# DLBCL Relapse, Resistant Cases and Transplantation

**Koen van Besien, Sonali M. Smith**

The University of Chicago, Chicago, USA

**Treatment of Relapsed and Refractory DLBCL**

More than half of patients with aggressive lymphoma, initially entering remission with combination chemotherapy will relapse. The standard treatment approach for such patients is to deliver salvage chemotherapy followed by consolidative autologous stem cell transplantation in patients demonstrating chemosensitivity. Patients with chemorefractory disease and patients relapsing following an autologous stem cell transplant have an overall poor prognosis and should be considered for allogeneic stem cell transplantation or for clinical trials with investigational agents.

The optimal salvage regimen is not known, and there are no phase III prospective randomized trials comparing various combinations. Most of the data is from phase II trials, and the choice of treatment is often influenced by both patient features and physician preferences. Some commonly used regimens include DHAP (dexamethasone, cytarabine, cisplatin), ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin), ICE (ifosfamide, carboplatin, etoposide), IE (ifosfamide, etoposide), MINE (mesna, ifosfamide, mitoxantrone, etoposide) and EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin), among others. The DHAP regimen is one of the first salvage regimens to be designed. In the Parma trial, patients with relapsed lymphomas receiving DHAP had an overall response rate of 58%, but the 5 year event-free survival and overall survival of patients not subsequently transplanted were only 12% and 32%, respectively.

Ifosfamide-based regimens are gaining in popularity, partly due to the ability to escalate the ifosfamide, and also because they are excellent stem cell mobilizing regimens. Overall response rates are over 60%, although the complete response rate is only 24%. The major advantage to improving salvage regimens is to demonstrate chemosensitivity, since this is arguably the most crucial characteristic determining outcome following autologous stem cell transplantation in aggressive lymphomas. Of the ifosfamide-based salvage regimens for aggressive lymphomas, extensive data has been published on the ICE (ifosfamide, carboplatin, etoposide) regimen developed at the Memorial Sloan Kettering Cancer Center (MSKCC). In an initial publication, investigators at MSKCC treated 163 consecutive transplant-eligible patients with relapsed or refractory aggressive NHL with 3 cycles of the ICE regimen. The overall response rate was 66%, allowing 89% of patients to proceed to a planned autologous stem cell transplant. There was minimal non-hematologic toxicity, although a third of patients had greater than grade 3 thrombocytopenia. All patients received growth factor support during each cycle of treatment. There are several other high dose ifosfamide-based regimens that are in widespread use, and all appear to be effective at stem cell mobilization. However, despite high activity, none of these regimens are curative unless followed by a consolidative transplant procedure.

The addition of rituximab to salvage regimens appears to substantially improve the response rate. For example, Kewalramani and colleagues

show that the overall response rate and complete response rate increases to 81% and 55%, respectively, when adding rituximab to the ICE regimen. Although not specifically demonstrated for large cell lymphoma, rituximab also serves as an "*in vivo* purge" during stem cell collection [79,80]and is likely to be an important component of most pre-transplant salvage regimens for CD20-positive malignancies.

**New Investigational Drugs:**

There are a multitude of promising investigational agents being pursued for the treatment of lymphomas. These include proteosome inhibitors (bortezomib or Velcade®), anti-Bcl-2 agents (oblimersen sodium or Genasense®), anti-angiogenic agents, liposomal formulations of standard chemotherapeutic agents (liposomal vincristine, liposomal doxorubicin), newer monoclonal antibodies (epratuzamab), and radiolabelled monoclonal antibodies (ibritumomab tiuxetan or Zevalin®, tositumomab or Bexxar®). Phase II and III studies are ongoing, and several of the most active agents in preliminary studies are being incorporated into front-line regimens.

We have had a particular interest in the development of ixabepilone and of temsirolimus in the management of recurrent or refractory large cell lymphoma, both drugs have excellent efficacy in large cell lymphoma and have induced remission in otherwise refractory patients. Both have a favorable toxicity profile.

**Transplantation in the management of recurrent lymphoma**

Patients receiving autologous stem cell transplants for chemotherapy-sensitive relapsed non-Hodgkin lymphoma have significantly superior survival compared to those receiving conventional chemotherapy. For example, in one large trial 5-year survival was 46% in the transplant group vs. 12% in the group receiving chemotherapy. (The very rare patient with an International Prognostic Index (IPI) score of 0 at the time of relapse appears to do equally well with chemotherapy or transplant.) Most now accept autologous SCT as the best therapy for relapsed, chemotherapy-sensitive lymphoma. The introduction of rituximab has improved the prognosis of aggressive B-cell lymphoma and rituximab may also have a role in the peri-transplant management of patients with aggressive lymphoma. When given before transplant it may have a purging effect. It is also given post-transplant in an effort to reduce recurrence. Interestingly, patients given rituximab before or after transplant are prone to severe but transient neutropenia, the mechanism of which is poorly understood.

Allogeneic transplantation has not been as extensively utilized for aggressive lymphoma. Although relapse rates are lower than after autologous transplantation, the risk for TRM is greater after allogeneic SCT. The role of a GVL effect continues to be investigated but the aggressive growth of the tumor may not allow for the full benefit of immunotherapy. Allogeneic transplantation may be preferable in some patient subsets such as those who fail to mobilize, have marrow involvement or have failed a previous autologous transplantation. Allogeneic SCT may also be preferable for patients with peripheral T-cell lymphoma, who have high recurrence rates after autologous transplantation.

Mantle cell lymphoma is a relentless illness with high recurrence rates after CHOP-rituximab therapy. Many centers now recommend consolidation with autologous transplantation in first remission with extremely promising results. For patients with recurrent mantle cell lymphoma, allogeneic transplantation is preferred.

**References**


1. S. M. Smith and K. van Besien. Treatment approach to diffuse large B-cell lymphoma. In: *Clinical malignant hematology*, edited by M. A. Sekeres, M. Kalaycio, and B. J. Bollwell, New York:Mc Graw Hill, 2007, p. 531-542
2. H. C. Fung, M. Higman, and K. van Besien. Stem Cell Transplantation. In: *ASH-SAP*, edited by M. Kahn and S. A. Gregory,American Society of Hematology, 2007, p. 328-360.
3. S. M. Smith and K. van Besien. mTor inhibition in lymphoma: A rational and Promising Strategy. *Letters in Design and Drug Discovery* 4:224-231, 2007.