ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION FOR LYMPHOMA: CONTINUING PROGRESS

Hillard M. Lazarus

Department of Medicine, Case Comprehensive Cancer Center, University Hospitals Case Medical Center, Case Western Reserve University, Cleveland, USA

Nearly all autologous hematopoietic cell transplant (HCT) procedures use blood rather than bone marrow as the graft source; this product provides faster hematopoietic recovery after myelosuppression and the collection procedure is easier to perform, cheaper, and less hazardous. Currently, autologous HCT has become the standard of care for both non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL) patients who have experienced relapse, or who have persistent disease despite aggressive chemo-radiation therapy. Autologous HCT may be curative in nearly half such patients but is less effective in patients with chemo-resistant relapse. These findings are explained by an increase in relapse risk due to a lack of graft-versus-lymphoma (GVL) effect, and because of re-infusion of malignant cells. Further, recipients of autologous HCT do not have normal life expectancies. Late relapse and the increased risk of therapy-related myeloid neoplasm (t-MN), the new WHO term that covers the entire spectrum of myelodysplastic syndrome and acute myeloid leukemia arising after cytotoxic therapy, account for these observations (1-5).

Allogeneic HCT, usually employing marrow as the graft source, is a potential therapeutic option especially for patients with matched sibling donors and higher risk disease. Potential advantages of allogeneic HCT include the use of a tumor-free graft and a GVL effect that may reduce the risk of relapse in addition to a reduction of the risk of t-MN. Acute and chronic graft-versus-host disease (GVHD) and high rates of opportunistic infection, however, may lead to high transplant- or treatment-related mortality (TRM) and morbidity that offset the benefits of this approach. To date, there are few prospective, randomized reports comparing autologous versus allogeneic HCT for lymphoma and most comparison reports are small, retrospective, and single institution trials comprising heterogeneous histologic NHL subtypes.

Myeloablative Allogeneic HCT in Lymphoma

Van Besien (6), for the Center for International Blood and Marrow Transplant Research (CIBMTR), retrospectively analyzed outcomes of 283 patients receiving unrelated donor (URD) myeloablative allogeneic HCT performed between 1991 and 2004. Death at 100 days was high at 39% and only 73 (26%) patients are alive. Estimated 5-year overall survival (OS) and failure free survival percentages are 24% and 22%, respectively. Increasing age, decreased performance status and refractory disease adversely impacted upon OS. Follicular lymphoma (FL) and peripheral T cell lymphoma patients had improved survival compared to aggressive B cell lymphomas. Early mortality was high but long-term failure-free survival is possible after URD HCT. Lazarus (7), on behalf of the CIBMTR, retrospectively compared outcomes of 916 diffuse large cell (DLC) lymphoma patients undergoing first autologous (N = 837) versus myeloablative allogeneic HCT (N = 79) between 1995 and 2003. Allogeneic HCT recipients were more likely to have high-risk disease features including more advanced stage, greater prior chemotherapy exposure, and resistant disease. Although allogeneic HCT was associated with a higher TRM at one year, treatment failure and mortality, the risk of disease progression was similar in the 2 groups. In fact, for one-year survivors, no significant differences were observed for TRM, progression, progression-free (PFS) or OS. TRM and overall mortality were increased with older age (>50 years), lower perfor-
mance score and chemoresistance. Although early mortality was higher, myeloablative allogeneic HCT was associated with a similar risk of disease progression compared to lower risk patients receiving autologous HCT.

Data from these studies show that myeloablative allografts tend to be reserved for patients with more aggressive disease (marrow and CNS involvement as well as primary refractory disease). TRM rates remain high but there still may be a role for this approach in select patients such as peripheral T cell lymphoma.

**Reduced-Intensity Conditioning (RIC) Allogeneic HCT**

Given the higher TRM and an increased probability that many patients have comorbid illnesses that preclude use of the myeloablative regimens, most investigators have switched to using RIC for allogeneic HCT. This strategy relies predominantly upon the donor hematopoietic cells exerting a GVL effect rather than depending upon cytotoxic agents. To date, most literature suggests that the GVL effect varies with histology, the strongest such effect is observed with indolent lymphoma and mantle cell lymphoma and less anti-tumor responses with aggressive lymphoma and HL.

Armand and colleagues (8) retrospectively analyzed the outcomes of 87 advanced lymphoma (36 HL and 51 NHL) patients who underwent RIC HCT using fludarabine and low-dose busulfan; 68% previously had undergone autologous HCT. Non-relapse mortality (NRM) at one year was 13% and cumulative incidence of progression at three years was 49%. Three-year OS was 56% for patients with HL, 81% for indolent NHL, 42% for aggressive NHL, and 40% for mantle cell lymphoma. Advanced age and elevated serum LDH predicted for worse OS while indolent NHL histology was favorable. These results emphasize the importance of lymphoma histology for patients undergoing RIC HCT.

### Table 1. Reduced-intensity conditioning allogeneic hematopoietic cell transplant trials in diffuse large cell lym

<table>
<thead>
<tr>
<th>First Author</th>
<th>No. Patients</th>
<th>Progression-free Survival</th>
<th>Overall Survival</th>
<th>Non-Relapse Mortality</th>
<th>Relapse/progression Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sirvant (9)</td>
<td>68</td>
<td>49%</td>
<td>49%</td>
<td>23%</td>
<td>41%</td>
</tr>
<tr>
<td>Thompson (10)</td>
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<td>48%</td>
<td>47%</td>
<td>33%</td>
<td>32%</td>
</tr>
<tr>
<td>Rezvani (11)</td>
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<td>35%</td>
<td>45%</td>
<td>25%</td>
<td>41%</td>
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</table>

### Table 2. Prospective hematopoietic cell transplant trials in follicular lymphoma

<table>
<thead>
<tr>
<th>First Author</th>
<th>No. Patients</th>
<th>Progression-free Survival</th>
<th>Overall Survival</th>
<th>Treatment-Related Mortality</th>
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<tbody>
<tr>
<td>Khouri (13)</td>
<td>53</td>
<td>83%</td>
<td>85%</td>
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<tr>
<td>Morris (14)</td>
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<td>65%</td>
<td>73%</td>
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<tr>
<td>Shea (15)</td>
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<td>71%</td>
<td>76%</td>
<td>7%</td>
</tr>
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</table>

### DLC Lymphoma and Allogeneic HCT

Three trials examined the use of RIC and allogeneic HCT for relapsed disease (Table 1). Most patients were treated for relapse after an autologous HCT and received a fludarabine-containing RIC regimen. Sirvent (9), for the SFGM, reported 49% OS and PFS in 68 patients. NRM (23%) and relapse/progression (41%) accounted for the failures. Thomson (10), reporting outcome in 48 patients on behalf of a United Kingdom group, had similar PFS and OS rates but slightly higher NRM and slighter reduced tumor recurrence/progression rates. The type of donor (matched unrelated versus matched related) did not significantly affect overall outcome. Finally, in a series of 31 DLC lymphoma patients, Rezvani and colleagues (11) at the Fred Hutchinson Cancer Research Center (FHCRC) similarly noted a 35% FFS and 45% OS after RIC allogeneic HCT.

The observation that nearly half the patients who had exhibited disease-progression after a previous autologous HCT could be salvaged with a RIC allograft is a striking result. Further, the successful use of URDs as the graft source is important. As in the case for autologous HCT, lymphoma under better control at time of transplant (chemo-sensitive rather than chemo-resistant disease) favorably affected outcome.

### FL and Allogeneic HCT

**Myeloablative conditioning versus RIC**

Hari and the CIBMTR (12) compared 120 patients given myeloablative conditioning regimens versus 88 subjects receiving RIC; all subjects received HLA-identical grafts.

Use of RIC regimens increased from <10% of allogeneic transplants in 1997 to >80% in 2002 signaling a major shift in practice. At 3 years, OS for the myeloablative and RIC cohorts were 71% and 62% (p =0.15) and PFS, 67% and 55% (p=0.07), respectively. Patient outcomes for myeloablative
conditioning and RIC are similar but the increased risk of late disease progression after RIC is cause for concern.

**Prospective HCT Trials in FL**

Three prospective RIC fludarabine-containing HCT trials have been reported (Table 2).

Khouri and colleagues (13) at the MD Anderson analyzed the outcome of 47 patients given RIC with fludarabine, cyclophosphamide and high-dose rituximab (1000 mg/m²). At a median (range) follow up of 60 (19-94) months, only two patients relapsed and PFS and OS rates were 85% and 83%, respectively. GVHD rates were very low, possibly reflecting the contribution of high-dose rituximab to the tacrolimus and methotrexate prophylaxis. Morris and colleagues (14) in the United Kingdom reported the outcomes after RIC in 51 (41 low grade and 10 mantle cell) NHL patients, many of whom had a relapse after a prior autograft. With a median (range) follow-up of 36 (18-60) months, actuarial three-year OS rates were 60% for mantle cell and 73% for low grade NHL. Extremely low TRM and GVHD rates were noted, even when matched related donors were unavailable. In a preliminary communication, Shea for the CALGB (15) reported that infusion of G-CSF mobilized hematopoietic progenitors after a fludarabine and cyclophosphamide regimen was associated with very low TRM and favorable OS and PFS rates. These encouraging results indicate that FL is sensitive to the GVL effect and long-term DFS can be obtained at the cost of acceptable TRM. The retrospective analyses show no obvious differences between the myeloablative conditioning versus the RIC regimens although tumor progression rates are higher with the latter. The on-going multicenter trial (# 0701) in the USA conducted via the Blood and Marrow Clinical Trials Network (BMT CTN) is designed to validate the fludarabine-cyclophosphamide and high-dose rituximab regimen reported by Khouri et al (13).

**Mantle Cell Lymphoma**

Autologous HCT in patients beyond first complete remission is relatively ineffectual and and late relapses continue to plague this approach even in first remission autograft recipients (4). Two groups have conducted prospective allogeneic HCT in this disorder.

Sorror of the FHCRC (16) administered a single fraction of total body irradiation ± fludarabine as RIC in a patient population of which 40% previously had undergone an autograft. At a 33 months median follow-up, PFS (52%) and OS (58%) rates were good and NRM was low at 27%. Tam and co-workers (17) at the MD Anderson reported the long-term outcome of a risk-adapted transplantation strategy for mantle cell lymphoma in 121 patients enrolled in sequential transplantation protocols. At a 56 month median follow-up in the RIC allogeneic transplant group (a number of whom previously underwent an autograft), similar PFS (46%) and OS (53%) rates were reported along with a lower NRM at 9%. The major determinant of death was immunosuppression for chronic GVHD. These studies illustrate that long-term PFS and OS are possible in mantle cell lymphoma using a RIC regimen, even for patients with relapsed or refractory disease.

**HL**

The vast majority of patients who subsequently undergo an allogeneic HCT for HL already have failed an autologous HCT. Several investigators have reported that this patient population fares much worse with myeloablative conditioning and thus the approach generally is to use RIC in this patient population.

Robinson and colleagues (18) of the EBMT retrospectively analyzed 285 patients who underwent RIC, 80% of whom previously received an autograft; 25% had refractory disease. A variety of conditioning regimens were used (most containing fludarabine). This group observed that NRM was increased in patients with chemo-refractory disease, poor performance status and age >45 years. For patients with no such risk factors, NRM at three-years was 12.5% compared to 46.2% for patients with 2 or more risk factors. The use of an URD had no adverse effect on the NRM. Further, the development of chronic GVHD was associated with a lower relapse rate. Poor performance status and active disease at transplant portended a worse prognosis, e.g. three-year PFS and OS rates were 42% and 56%, respectively, in patients with no risk factors compared to 8% and 25%, respectively, for patients with one or more adverse risk factors. Sureda et al (19) for the EBMT retrospectively reviewed 168 HL patients undergoing first allogeneic HCT (RIC, N = 89; myeloablative conditioning, N = 79). NRM and OS significantly were reduced in the RIC group. Chronic GVHD also significantly decreased the incidence of relapse. These analyses
indicate the existence of a graft-versus-HL effect as has been reported earlier by others (20). Further, chemo-sensitivity at time of HCT is a reliable predictor of outcome. The graft donor type (matched related versus URD) does not significantly affect survival and one-third to one-half of patients may be cured with a RIC allogeneic HCT. The optimal conditioning regimens remain to be determined.

**New Initiatives**

Many new strategies are being pursued in this area including the development of more effective conditioning regimens. In addition to the use of high-dose rituximab described above, other approaches to meet the challenges of acute and chronic GVHD include the continued exploration of Campath (anti-CD52 monoclonal antibody) therapy as well as sirolimus prophylaxis. The latter agent appears to control/prevent GVHD yet also reduce relapse rates, a significant advantage in the RIC HCT setting (21).

Many patients do not have matched-related or matched-unrelated donors available and other novel strategies include using umbilical cord blood (UCB) as a graft source. Brunstein (22) and the University of Minnesota reported exciting data in their series of single (N=9) and double (N=56) UCB transplants. Rodrigues (23), for the Eurocord-Netcord, also noted excellent outcomes in their retrospective series of 104 patients that included many failed autologous HCT.

**Conclusions**

Allogeneic HCT studies demonstrate the existence of a GVL effect that varies with histologic subtype and is appealing if this result can be harnessed. Although most subjects already experienced a relapse after a prior autograft, a large number of patients can be salvaged provided their disease is not chemo-refractory. Unanswered questions include the determination of the optimal conditioning regimen and when to offer an allogeneic HCT over an autologous HCT.

**References**


