



Advances

Your Concise Update On Transplant Research

in Transplantation

Special Edition

Special Non-Hodgkin Lymphoma Edition

Welcome to a special edition of *Advances in Transplantation*, a National Marrow Donor Program (NMDP) newsletter that summarizes the latest research in hematopoietic cell transplantation. This issue highlights research on transplant therapy for non-Hodgkin lymphoma published in medical journals and presented at major medical meetings in the past year.

In this issue:

- HCT as salvage therapy in DLBCL 1
- HCT offers long-term disease control in PTCL 2
- Auto- vs. allo-transplant in relapsed FL..... 3
- Radioimmunotherapy prior to RIC allo-HCT..... 4
- Randomized CHOP±R vs. CHOP±R plus ASCT in high-risk diffuse NHL..... 6
- PET scans predict outcomes in lymphoma..... 6

Study assesses role of allo-HCT as salvage therapy in DLBCL

For patients with diffuse large B-cell lymphoma (DLBCL) who undergo allogeneic transplant as a salvage therapy following a relapsed autologous transplant the 3-year overall survival is 52.2%. These results are from a study of 101 such patients published in the *Journal of Clinical Oncology* in 2011. [1]

Patients in the study were a median age of 46 years (range, 18-66) at time of allogeneic hematopoietic cell transplant (HCT), and were identified in the European Group for Blood and Marrow Transplantation (EBMT) database. Thirty-seven patients underwent transplantation using myeloablative conditioning and 64 received reduced-intensity pre-transplant conditioning.

Patients with a long remission after autologous transplantation and with sensitive disease at allogeneic transplantation are the best candidates for this approach.

Seventy-two patients were transplanted using an HLA-identical sibling donor, and 29 had a matched unrelated donor. Seventy-six patients received peripheral blood stem cells and 25 received bone marrow.

Prior to autologous transplantation, 33 patients were in complete remission, 31 in partial remission, and 37 had refractory disease. At time of allogeneic transplant, 75 patients were chemosensitive and 26 patients were chemorefractory.

HCT as salvage therapy in DLBCL: continued on page 5

Long-term disease control after allo-HCT for peripheral T-cell lymphoma

In a study of 37 patients with peripheral T-cell lymphoma (PTCL), allogeneic transplantation resulted in a 5-year overall survival of 52.2%. The results of this consecutive case series were published in *Leukemia & Lymphoma* in 2011. [2]

Patients with PTCL in this single-institution study underwent allogeneic transplantation if they were ineligible for autologous transplantation due to very aggressive histologies or had a subtype of cutaneous T-cell lymphoma, for which autologous transplantation offers poor long-term disease control.

“Long-term disease control is possible after allogeneic HCT in patients with peripheral T-cell lymphoma with advanced disease.”

– Jasmine Zain, M.D.

Median age of patients was 40 years (range 7-72), 26 (70%) had a matched sibling donor and 11 (30%) had a matched unrelated donor. Twenty-two (60%) patients received reduced-intensity conditioning regimens, 2 (5%) received non-myeloablative conditioning, and 13 (35%) received myeloablative conditioning. Twenty-five (68%) patients had either relapsed or progressive disease.

At five years post transplant, cumulative incidences of non-relapse mortality and relapse/progression were 28.9% and 24.3%, respectively. Five-year overall survival (OS) and progression-free survival were 52.2% and 46.5%, respectively. These results led the authors to note that “relapse/progression curves reached and maintained plateaus after 1 year post transplant, demonstrating that long-term disease control is possible after allo-HCT in patients with peripheral T-cell lymphoma with advanced disease.”

In a univariate analysis, no statistically significant variables for survival or relapse were identified and the subgroup of 13 patients with cutaneous T-cell lymphomas did not have significantly different outcomes than patients with other PTCL histologies.

Patients in complete or partial remission (CR/PR) prior to transplant showed a trend toward better 5-year overall survival, at 72.9% vs. 43.2% for patients not in CR/PR, but this difference was not statistically significant ($p=0.07$).

An editorial commentary accompanying the article notes that the “43% 5-year OS for chemoresistant patients compares favorably to previous reports, and implies that there is hope for disease control even in patients with very high-risk disease.” [3] ■

NHL TRANSPLANT CONSULTATION GUIDELINES

HCT Clinical Guidelines are available in a mobile app.

The intent of these evidence-based guidelines is to identify patients at risk of disease progression and, therefore, which patients should be evaluated for transplantation. [12] Including non-Hodgkin lymphomas:

- Follicular
- Diffuse Large B-Cell
- Mantle Cell



Download the free app now

HCT Guidelines



App Download



Auto-HCT vs. reduced-intensity allo-HCT in chemosensitive FL

In a multi-center study published in 2011, patients with chemosensitive follicular lymphoma (FL) beyond first complete response or first partial response had an overall survival of 73% after autologous transplantation and 100% after allogeneic transplantation at a median follow-up of 36 months. [4] These results led the authors to conclude that both autologous and reduced-intensity allogeneic transplantation can be appropriate therapies for relapsed patients.

In this prospective trial by the Blood and Marrow Transplant Clinical Trials Network (BMT CTN), 30 patients between August 2004 and February 2006 with relapsed, chemotherapy-sensitive FL were assigned to a treatment arm based on the availability of an HLA-matched sibling donor (MSD).

This study cannot conclusively determine which type of transplant is more effective, but the high survival seen in this and in previous reduced-intensity HCT studies “lends compelling support to a further study of this modality.” – Marcie Tomblyn, M.D.

Patients with a donor received reduced-intensity fludarabine/cyclophosphamide conditioning, plus pre- and post-transplant rituximab. Patients without a donor were assigned to the autologous stem cell transplant (ASCT) arm. The study closed early because of slow accrual toward an original goal of 75 enrolled patients.

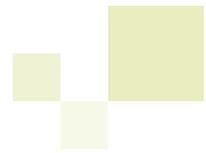
Median age of patients was 48 (range, 40-64) in the allogeneic HCT arm and 50 (range, 36-66) in the ASCT arm. All patients, regardless of planned ASCT or allogeneic HCT, received chemotherapy with rituximab and cyclophosphamide within 6 weeks after enrollment.

Progression-free survival (PFS) was 63% in ASCT recipients and 86% in allogeneic HCT recipients. No differences in survival between the two arms were statistically significant.

No recipients experienced grade II-IV acute GVHD, and two patients developed extensive chronic GVHD. Two recipients in the ASCT arm died from infections, and one had fatal pneumonitis.

Lead author Dr. Marcie Tomblyn of the H. Lee Moffitt Cancer and Research Center, Tampa, Florida, noted that both ASCT and reduced-intensity allogeneic HCT result in “promising” 3-year OS and PFS in patients with relapsed FL.

This study cannot conclusively determine which type of transplant is more effective, noted Dr. Tomblyn, but the high survival seen in this and in previous reduced-intensity HCT studies “lends compelling support to a further study of this modality.” The BMT CTN is currently conducting a phase II multi-center trial studying the efficacy of non-myeloablative conditioning HCT in relapsed FL patients (BMT CTN 0701). ■



TWO REVIEW PUBLICATIONS: Treatment options for lymphoma

Allogeneic transplantation for lymphoma

A comprehensive overview of using allogeneic transplantation to treat patients with lymphoma by Drs. Chakraverty and Mackinnon was published in the *Journal of Clinical Oncology*. [5]

In their review, the authors discuss the graft-versus-lymphoma effect in Hodgkin lymphoma, follicular lymphoma, diffuse large B-cell lymphoma, mantle-cell lymphoma, and T-cell lymphoma. Also discussed is the role of reduced-intensity conditioning (RIC) transplantation in lymphoma patients, and the need for risk-adapted trials in evaluating RIC transplantation in relation to immunochemotherapy or autologous transplantation.

The authors note, “the last 10 years have witnessed a dramatic shift in how allogeneic transplantation is performed, with increasing numbers of patients receiving less toxic, non-myeloablative or reduced-intensity conditioning (RIC) regimens that have broadened the applicability of this therapeutic approach.”

Transformed NHL arising from follicular lymphoma

A detailed discussion on treatment options for transformed non-Hodgkin lymphoma arising from follicular lymphoma by Drs. Reddy and Savani was published in *Biology of Blood and Marrow Transplantation*. [6]

The authors discuss the biological mechanism of transformation, the prognostic implications of early versus late transformation, emerging novel therapies, clinical outcomes using standard chemotherapy and radioimmunotherapy, and the role of autologous stem cell transplantation as a salvage regimen.

The authors also discuss improvements in supportive care and other advances in the last decade that have significantly improved outcomes in allogeneic hematopoietic cell transplantation (HCT), and discuss the optimal timing of HCT to further improve outcomes in patients with transformed lymphoma. ■

Radioimmunotherapy prior to RIC allo-HCT in advanced FL

A 2-year overall survival of 83% was observed in a single-center study of 12 patients with relapsed, refractory, or transformed follicular lymphoma (FL) receiving radioimmunotherapy (yttrium-90) to reduce tumor load prior to reduced-intensity conditioning (RIC) transplantation. Study results were published in *Bone Marrow Transplantation* in 2011. [7]

The researchers hypothesized that administering radio-immunoconjugates prior to a reduced-intensity transplant might enhance cytoreduction and allow more time for a graft-versus-lymphoma effect to develop without the associated toxicity in a fully ablative conditioning regimen.

Median age of patients was 55 years (range 40-66), with a median of 5 (range 2-10) lines of prior therapy. Reduced-intensity conditioning consisted of fludarabine and low-dose intravenous busulfan, and patients received peripheral blood stem cells or umbilical cord blood from matched or mismatched, related or unrelated donors.

Cumulative incidence of grade II-IV acute GVHD at 100 days was 17%. Cumulative incidence of chronic GVHD at 12 months was 63% (7 of 11 evaluable patients); however only one of these patients had severe chronic GVHD. Two-year non-relapse mortality was 18% and 2-year overall survival and progression-free survival were 83% and 74%, respectively.

Lead author Dr. Karim Abou-Nassar concluded that radioimmunotherapy treatment followed by reduced-intensity allogeneic transplantation “is associated with favorable outcomes including acceptable rates of GVHD and relapse in advanced FL patients, and warrants prospective studies.” ■

FOUR-PART CME SERIES

Management of Advanced NHL marrow.org/md-NHL-CME

Explore the latest data on front-line and salvage therapies, including transplant, for patients with NHL.

- **Follicular lymphoma**, Ginna Laport, M.D.
- **Mantle cell lymphoma**, Ajay Gopal, M.D.
- **Diffuse Large B-Cell Lymphoma**
Philippe Armand, M.D., Ph.D.
- **T-cell lymphoma**, Julie Vose, M.D.

This activity was developed through a collaboration between the National Marrow Donor Program and Medscape, LLC.

References

1. van Kampen RJW, Canals C, Schouten HC, et al. Allogeneic stem-cell transplantation as salvage therapy for patients with diffuse large B-cell non-Hodgkin's lymphoma relapsing after an autologous stem-cell transplantation: An analysis of the European Group for Blood and Marrow Transplantation Registry. *J Clin Oncol*. 2011; 29(10): 1342-1348.
2. Zain J, Palmer JM, Delioukina M, et al. Allogeneic hematopoietic cell transplant for peripheral T-cell non-Hodgkin lymphoma results in long-term disease control. *Leuk Lymphoma*, 2011; 52(8): 1463-1473.
3. Ramsdale E, van Besien K. Allogeneic transplant for peripheral T-cell lymphoma: a sparkle of hope and many questions. *Leuk Lymphoma*, 2011; 52(8): 1415-1417.
4. Tomblyn MR, Ewell M, Bredeson C, et al. Autologous versus reduced-intensity allogeneic hematopoietic cell transplantation for patients with chemosensitive follicular non-Hodgkin lymphoma beyond first complete response or first partial response. *Biol Blood Marrow Transplant*. 2011; 17(7): 1051-1057.
5. Chakraverty R, Mackinnon S. Allogeneic transplantation for lymphoma. *J Clin Oncol*. 2011; 29(14): 1855-1863.
6. Reddy N, Savani BN. Treatment options for transformed lymphoma: Incorporating allogeneic stem cell transplantation in a multimodality approach. *Biol Blood Marrow Transplant*. 2011; 17(9): 1265-1272.
7. Abou-Nassar KE, Stevenson KE, Antin JH, et al. 90Y-ibritumomab tiuxetan followed by reduced-intensity conditioning and allo-SCT in patients with advanced follicular lymphoma. *Bone Marrow Transplant*. 2011; published online Jan. 24.
8. Oliansky DM, Czuczman M, Fisher RI, et al. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the treatment of diffuse large B cell lymphoma: Update of the 2001 evidence-based review. *Biol Blood Marrow Transplant*. 2011; 17(1): 20-47.
9. Oliansky DM, Gordon LI, King J, et al. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the treatment of follicular lymphoma: An evidence-based review. *Biol Blood Marrow Transplant*. 2010; 16(4): 443-468.
10. Stiff PJ, Unger JM, Cook J, et al. Randomized phase III U.S./Canadian intergroup trial (SWOG S9704) comparing CHOP (+/-) R for eight cycles to CHOP (+/-) R for six cycles followed by autotransplant for patients with high-intermediate (H-Int) or high IPI grade diffuse aggressive non-Hodgkin lymphoma (NHL) [abstract]. *J Clin Oncol*. 2011; 29(15, Suppl.): abs. #8001.
11. Doderio A, Crocchiolo R, Patriarca F, et al. Pretransplantation [18-F] fluorodeoxyglucose positron emission tomography scan predicts outcome in patients with recurrent Hodgkin lymphoma or aggressive non-Hodgkin lymphoma undergoing reduced-intensity conditioning followed by allogeneic stem cell transplantation. *Cancer*. 2010; 116(21): 5001-5011.
12. NMDP/ASBMT Recommended Timing for Transplant Consultation, 2011. <http://www.marrow.org/md-guidelines>

Supported by an unrestricted educational grant from Otsuka America Pharmaceutical, Inc., provided to the National Marrow Donor Program through The Be The Match FoundationSM, the funding partner of the NMDP.



Otsuka America Pharmaceutical, Inc.

Survival after allogeneic HCT in DLBCL		
OUTCOME	1-YEAR	3-YEAR
Progression-free survival	51.5%	41.7%
Overall survival	64.7%	52.2%

Table 1. Survival after allogeneic transplantation in DLBCL patients relapsing after autologous transplant.

Refractory disease was the only significant adverse factor for relapse or progression after allogeneic transplant identified in multivariate analysis (RR, 2.6; 95% CI, 1.1 to 6; p=0.03). Time to relapse after autologous transplant of <12 months was significantly associated with lower progression-free survival (PFS) (p=0.03).

Three-year non-relapse mortality (NRM) was 28.2% and risk of relapse was 30.1%. NRM was significantly higher in patients ≥45 years old (p=0.01), in patients relapsing <12 months after autologous transplantation (p=0.01) and in those receiving bone marrow (p=0.003).

In a univariate comparison, reduced-intensity conditioning was associated with a lower 3-year NRM compared to myeloablative regimens: 20% vs. 41%, respectively (p=0.05).

Lead author Dr. Roel van Kampen concluded that patients with a long remission after autologous transplantation and with sensitive disease at allogeneic transplantation are the best candidates for this salvage therapy following failed autologous transplantation.

With findings indicating no significant differences in outcomes in transplants using HLA-identical sibling donors versus matched unrelated donors, Dr. van Kampen suggested that a matched unrelated donor should be considered for allogeneic transplant candidates who do not have an HLA-identical sibling donor available. ■

EVIDENCE-BASED REVIEWS: Transplant in diffuse large B-cell and follicular lymphoma

The American Society for Blood and Marrow Transplantation (ASBMT) publishes evidence-based reviews outlining the role of hematopoietic cell transplantation (HCT) in treating patients with hematopoietic disorders. These consensus reviews from a panel of experts include recommendations on which patients would benefit most from HCT, the timing of HCT, pre-transplant induction chemotherapy, donor selection, transplantation techniques, and areas of needed research.

ASBMT recently published an update to a 2001 review on HCT in diffuse large B-cell lymphoma (DLBCL) [8] and a new evidence-based review on HCT in follicular lymphoma (FL). [9]

ASBMT update: HCT in diffuse large B-cell lymphoma

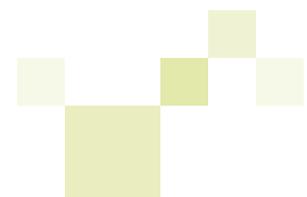
ASBMT report included these recommendations:

- Autologous stem cell transplantation provides a significant survival benefit and is recommended as part of salvage therapy for patients with chemosensitive relapsed DLBCL.
- Autologous transplantation is not recommended for patients who achieve only a partial response to an abbreviated (3 cycles) induction regimen.
- There are equivalent survival outcomes after autologous and allogeneic HCT.
- New data published since the original review are insufficient to recommend reduced intensity versus myeloablative conditioning for allogeneic HCT.

ASBMT: HCT in follicular lymphoma

Unanimous consensus report on FL:

- Autologous HCT is recommended for transformed FL.
- There are insufficient data to make a recommendation on the efficacy of autologous HCT as first-line versus salvage therapy.
- There are insufficient data comparing autologous transplant and myeloablative allogeneic HCT to recommend one option over the other.
- In allogeneic HCT, an HLA-matched unrelated donor appears to be as effective as an HLA-matched related donor using reduced-intensity conditioning. ■



Randomized CHOP±R vs. CHOP±R plus ASCT in diffuse NHL

A randomized trial comparing CHOP±R vs. CHOP±R plus autologous stem cell transplantation (ASCT) in patients with advanced stage high-intermediate and high-diffuse aggressive NHL has found that early ASCT improves progression-free survival for responders, including those induced with CHOP±R. This inter-group study of 253 high-risk patients was led by Southwest Oncology Group (SWOG) and the results were presented at the 2011 annual meeting of the American Society of Clinical Oncology. [10]

Patients up to age 65 were enrolled in first remission with bulky stage II, III, and IV high-intermediate and high-diffuse NHL between 1997-2007 at 40 centers. Disease stage was assessed using International Prognostic Index (IPI) criteria.

Patients enrolled between 2003-2007 received rituximab with induction CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) chemotherapy when other studies demonstrated a significant survival advantage for CHOP-R over CHOP alone.

Patients were then randomized to a chemotherapy-only arm to receive an additional 3 cycles of CHOP±R (n=128) or to the autologous stem cell transplantation (ASCT) arm to receive one CHOP±R cycle and then undergo ASCT (n=125).

As shown in Table 2, 2-year progression-free survival (PFS) was significantly higher in chemotherapy plus ASCT patients than in patients treated with chemotherapy only.

Patients with high IPI scores benefitted most from ASCT, noted lead author Dr. Patrick J. Stiff of Loyola University Hospital. Two-year PFS in high IPI patients was 75% and 41% in the ASCT arm vs. chemotherapy only arm, respectively (p=0.02).

Dr. Stiff also noted that 62 (48%) of patients in the chemotherapy-only arm relapsed after therapy. Of these, 29 underwent salvage ASCT, with 11 achieving a second complete remission at time of analysis. ■

ASCT significantly prolongs PFS in patients

2-YEAR OUTCOME	CHEMOTHERAPY + ASCT (N=125)	CHEMOTHERAPY ONLY (N=128)	HR (95% CI)	P-VALUE
PFS	69%	56%	1.72 (1.18-2.51)	0.005
OS	74%	71%	1.24 (0.81-1.91)	0.16

Table 2. Outcomes in patients treated with induction therapy randomized to undergo ASCT or 3 additional cycles of chemotherapy. CI = confidence interval, PFS = progression-free survival, OS = overall survival.

Pre-transplant PET scans predict outcomes in lymphoma

A study of 80 patients with lymphoma (46 Hodgkin lymphoma, 34 aggressive non-Hodgkin lymphoma) has demonstrated the predictive value of positron emission tomography (PET) scanning before reduced-intensity allogeneic transplantation. [11]

All patients in this multi-center retrospective study had chemotherapy-sensitive disease. Median age of patients was 36 years (range, 17-65) and underwent allogeneic transplantation using grafts from HLA-matched siblings (n=43), matched unrelated donors (n=20), or haploidentical donors (n=17).

Forty-two patients had negative PET studies, and 38 patients had positive PET studies. Patients who had negative PET studies before undergoing allogeneic transplantation had significantly better 3-year overall survival and progression-free survival than patients with positive PET studies: 76% vs. 33%; (p=0.001) and 73% vs. 31%; (p=0.001), respectively.

Lead researcher Dr. Anna Doderio concluded that PET scanning appears to be an accurate tool for assessing prognosis in lymphoma patients who are eligible for reduced-intensity allogeneic transplantation. ■