning regimen. At a median follow-up of 23 weeks, half of the patients were alive and free of disease.

The EBMT Lymphoma Working Party presented the results of a retrospective analysis on the treatment outcomes of 68 patients with HIV lymphoma who underwent autoHCT using predominantly BEAM conditioning (n = 65). The cumulative incidence of NRM was 7.5% at 12 months, mainly from bacterial infections, and the cumulative incidence of relapse was 30.4% at 24 months. At a median follow-up of 32 months, PFS and OS rates were 56.5% and 61%, respectively. The status of disease at transplant and chemotherapy sensitivity correlated well with outcomes.

These results confirm that autoHCT in patients with HIV lymphoma is feasible, safe, and effective. In most studies, the patients continued HAART therapy throughout the peritransplant period. While survival, relapse, and NRM are similar to those seen in HIV-negative patients, 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 autoHCT for chemotherapy-sensitive aggressive B-cell lymphoma and HL in patients with HIV infection. In addition to lymphoma and transplant-related outcomes, this trial will look at HIV biology, HIV lymphoma tumor markers, and other correlative studies.

Allogeneic Transplantation

Initial attempts to utilize alloHCT for patients with HIV infection before HAART was available to treat HIV infection resulted in poor outcomes. More recently, several case reports have suggested benefit with alloHCT in this patient population. AlloHCT in patients with malignancy and HIV infection has particular challenges, including the risk of opportunistic infection before and after transplant, the high frequency of other concomitant viral infections, the potential impact of HIV in bone marrow environment and immune reconstitution following transplant, and the potential for complex interactions between HAART, high-dose therapy, and immunosuppressive agents.

The CIBMTR retrospectively evaluated the results of alloHCT in 23 HIV-positive patients who received transplants between 1987 and 2003 and included patients transplanted prior to the advent of HAART. The median age at transplant was 32 years, and 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 source was HLA-identical sibling donors. The median time to neutrophil engraftment was 16 days, the cumulative incidence of grade II to IV acute GVHD was 30%, and the 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, and the primary causes of death were organ toxicity and infection. These data demonstrate that despite initial mortality due to organ damage and infection, several patients achieved long-lasting remission. With currently available therapy, development of AIDS can be delayed for decades with minimal morbidity; therefore, HIV should not be considered a contraindication for alloHCT. Prospective studies with modern HAART and transplant support are needed. A prospective trial by the BMT CTN (CTN 0903) is enrolling patients with HIV infection and malignancy or bone marrow failure to assess the day-100 mortality of alloHCT in these patients.

Mantle Cell Lymphoma

Mantle cell lymphoma (MCL) comprises 5% to 10% of all NHL, affecting primarily older patients; the median age at diagnosis is 60 years. The disease carries the genetic hallmark t(11;14)(q13;q32), which juxtaposes the immunoglobulin heavy chain promoter to the transcription unit of the proto-oncogene \textit{CCND1}. The translocation leads to deregulated expression of cyclin D1, which is thought to be central in the pathogenesis of the disease. It is considered incurable with conventional chemotherapy, and it is characterized by an aggressive course with a median survival of 3 years. With intensified induction regimens and the addition of rituximab, a higher proportion of patients achieve complete remission and longer DFS. However, after long follow-up, survival curves do not plateau and there is a continuous pattern of relapse, suggesting that no patients are cured.
**Autologous Transplantation**

Several small single-center trials in the 1990s showed disappointing results when autoHCT was used in relapsed MCL or after several lines of therapy. The EBMT and the Autologous Bone Marrow Transplant registries collected data on 195 patients with MCL who underwent an autoHCT 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 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 who received transplants in first remission (CR1). These retrospective data suggested a significant role for autoHCT consolidation in CR1. Based on these results, the European MCL network designed a prospective randomized trial comparing consolidation with myeloablative radiochemotherapy followed by autoHCT to IFN-α maintenance in first-remission patients. Most patients received CHOP induction as the initial therapy for 4 to 6 courses. Those who achieved a complete or partial response were randomized to mobilization with BEAM plus dexamethasone (dexamBEAM) followed by autoHCT using cyclophosphamide/TBI as conditioning or two additional courses of dexamBEAM consolidation. Of 122 evaluable patients, 62 received autoHCT and 60 received IFN maintenance. The median PFS time was significantly better for the transplant arm, 39 months vs 17 months ($P = .01$); however, OS was not different and a continuous pattern of relapse was observed.

Similar to DLBCL, rituximab has become part of the initial treatments, mobilization regimens, and autoHCT conditioning regimens for MCL. Small single-center trials showed the feasibility of this approach and suggested improved outcomes after induction with CHOP or hyperCVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone), with the addition of rituximab, followed by autoHCT. Vose et al reported in abstract format that the initial induction regimen may affect the final results, with intensive induction achieving a better PFS.

The Nordic Lymphoma Group published the largest prospective multicenter trial using intensive induction with chemoimmunotherapy followed by consolidation with autoHCT. In the second Nordic MCL 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 (carmustine, etoposide, cytarabine, and melphalan/cyclophosphamide) with rituximab in vivo purging. The 6-year OS, EFS, and PFS rates were 70%, 56%, and 66%, respectively, with no relapses occurring after 5 years, suggesting that a proportion of patients may be cured. When compared with the previous Nordic MCL trial, the addition of rituximab and high-dose cytarabine appeared to dramatically improve 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 alloHCT.

The 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, followed by high-dose carmustine, etoposide, and cyclophosphamide conditioning and autoHCT. 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 autoHCT.

In summary, the use of autoHCT as consolidation in CR1 and the addition of rituximab and high-dose cytarabine have markedly improved the OS and PFS of patients with MCL. A definitive trial is needed to compare intensive chemoimmunotherapy induction with or without autoHCT in CR1. However, in the absence of such a trial, some of the recent studies have shown that consolidation with autoHCT may be associated with a plateau in survival curves, suggesting that in a proportion of patients MCL has been eradicated.

**Allogeneic Transplantation**

Small numbers of patients with MCL have been treated with alloHCT. Most MCL patients are older than 60 years at diagnosis and are typically excluded from this approach. Although myeloablative alloHCT has been associated with a TRM in the range of 30% to 40% in patients with MCL, long-term remissions and cures have been described even in those patients who failed autoHCT.

To reduce toxicity and mortality in these heavily pretreated and frequently older patients, RIC alloHCT 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 postgrafting immunosuppression with cyclosporine and mycophenolate mofetil. HLA-matched related patients (n = 16) or unrelated patients (n = 17) with relapsed refractory MCL were transplanted. Relapse and NRM rates 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. At 2 years, the OS rate was 65% and the DFS rate was 60%. The high response and low relapse suggested an active graft-vs-tumor response. Tam et al published mature results of RIC alloHCT 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, the median PFS duration was 60 months and the median OS had 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 alloHCT with or without alemtuzumab.75 Regimens included fludarabine-melphalan, BEAM, or fludarabine-busulfan. Approximately 60% of the patients had a sibling donor, 90% received peripheral blood grafts, and 57 of the 70 patients received alemtuzumab. In this heterogeneous group, the 1-year NRM rate was 18%, the cumulative risk of relapse at 5 years was 65%, the 5-year OS rate was 37%, and the 5-year DFS rate was 14%. Donor lymphocyte infusions were given to 27 patients; all but 1 patient had received alemtuzumab as part of the conditioning regimen. The 3-year OS rate for patients who received donor lymphocyte infusions for relapse was 79%, indicating a powerful graft-vs-malignancy effect.

Based on these reports, alloHCT appears to be effective therapy for relapsed and refractory MCL and the only one associated with long-term remission. However, the toxicity of this approach must be considered, and certain patients may be unable to tolerate this approach late in the disease course. Those patients should be considered for experimental agents for disease management. Alternatively, earlier referral for discussion of transplantation is certainly warranted since the safety and tolerability of RIC alloHCT have allowed older and heavily pretreated patients to benefit from this promising therapy.

T-Cell Lymphoma
Peripheral T-cell lymphoma (PTCL) and natural killer/T-cell lymphoma constitute a rare and very heterogeneous group of NHL. In Western countries, they account for 10% to 15% of all adult lymphomas, but the frequency has a high geographic variation around the world. With the notable exception of anaplastic large-cell lymphoma ALK(+)(anaplastic large-cell kinase-positive), PTCL carries a poor prognosis with low OS and DFS with conventional chemotherapy, and most patients die of the disease. Peripheral T-cell lymphoma—not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AITL), and anaplastic large-cell lymphoma (ALCL) account for 75% to 80% of the T-cell lymphoma cases in the United States.76

Autologous Transplantation
Given the poor outcome of conventional therapy, several groups have explored the use of intensification with high-dose therapy and autoHCT as part of the initial treatment. Corradini et al77 published the results of two prospective phase II trials, investigating the role of high-dose sequential chemotherapy followed by autoHCT in 62 patients with PTCL. Conditioning regimens consisted of mitoxantrone plus melphalan or BEAM. In an intent-to-treat analysis, 74% of patients completed the planned therapy, and 25% did not proceed to transplant primarily due to disease progression. At a median follow-up of 76 months, the estimated 12-year OS, DFS, and EFS rates were 34%, 55%, and 30%, respectively. On multivariate analysis, patients in CR had a significant improvement in OS and EFS.77

The Gel-Tamo Study Group investigators published their experience in 26 patients with PTCL, excluding ALCL ALK(+).78 Patients received 3 courses of mega-CHOP (dose-escalated CHOP) and, if the gallium scan was negative, 1 additional course followed by autoHCT. Those who remained positive received 2 courses of ifosfamide and etoposide and, if in partial remission (PR), went to autoHCT. After autoHCT, 19 patients were in CR. Six patients were not transplanted, 5 due to progressive disease and 1 due to lethal toxicity. At 2 years following transplant, OS and PFS were 73% and 53%, respectively. In those who actually went to transplant, OS and PFS rates were 84% and 56%.

Mercadal et al79 reported the results of a phase II trial in 41 patients with PTCL. Induction chemotherapy included high-dose CHOP, alternating with etoposide, cisplatinum, cytarabine, and prednisone for a total of 6 courses. Responders received autoHCT. Only 20 patients achieved complete or partial response, and 17 proceeded to transplant. With a median follow-up of 3.2 years (range, 0.5–8.1 years), the PFS and OS rates at 4 years were 30% and 39%, respectively. In the largest published trial, Reimer et al80 reported a prospective multicenter study including 83 patients with PTCL. Initial induction was 4 to 6 courses of CHOP followed by mobilization chemotherapy with miniBEAM or with etoposide, methyprednisolone, cytarabine, and cisplatinum. Patients in complete or partial remission underwent conditioning with cyclophosphamide and TBI followed by autoHCT. Fifty-five patients received transplants; progressive disease was the predominant reason for not proceeding to transplant. In intent-to-treat analysis, with a median follow-up of 33 months, the estimated 3-year OS and DFS rates for patients in CR were 48% and 53%, respectively.

Collectively, these publications suggest that consolidation of CR1 with autoHCT is feasible and safe. However, up to one-third of patients may never receive transplant, mostly due to progressive disease, thus pointing to the need for better induction regimens. The results suggest improvement in OS and DFS when compared with chemotherapy alone. However, only a prospective randomized trial comparing chemotherapy with or without consolidation with autoHCT will definitely answer this question. Given the rarity of T-cell lymphoma, such a trial will require multicenter participation.
In the setting of relapsed disease, autoHCT has shown results comparable to those achieved in relapsed aggressive B-cell lymphoma. Long-term DFS was reported in 30% to 50% of patients, making autoHCT effective therapy for this indication. In patients with refractory disease, the outcome remains poor and other strategies are needed.81,83

Allogeneic Transplantation
AlloHCT has been proposed for the treatment of PTCL for several reasons. It allows the use of a "clean" graft devoid of malignant cells, and it may provide immunotherapy through a graft-vs-lymphoma effect. These potential benefits are offset by the high transplant-related morbidity and mortality associated with the intensity of myeloablative conditioning regimens. While reducing the intensity of the conditioning may decrease transplant-related morbidity and mortality, GVHD remains a frequent complication independent of the conditioning.

The largest published study is a retrospective analysis of 77 patients with a median age at diagnosis of 36 years who underwent alloHCT for PTCL in France.84 PTCL-NOS, ALCL, and AITL accounted for 65 cases. One-quarter of the patients had failed a previous autoHCT. At transplant, 31 patients were in CR, 23 in PR, and 23 had stable, progressive, or refractory disease. Myeloablative conditioning was used in 57 patients (TBI based on 38 patients). The median follow-up for survival was 43 months. The 5-year OS and EFS rates were 57% and 53%, respectively. Patients with AITL had the best outcome, with 5-year OS and EFS rates of 80%. Two patients achieved long-lasting remission after donor lymphocyte infusions. TRM was 34% at 5 years, and a plateau in survival was reached after 20 months. The number of chemotherapy lines, the disease status at transplantation, and the occurrence of acute GVHD grade III–IV affected both OS and EFS. AlloHCT was effective, with a risk of relapse lower than 15%. However, TRM was high, thus limiting the benefit of this approach.84

In similar fashion to other lymphoma subtypes, RIC alloHCT has been evaluated in PTCL. Corradini et al85 published a prospective phase II trial using a reduced-intensity regimen of thiotepa, cyclophosphamide, and fludarabine in 17 patients with PTCL with a median age of 41 years. Eight patients had failed a previous autoHCT and 16 received sibling transplants. GVHD prophylaxis was cyclosporine and methotrexate, and 3 patients with mismatched grafts received alemtuzumab. The estimated 3-year OS and PFS rates were 81% and 64%, respectively, with a remarkably low TRM rate of 6% at 2 years. These results appear promising, particularly in this population of heavily pretreated patients. Shustov et al86 published the results of a nonmyeloablative conditioning with fludarabine, 2 Gy TBI, and posttransplant immunosuppression with cyclosporine and mycophenolate mofetil. Of the 17 patients included, 6 had failed a previous autoHCT and 5 had refractory disease. The median age at transplanta-

tion was 57 years. After a median follow-up of 3.3 years among surviving patients, the estimated probabilities of 3-year OS and PFS were 59% and 53%, respectively, while the estimated probabilities of NRM and relapse at 3 years were 19% and 26%.

In summary, the use of RIC alloHCT appears to reduce TRM and allow transplant in older and heavily pretreated patients with OS and PFS rates that are comparable to those achieved with myeloablative conditioning in younger patients. The role of alloHCT in PTCL is evolving and remains undefined. Certain entities such as hepatosplenic T-cell lymphoma, adult T-cell leukemia/lymphoma, and systemic extranodal NK/T-cell lymphoma carry such a poor prognosis that alloHCT may be justified as part of the initial treatment. In other cases, the use of prognostic indexes such as the IPI identifies patients with extremely high risk of relapse who may also benefit from an allograft. Only prospective multicenter trials will define the role of alloHCT in these aggressive lymphomas.

Hodgkin Lymphoma
Current chemotherapy ± radiation therapy results in long-term DFS for about 80% of newly diagnosed patients with HL. However, for the remaining 20%, alternative therapies are required.87 The major obstacles to success in these 20% include ongoing risks of relapse and toxicities of multiple sequential therapies required for disease control.

Autologous Transplantation
The randomized trial from the British National Lymphoma Investigation demonstrated improved PFS for patients who received high-dose chemotherapy and autoHCT compared to a conventional salvage regimen (53% vs 10%, P = .025).88 The study closed early due to patient resistance to randomization. Since that time, multiple single-institution studies and registry analyses have supported the use of autoHCT in the setting of relapsed/refractory HL.89,93 Recently, data from the Royal Marsden group found encouraging 5- and 10-year PFS and OS survival in a cohort of 195 patients who received transplants between 1985 and 2005.94 Five-year PFS was 44% (95% CI, 37%–51%) and 10-year PFS was 37% (95% CI, 29.5%–44%). Five-year OS was 55% (47%–62%), and 10-year OS was 49% (41%–57%).94 Predicting inferior PFS and OS on multivariate analysis included a Hasenclever score at autoHCT of ≥ 3 (PFS = RR of death/progression 95% CI, 1.6 [1.1–2.3], P = .01; OS = RR of death 95% CI, 1.6 [1.0–2.6], P = .04) and chemotherapy-resistant disease or PR at the time of autoHCT (resistant disease: PFS = 3.8 [2.2–6.5], P < .0001; OS = 5.08 [2.7–9.5], P < .0001; PR = 1.9 [1.2–3.04], P = .004; OS = 1.7 [0.9–3.1], P = .07). Despite higher risks of death and progression in patients with refractory disease, data suggest that a subset of these patients do respond to autoHCT. A retrospective analysis of 64 patients with chemotherapy-resistant
Allogeneic Transplantation

Modalities to minimize relapse after alloHCT and alternative therapies for those who do relapse are warranted. Targeted therapies such as the anti-CD30 antibody conjugated to an antitubulin drug (Brentuximab vedotin [SGN-35]) have shown promise in patients with relapsed/refractory HL. This agent is currently in a randomized phase III placebo-controlled trial as maintenance therapy following alloHCT. Alternatively, RIC allogeneic transplantation (RIC alloHCT) is an option in appropriate candidates despite a somewhat higher treatment-related mortality for patients with HL compared to other histologies. Two retrospective analyses demonstrated improved PFS and OS compared to additional salvage therapy for patients treated with this approach after suffering disease relapse following autoHCT. More importantly, outcomes with related vs unrelated donors do not appear to be different.

Following RIC alloHCT, the reported 2-year PFS and OS rates ranged from 20% to 39% and 37% to 66%, respectively, and the NRM rates ranged from 20% to 30% at 1 year. The cumulative incidences of acute and chronic GVHD in these studies are comparable to RIC alloHCT for other diseases. Refractory disease (defined as no response or progression to most recent therapy) and poor performance status (Karnofsky < 80%) at transplant predicted inferior PFS and OS and higher NRM.

In summary, autoHCT provides improved outcomes in patients with relapsed and/or refractory HL. However, there remains a persistent risk of relapse, and either improved salvage regimens, augmented conditioning regimens, or maintenance therapies must be studied to improve outcomes. For patients who relapse after autoHCT, prompt consideration of RIC alloHCT is important. Referral to a transplant center for coordination of donor search and discussions of salvage regimens may improve outcomes.

Conclusions

Both autoHCT and alloHCT have clear roles in the management of the heterogeneous disease known as lymphoma. The timing and the type of transplantation are continually being refined. However, early referral to a transplant center is warranted for patients with these diseases. The low TRM of autoHCT and acceptable TRM following RIC alloHCT permit patients once considered too old or too unfit to receive these beneficial therapies.

References


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