A comprehensive overview of using allogeneic blood and marrow transplantation (BMT) to treat patients with diffuse large B-cell lymphoma (DLBCL) has been published in Bone Marrow Transplantation by a team of international experts. [1] In their review, Dr. Evgeny Klyuchnikov et al. note that despite overall improvements in outcomes of patients with DLBCL, approximately 30-40% will develop relapsed or refractory disease.

The authors review the current standard of care for relapsed and refractory DLBCL, including the incorporation of new and novel immunomodulatory agents, kinase inhibitors and A-B toxin conjugates. Their review focuses on research results that can help clinicians identify which relapsed and refractory DLBCL patients are most likely to benefit from autologous BMT versus allogeneic BMT.

They then propose an algorithm that identifies a subgroup of relapsed/refractory DLBCL patients for whom autologous BMT is unlikely to be of benefit, and for whom allogeneic BMT is likely to be the best treatment choice.

In their algorithm, the authors recommend that patients who have already failed an autologous transplant should remain candidates for allogeneic transplantation. Data from the National Marrow Donor Program (see Table 2, page 3) show a comparable two-year survival of 55% for allogeneic transplantation in patients with NHL regardless of whether they had or had not undergone a prior autologous transplant in the most recent time period between 2009-2011. [2]

Current research indicates that myelosuppressive allogeneic BMT has no clear survival advantage over reduced-intensity allogeneic transplants for patients with relapsed and refractory DLBCL, according to the authors. But they note that myeloablative, rather than reduced-intensity transplant, may result in better disease control in the subgroup of DLBCL patients who are young and fit, with high-risk disease.

For older DLBCL patients, those with comorbid conditions, or those with prior autologous BMT, the authors recommend reduced-intensity conditioning BMT, especially for patients in a complete remission prior to allogeneic transplantation. The ideal clinical situation, say the authors, would be to assay for several potential therapeutic targets in order to select the best regimen for an individual patient. Then, combine the selected intervention with either autologous BMT or allogeneic BMT, depending on the specific patient and disease characteristics.

The authors note that many patients with NHL undergo transplant at an advanced stage, and that an earlier implementation of allogeneic BMT would likely be a more effective strategy in most of these patients. They further note that physicians could combine allogeneic BMT with new and novel agents during or after transplant, and/or with interventions designed to enhance the graft-versus-lymphoma effect.

Finally, the authors propose new prospective clinical trials to move the field forward in selecting the best treatment based on specific patient and disease characteristics.

View the Klyuchnikov et al. article and algorithm at: http://tinyurl.com/DLBCL-BMT


2. CIBMTR analysis of NMDP facilitated transplants 2013.
Tandem auto-allo BMT in patients with high-risk relapsed NHL

A 2013 study of high risk NHL patients has demonstrated very good outcomes for a transplantation procedure using a high-dose autologous transplant followed closely with a reduced-intensity allogeneic transplant. At a median follow-up of 46 months from allogeneic transplant, five-year survival was 77% and the progression-free survival was 68%. [1]

The authors note that a tandem autologous-allogeneic transplantation approach combines the cytodestruction of an autologous BMT with the graft-versus-lymphoma (GVL) effect of an allogeneic BMT, and that a reduced-intensity allogeneic transplantation is the preferred regimen due to lower morbidity and transplant-related mortality (TRM).

A tandem autologous-allogeneic transplantation approach has the advantage of combining autologous cytodestruction with an allogeneic graft-versus-lymphoma effect.

In this retrospective analysis of 34 patients transplanted at two transplant centers between 2002 and 2010, donors were HLA-identical siblings (n=29) or 10/10-matched unrelated individuals (n=5). Median age of patients was 47 years (range, 27-68). Patients were classified as high-risk due to poor prognostic factors, including chemorefractory disease, relapse after prior autologous BMT, and unfavorable relapse either after first or second therapeutic line.

Median interval between autologous BMT and allogeneic BMT was 77 days (range, 36-191), and median prior therapeutic lines before tandem transplantation were two (range, 1-4). At time of allogeneic BMT, 16 patients were in complete remission, 13 were in partial remission and five had progressive disease.

Successful engraftment of allogeneic stem cells occurred in all patients. Ten patients developed grade II/IV acute graft-versus-host disease (GVHD), and 15 patients developed chronic GVHD, with a cumulative incidence of 29% (range, 14-44) and 45% (range, 27-63), respectively. Other key results include:

- Disease relapse or progression: n=6 (18%)
- 100-day TRM: 0%
- Two-year TRM: 6%

The researchers, led by Dr. Roberto Crocchiolo of the Institut Paoli-Calmettes in Marseille, France, note that in these high-risk patients, the search for an allogeneic donor was started at the beginning of the salvage regimen. Dr. Crocchiolo noted that this strategy can be very important to the success of a tandem transplantation procedure, as minimizing the time between the autologous transplant and the follow-up allogeneic transplant yields the best results.

Editor’s note: The University of Kansas Cancer Center Blood and Marrow Transplant Program can perform tandem autologous-allogeneic transplants for patients in which this therapy is indicated.

NHL outcomes improving over time

Allogeneic blood and marrow transplantation (BMT) outcomes have steadily improved over the last decade due to several clinical advances, including improved donor-patient HLA matching and better post-transplant care.

The outcomes of unrelated donor BMT for adult patients with NHL are shown in Table 2. Survival is shown for allogeneic BMT recipients with and without a prior autologous transplant. Between 2000 and 2011, two-year survival for allogeneic BMT recipients has increased 13% in patients with no prior autologous BMT and 16% in patients following an autologous BMT. Corresponding one-year survival increases are 14% and 22%, respectively.

Survival in adults with NHL after first allogeneic BMT

<table>
<thead>
<tr>
<th>Without Prior Auto-BMT</th>
<th>With Prior Auto-BMT</th>
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<tbody>
<tr>
<td>2010-2011</td>
<td>2012-2013</td>
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<tr>
<td>1-year survival</td>
<td>2-year survival</td>
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<tr>
<td>36%</td>
<td>29%</td>
</tr>
<tr>
<td>46%</td>
<td>38%</td>
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<td>61%</td>
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<td>60%</td>
<td>51%</td>
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Disease relapse or progression: n=6 (18%)

Improved outcomes have led to an increase in the number of allogeneic and autologous transplants performed in patients with NHL despite a continuing trend toward an older median age of transplant recipients. Figure 1 shows the increase in the number of transplants facilitated by the NMDP for NHL from 2001-2012.

NMDP Unrelated Donor Transplants in Adults with NHL

<table>
<thead>
<tr>
<th>Year</th>
<th>Transplants</th>
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<tbody>
<tr>
<td>2001-2002</td>
<td>1200</td>
</tr>
<tr>
<td>2003-2004</td>
<td>1000</td>
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<tr>
<td>2005-2006</td>
<td>800</td>
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<tr>
<td>2007-2008</td>
<td>600</td>
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<tr>
<td>2009-2010</td>
<td>400</td>
</tr>
<tr>
<td>2011-2012</td>
<td>200</td>
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</tbody>
</table>

Figure 1. Distribution of unrelated donor transplants, by age, 2001-2012 for NHL facilitated by the NMDP [2].

To enroll a patient

Contact the referral specialist at The University of Kansas Cancer Center Blood and Marrow Transplant Program: 913-945-7113. Visit kucancercenter.org/clinicaltrials to learn about this and additional BMT and hematological malignancy clinical trials.
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Editor’s note: The University of Kansas Cancer Center Blood and Marrow Transplant Program can perform tandem autologous-allogeneic transplants for patients in whom this therapy is indicated.

In this study, 27 patients received an allogeneic transplant with an allogeneic graft-vers-lymphoma effect. Patients were classified as high-risk NHL due to poor prognostic factors, including chemorefractory disease, relapse after prior autologous BMT, and unfavorable relapse either after first or second therapeutic line. Median interval between autologous BMT and allogeneic BMT was 77 days (range, 36-191), and median prior therapeutic lines before tandem transplantation were two (range, 1-4). At time of allogeneic BMT, 16 patients were in complete remission, 13 were in partial remission and five had progressive disease.

Hemato-oncology Program has the advantage of combining autologous cytoablation with an allogeneic graft-versus-lymphoma effect.

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<tbody>
<tr>
<td>1-year survival with prior auto-BMT</td>
<td>36%</td>
<td>46%</td>
<td>61%</td>
</tr>
<tr>
<td>2-year survival with prior auto-BMT</td>
<td>29%</td>
<td>38%</td>
<td>50%</td>
</tr>
<tr>
<td>1-year survival without prior auto-BMT</td>
<td>17%</td>
<td>43%</td>
<td>54%</td>
</tr>
<tr>
<td>2-year survival without prior auto-BMT</td>
<td>12%</td>
<td>35%</td>
<td>46%</td>
</tr>
</tbody>
</table>

Table 2. Outcomes of BMT for adult patients with NHL using NMDP donors. [3]

Improved outcomes have led to an increase in the number of allogeneic and autologous transplants performed in patients with NHL despite a continuing trend toward an older median age of transplant recipients. Figure 1 shows the increase in the number of transplants facilitated by the NMDP for NHL from 2001-2012.

NHL referral timing guidelines for transplant consultation

The National Marrow Donor Program (NMDP) and the American Society for Blood and Marrow Transplantation (ASBMT) have jointly developed guidelines to identify patients with hematologic disorders who are at risk of disease progression and, therefore, should be evaluated for transplantation. These guidelines are based upon current clinical practice, medical literature and evidence-based reviews. Table 1 shows an excerpt of these guidelines for patients with NHL.

For some patients, early transplant may be indicated; for others, transplant may be needed later or not at all. Because appropriate planning and early donor identification are critical for optimal outcomes, early consultation with a transplant specialist at The University of Kansas Cancer Center Blood and Marrow Transplant Program is recommended.

The University of Kansas Cancer Center Blood and Marrow Transplant Program offers resources for medical professionals, including our center-specific referral guidelines for NHL. View the resources and guidelines by visiting kucancercenter.org/bmstransplant.

Joint 2013 NMDP/ASBMT guidelines for transplant consultation

Non-Hodgkin Lymphoma

- Follicular Lymphoma
  - Poor response to initial treatment
  - Initial remission duration <12 months
  - First relapse
  - Transformation to diffuse large B-cell lymphoma
- Diffuse Large B-Cell or High-Grade Lymphoma
  - At first or subsequent relapse
  - CRS for patients with high or intermediate IP risk
  - No CR with initial treatment
  - Second or subsequent remission

Mantle Cell Lymphoma

- After initiation of therapy

Other High-Risk Lymphomas

- After initiation of therapy

Table 1. Recommended timing for transplant consultation for patients with NHL. [1]