

The Role of Hematopoietic Stem Cell Transplantation in Non-Hodgkin Lymphoma

Mary Lee H. Villanueva, MD, and Julie M. Vose, MD

Dr. Villanueva is a Clinical Oncology Fellow in the Department of Internal Medicine, Section of Hematology/Oncology, where Dr. Vose is Neumann M. and Mildred E. Harris Professor of Medicine and Chief at the University of Nebraska Medical Center, Omaha, Neb.

Address correspondence to:
Mary Lee H. Villanueva, MD, Department of Internal Medicine, Section of Oncology/Hematology, 987680 Nebraska Medical Center, Omaha, NE 68198;
Tel: 402-559-5520; Fax: 402-559-6520;
E-mail: mvillanueva@unmc.edu.

Abstract: Hematopoietic stem cell transplantation has become an increasingly important treatment modality for hematologic malignancies. Autologous stem cell transplantation has become the standard of care in relapsed high-risk diffuse large B-cell lymphoma (DLBCL) patients who respond to reinduction therapy. The exact role of allogeneic transplantation in DLBCL is still unknown and it appears to be useful in only a select group of patients. The exact role of hematopoietic stem cell transplant in follicular lymphoma is evolving. The treatment of mantle cell lymphoma is challenging and stem cell transplantation may play an important role, as our understanding of the biology and natural history of this disease improves. This review focuses on studies evaluating the role of stem cell transplantation in non-Hodgkin lymphoma.

The non-Hodgkin lymphomas (NHLs) comprise a heterogeneous group of malignancies. NHL includes both B-cell and T-cell malignancies, of which 90% are B-cell malignancies. The two most common B-cell neoplasms are diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma. An estimated 55,000–60,000 new cases of NHL are diagnosed annually in the United States.¹

Overall, NHL has a high rate of response to chemoradiotherapy. The most widely accepted treatment modality is chemotherapy with or without consolidation chemotherapy.² Hematopoietic stem cell transplantation (SCT) has become an increasingly important treatment modality for hematologic malignancies since its introduction into clinical practice. This review highlights the use of both autologous (auto-SCT) and allogeneic (allo-SCT) transplantation in DLBCL, follicular lymphoma, and mantle cell lymphoma.

Diffuse Large B-Cell Lymphoma

Autologous Transplant

DLBCL is the most common NHL, with a cure rate of approximately 50%. It is known that patients with intermediate- to high-grade disease have a worse prognosis if they relapse.^{3,4} At relapse, the chance for cure with conventional chemotherapeutic agents is low. Two important studies have shown that the combination of high-dose chemotherapy combined with auto-SCT can lengthen

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the duration of remission. Philip and colleagues⁴ showed that patients with chemosensitive DLBCL at first relapse have a 40–50% chance of long-term disease-free survival (DFS) following auto-SCT. The PARMA study⁵ was a prospective study that randomized patients who responded to two courses of conventional chemotherapy to either further chemotherapy or auto-SCT. At 5 years, the event-free survival (EFS) was 46% for the transplant arm and 12% for the chemotherapy arm ($P=.001$). The overall survival (OS) was 53% for transplant and 32% for chemotherapy ($P=.038$). In a retrospective analysis of the PARMA study, patients were classified according to the age-adjusted international prognostic index (IPI). For patients with an age-adjusted IPI score of 0, there was no difference in OS, but if the age-adjusted IPI score was 1 or greater, there was a significant difference in progression-free survival (PFS) favoring the transplanted arm ($P<.0001$).⁶ Based on these results, auto-SCT has become the standard of care in relapsed high-risk patients who respond to reinduction therapy.⁷

The use of auto-SCT in first relapse has stimulated studies evaluating the use of intensive chemotherapy and auto-SCT as first-line therapy in high-risk patients who have attained a first complete remission (CR). Gulati and coauthors⁸ and Nademane and coauthors⁹ reported the potential benefit of high-dose therapy and auto-SCT as consolidation therapy for poor-prognosis patients in first CR after initial therapy. The results of larger, prospective randomized trials, however, have yielded conflicting results, as outlined in Table 1.^{10–20} The observed differences may be due to heterogeneity in patient selection, pathologic subtype, choice and extent of induction therapy, randomization, and statistical power to observe treatment effects.

A study by Haioun and coworkers,²¹ the LNH87-2 trial, enrolled 916 patients, of whom 451 presented with two or three risk factors. After reaching a CR after induction therapy, patients were randomized to high-dose methotrexate, ifosfamide, etoposide, asparaginase, and cytarabine or cyclophosphamide, carmustine, etoposide, and auto-SCT. At 5 years, there was no significant difference in either EFS or OS in the study arms. However, a retrospective subset analysis based on patients who were high-intermediate- or high-risk as defined by the IPI demonstrated a significant advantage in DFS and OS for the auto-SCT arm. After a median follow-up of 8 years, the DFS and OS rates for auto-SCT versus sequential chemotherapy were 55% and 39% ($P=.02$) and 64% and 49% ($P=.04$), respectively.¹⁴

Gianni and colleagues¹² also showed an EFS advantage for the auto-SCT arm only when a retrospective analysis was performed on patients with high-intermediate- or high-risk disease as defined by the IPI. At 5 years, the EFS

was 76% for patients receiving auto-SCT compared to 49% for those receiving chemotherapy ($P=.004$). The OS at 7 years was only marginally significant in the auto-SCT arm (81% vs 55%; $P=.09$).

There are also multiple trials that have contradictory results. Gisselbrecht and coworkers,¹⁶ in the LNH93-3 trial, randomized 370 poor-prognosis patients with aggressive lymphomas to standard chemotherapy or auto-SCT after an experimental shortened induction regimen. OS and EFS were better in the standard chemotherapy arm. OS and EFS for the standard chemotherapy and auto-SCT arms were 60% and 46% ($P=.007$) and 52% and 39% ($P=.01$), respectively. Kaiser and colleagues¹⁷ randomized 312 patients with at least a minor response after two cycles of CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone) to receive three further cycles of CHOEP and radiotherapy or one further cycle of CHOEP followed by auto-SCT and radiotherapy. OS was 63% for the chemotherapy arm and 62% for auto-SCT ($P=.68$).

From these studies it appears that utilizing auto-SCT in first CR is most beneficial to patients who have received full-dose standard chemotherapy, whose disease is under control, and who are high-intermediate- or high-risk as defined by the IPI. It is also important to note that these studies were conducted before the use of rituximab (Rituxan, Genentech/Biogen Idec) and chemoimmunotherapy.²²

Ongoing studies include a cooperative study, S9704, by the Southwest Oncology Group, the Eastern Cooperative Oncology Group, Cancer and Leukemia Group B, and the National Cancer Institute of Canada. S9704 is a prospective, randomized phase III trial comparing early versus delayed high-dose therapy in patients with high-intermediate- and high-risk DLBCL by IPI score. Patients are randomized to either CHOP-R (cyclophosphamide, doxorubicin, vincristine, prednisone, and rituximab) for six cycles and auto-SCT or to CHOP-R for eight cycles followed by auto-SCT only if the patient relapses. This study will help answer the question of whether auto-SCT has a role as initial therapy in poor-prognosis patients with aggressive NHL.²³

Rituximab, a chimeric monoclonal antibody that targets the CD20 molecule on the B-cell surface, is also currently being used for the treatment of NHL. Results have shown that rituximab is an effective means of *in vivo* purging of tumor cells prior to transplantation²⁴ and may prevent relapse by eradication of residual tumors when utilized after transplantation.²⁵

Radioimmunotherapy (RIT) has led to the use of these agents as part of the conditioning regimen prior to auto-SCT. RIT combines radiotherapeutic and immune mechanisms to target and destroy tumor cells and has

Table 1. Autologous Transplantation as Part of Initial Treatment Strategy for Aggressive NHL

Study	Patient Population	n	Therapy	PFS, %	P value	OS, %	P value	Time, mos
HOVON ¹⁰	Intermediate/ high-grade-PR	35	CHOP × 8	53	>.10	85	>.10	48
		34	CHOP × 4 + ASCT	41 (EFS)		56		
Italian ¹¹	Aggressive-PR	27	DHAP × 6	52	.3	59	.4	55
		22	ASCT	73		73		
Milan ¹²	DLBCL	50	MACOP-B	49	.004	55	.09	55
		48	HDT + ASCT	76 (EFS)		81		
Italian NHLCSG ¹³	Aggressive	61	VACOP-B	48	.4	65	.5	42
		63	VACOP-B + ASCT	60		65		
GELA LNH87-2 ¹⁴	Aggressive-first CR	111	A/NCVB × 4 + sequential therapy	39	.02	49	.04	96
		125	A/NCVB × 4, MTX + CBV + ASCT	55		64		
EORTC ¹⁵	Aggressive CR/PR	96	CHVmP/BV × 8	56	.71	77	.34	53
		98	CHVmP/BV × 6 + ASCT	61		68		
GELA LNH93-3 ¹⁶	Aggressive	181	Multi-agent chemotherapy	51	.01	60	.007	60
		189	CEOP × 1, CVBP × 2, + ASCT	39 (EFS)		46		
German HGLSG ¹⁷	Aggressive	154	CHOEP × 5	49	.22	63	.68	46
		158	CHOEP × 3 + ASCT	59 (EFS)		62		
Italian ¹⁸	Aggressive	75	MACOP-B-12 weeks	49	.21	65	.95	24
		75	MACOP-B-8 weeks + ASCT	61		64		
GOELAMS ¹⁹	Aggressive	99	CHOP × 8	37	.037	56	.076	48
		98	CEEP × 2 + ASCT	55 (EFS)		71		
IIL ²⁰	DLBCL intermediate- high/high-risk	66	MegaCEOP × 4/8	NR	-	63	.06	78
		60	HDT + ASCT	NR		49		

ACVB = doxorubicin, cyclophosphamide, vindesine, and bleomycin; ACVBP = doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone; ASCT = autologous stem cell transplantation; CBV = cyclophosphamide, carmustine, etoposide; CEEP = cyclophosphamide, epirubicin, vindesine, and prednisone; CEOP = cyclophosphamide, epirubicin, vincristine, and prednisone; CHOEP = cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone; CHVmP/BV = cyclophosphamide, doxorubicin, teniposide, prednisone, bleomycin, and vincristine; CR = complete remission; CVBP = cyclophosphamide, vincristine, bleomycin, prednisone; DHAP = cisplatin, cytarabine, and dexamethasone; DLBCL = diffuse large B-cell lymphoma; ECVBP = epirubicin, cyclophosphamide, vindesine, bleomycin, and prednisone; EFS = event-free survival; F-MACHOP-B = flurouracil, methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin; HDT = high-dose therapy; MACOP-B = methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin; MTX = methotrexate; NCVB = mitoxantrone, cyclophosphamide, vindesine, and bleomycin; NR = not reported; OS = overall survival; PFS = progression-free survival; PR = partial remission; VACOP-B = etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin.

the advantage of targeting therapy to specific tumor sites with minimal effects on normal tissue. Several phase I/II studies using RIT with yttrium (Y)-90- and iodine (I)-131-labeled anti-CD20 antibodies (ibritumomab tiuxetan [Zevalin, Biogen Idec] and tositumomab/I-131 tositumomab [Bexxar, GlaxoSmithKline]) have shown promising results.²⁶⁻²⁸

At the University of Nebraska, we combined I-131 tositumomab with high-dose carmustine, etoposide, cytarabine, and melphalan (BEAM) followed by auto-SCT in 23 patients with chemotherapy-resistant relapsed or refractory B-cell NHL.²⁸ With a median follow-up of 38 months, the OS and EFS were 55% and 39%, respectively.

Currently, the Bone Marrow Transplant Clinical Trials Network is involved in a multicenter trial comparing rituximab/BEAM (carmustine, etoposide, cytarabine, and melphalan) versus I-131 tositumomab/BEAM prior to auto-SCT in patients with persistent or relapsed chemotherapy-sensitive DLBCL.

One group of patients that may benefit from an auto-SCT are those who never achieve a CR with conventional chemotherapy. It is known that treatment with salvage chemotherapy produces long-term DFS in few patients.^{29,30} Vose and coauthors³¹ evaluated 184 patients with diffuse aggressive NHL who underwent an auto-SCT after not achieving a CR with induction chemotherapy. The 3-year probability of survival in patients with a CR/unconfirmed CR after auto-SCT was 68% compared to 11% for patients with a partial response (PR) or no response ($P < .001$). The 5-year probabilities of PFS and OS were 31% and 37%, respectively. Patients who seem to benefit the most from this treatment strategy are those with chemosensitive disease, with good performance status, younger than 55 years of age, having received only one or two prior chemotherapy regimens, and having received either pretransplant or posttransplant involved-field radiation.

Allogeneic Transplant

The potential benefits of an allograft include a lymphoma-free graft, decreased rates of myelodysplastic syndrome and leukemia, and possibly a curative graft-versus-lymphoma (GVL) effect. The major disadvantages are increased morbidity and mortality related to the transplantation procedure, risk of graft-versus-host disease (GVHD), risks associated with immunosuppression, and age and donor restrictions.³² There is a paucity of quality trials in the literature.

Currently there are no randomized studies comparing allogeneic and autologous transplants but several retrospective reviews have been done. A case-control study from the European Bone Marrow Transplant Group (EBMT)

compared the efficacy of allogeneic and autologous bone marrow transplant in NHL.³³ Of the 101 patients undergoing allogeneic transplants, 43 patients had either intermediate- or high-grade lymphoma. The results in this subset comparing allogeneic versus autologous transplant failed to show a difference in either PFS (43% vs 49%; $P = \text{NS}$) or relapse (29% vs 35%; $P = \text{NS}$). In the subset with intermediate- and high-grade lymphomas, there was no clinically significant GVL effect.

Peniket and colleagues³⁴ performed an updated analysis of the EBMT data using multivariate analysis. The group further subdivided patients according to six histologies based upon the Working Formulation. Of the 1,185 patients receiving an allogeneic transplant as a first transplant, 147 were classified as intermediate-grade. At 4 years, the PFS rate was 34.6%, the OS rate was 38.3%, and the procedure-related mortality rate was 41.8% for the intermediate-grade histology. A matched analysis was performed. When comparing allogeneic and autologous transplants, the relapse rate was lower in the allogeneic groups for low-, intermediate-, and high-grade NHL as well as for lymphoblastic lymphoma; OS was better in the autologous group for all categories of lymphoma; and treatment-related mortality (TRM) was always worse in the allogeneic group (absolute numbers not given). It appears that the decrease in relapse rate in the allogeneic group may be secondary to GVL effect or lack of tumor contamination. Any reduction in relapse rate with the allogeneic transplant was offset by the mortality associated with the procedure. Others have also shown that relapse rates after allogeneic transplant are lower than relapse rates after autologous transplant.³⁵⁻³⁸

A more recent study compared the results of syngeneic, allogeneic, and autologous transplants for NHL using the databases of the International Bone Marrow Transplant Registry (IBMTR), the Autologous Blood and Marrow Transplant Registry (ABMTR), and the EBMT.³⁹ For intermediate-grade lymphoma there were no significant differences in relapse risk when allogeneic transplants were compared with syngeneic transplants. A higher risk of relapse was seen in those who received unpurged autografts than did syngeneic transplant recipients ($P = .08$). There were, however, no significant differences in relapse risk when unpurged and purged autografts were compared (relative risk [RR], 1.23; $P = .12$). The 5-year DFS was significantly worse for recipients of non-T-cell depleted allogeneic grafts compared to recipients of syngeneic grafts (RR, 1.85; $P = .03$), but no significant differences in DFS when recipients of T-cell-replete and T-cell-depleted allogeneic transplants were compared (RR, 1.16; $P = .61$). Nor were there significant differences in DFS when results of autologous and syngeneic transplants were compared (RR, 1.09; $P = .46$). If the GVL effect were clinically rele-

vant, the relapse rate would be expected to be lower in the allogeneic group, but this was not the case. This study was unable to demonstrate a meaningful GVL effect; however, the analysis provides evidence that tumor contamination may contribute to relapse after auto-SCT. It is also possible that the lower relapse rates seen in allogeneic transplants may be explained by other factors such as lack of tumor contamination. Currently, there is not a large amount of data regarding reduced-intensity conditioning (RIC) or nonmyeloablative allo-SCT in this group of patients.

It is also known that patients who relapse after an autologous transplant have a poor prognosis, with a median survival of less than 12 months.^{40,41} The use of allogeneic transplant may be an option in this subset of patients but most reports include a small number of patients with conflicting results.⁴²⁻⁴⁴ Radich and coworkers⁴⁵ evaluated 59 patients who underwent an allo-SCT after relapse following an auto-SCT. Of the 59 patients, 18 had lymphoma. The patients with lymphoma had probabilities of death without recurrence and relapse rates of 78% and 22%, respectively. The IBMTR reviewed 114 lymphoma patients (69 NHL, 35 Hodgkin disease) in the IBMTR/ABMTR who underwent a myeloablative allo-SCT after relapse following an auto-SCT from 1990 to 1999. Analysis showed a 5-year probability of OS and PFS of 24% and 5%, respectively, indicating that prolonged survival can be attained but few are cured.⁴⁶ There are also reports on the use of RIC or nonmyeloablative allo-SCT after auto-SCT in this group of patients, but longer follow-up is needed.^{47,48}

The exact role of allogeneic transplantation in DLBCL is still unknown. The data are limited and allogeneic transplantation appears to be useful in only a select group of patients.

Follicular Lymphoma

Follicular lymphoma is an indolent disease that is incurable with standard forms of chemotherapy. It continues to relapse after therapy, with a median survival of 7–10 years. Treatment includes combinations of conventional chemotherapy and monoclonal antibodies, RIT, new targeted agents, and auto- and allo-SCT. For a select few patients, “watch and wait” or involved-field irradiation may be the best therapy. The exact role of hematopoietic SCT in follicular lymphoma is evolving.

Autologous Transplant as Salvage Therapy

The use of high-dose myeloablative therapy followed by auto-SCT is a promising approach for advanced-stage disease. Auto-SCT can be utilized as salvage therapy for recurrent disease or as consolidation therapy in first remission. Tables 2⁴⁹⁻⁵⁵ and 3⁵⁶⁻⁵⁸ summarize the role of auto-SCT in relapse and in first remission.

The Group d'Étude des Lymphome d'Adulte trial compared results in patients who underwent high-dose therapy with auto-SCT or received standard treatment after relapse. Patients in the auto-SCT group had a significantly increased 5-year DFS rate compared to patients in the standard-treatment group: 42% versus 16% ($P=.0001$); 5-year overall survival rates were 58% versus 38%, respectively ($P=.0005$).⁵⁴ Schouten and colleagues⁵⁹ conducted an international randomized trial that compared standard chemotherapy versus unpurged auto-SCT versus purged auto-SCT in 140 patients with relapsed follicular lymphoma. At 2 years, the PFS rates for the chemotherapy, unpurged auto-SCT, and purged auto-SCT arms were 26%, 58%, and 55%, respectively. At 4 years, the OS rates were 46%, 71%, and 77%, respectively. A significant reduction in hazard ratios for OS was found when the combined transplantation arms were compared with the chemotherapy arm. There was also a similar PFS in the patients who received a purged or an unpurged auto-SCT. It is important to remember that these studies were initiated in the era before rituximab. Future trials must confirm that auto-SCT prolongs survival in recurrent follicular lymphoma after the use of rituximab and chemotherapy.

RIT is used in follicular lymphoma as part of the conditioning regimen prior to auto-SCT. The Seattle group conducted a phase I/II trial of I-131 tositumomab combined with etoposide and cyclophosphamide followed by auto-SCT in 52 patients with relapsed B-cell lymphomas including 38 follicular lymphoma patients.²⁶ The 2-year OS and PFS rates of all treated patients were 83% and 68%, respectively. The same group performed a multivariable comparison of 125 patients with follicular lymphoma treated with either high-dose I-131 tositumomab ($n=27$) or conventional high-dose therapy ($n=98$) and auto-SCT (historical controls).⁶⁰ Patients who received RIT had improved PFS and OS rates compared with the conventional high-dose chemotherapy group. The estimated 5-year PFS and OS rates were 48% and 67% for the RIT group and 29% and 53% for the conventional high-dose chemotherapy group, respectively.

Autologous Transplantation in First Remission

The use of auto-SCT in first relapse has stimulated studies evaluating the use of intensive chemotherapy and auto-SCT in advanced-stage follicular lymphoma patients in first remission. Several phase II clinical trials using auto-SCT as consolidation therapy in first remission of advanced-stage follicular lymphoma have demonstrated promising long-term results.⁶¹⁻⁶³

The German Low-Grade Lymphoma Study Group launched a randomized trial to compare myeloablative radiochemotherapy followed by auto-SCT or interferon- α maintenance therapy in first remission in patients less

Table 2. Autologous Hematopoietic Stem Cell Transplantation in the Treatment of Relapsed/Recurrent Follicular Lymphoma

First Author	N	Conditioning Regimen	DFS, %	OS, %	Time, yrs
Rohatiner ⁴⁹	121	Cy + TBI	64.4	80.9	2.5
Bociek ⁵⁰	174	NS	36 (EFS)	61	6
Freedman ⁵¹	153	Cy + TBI	42	66	8
Apostolidis ⁵²	99	Cy + TBI	63	69	5
Bierman ⁵³	100	Cy + TBI, BEAC	44	65	2.6
Brice ⁵⁴	83	NS	42	58	5
Cao ⁵⁵	92	CY + TBI + VP16 CY + BCNU + VP16	44	60	4

BCNU = carmustine; BEAC = carmustine, etoposide, cytarabine, cyclophosphamide; Cy = cyclophosphamide; DFS = disease-free survival; EFS = event-free survival; NS = not stated; OS = overall survival; TBI = total body irradiation; VP16 = etoposide.

Table 3. Autologous Hematopoietic Stem Cell Transplantation in First Remission of Follicular Lymphoma

Study	N	Consolidation	EFS, %	P value	OS, %	P value	Time, yrs
GLSG ⁵⁶	154	IFN- α maintenance	33.3 (PFS)	<.0001	NS	NS	4.2
	153	Cy + TBI +ASCT	64.7				
GOELAMS ⁵⁷	80	CHVP+ IFN- α	48	.050	82	.493	5
	86	Cy + TBI +ASCT	60				
GELA ⁵⁸	209	CHVP+ IFN- α	36	.5	74	.05	4.8
	192	Cy + TBI +ASCT	45				

ASCT = autologous stem cell transplantation; CHVP = cyclophosphamide, doxorubicin, teniposide, prednisone; Cy = cyclophosphamide; EFS = event-free survival; IFN- α = interferon- α ; NS = not stated; OS = overall survival; PFS = progression-free survival; TBI = total body irradiation

than 60 years of age.⁵⁶ Overall 240 patients were available for the comparison of auto-SCT and interferon- α . The 5-year PFS rate was 64.7% in the auto-SCT group compared to 33.3% in the interferon- α group ($P < .0001$), but the results were not mature enough to determine a significant difference in OS.

The French Group Ouest-der Leucemies et Autres Maladies du Sang (GOELAMS) randomized 172 patients with newly diagnosed advanced follicular lymphoma to either an immunochemotherapy regimen (cyclophosphamide, doxorubicin, teniposide, prednisone, and interferon) or high-dose therapy followed by auto-SCT.⁵⁷ At 5 years the EFS differed significantly between the auto-SCT arm and chemotherapy arm (60% \pm 6% vs 48% \pm 7%; $P = .05$). The advantage of auto-SCT was restricted to patients with a high-risk profile according to the Follicular Lymphoma International Prognostic Index (FLIPI) score greater than 2 (67% \pm 9% vs 20% \pm 10%, $P = .018$). In patients with a FLIPI score less than or equal to 2, the EFS rates were similar in the two groups. There was, however, no difference in OS between the groups

due to a higher risk of secondary malignancies in the auto-SCT arm.

These studies show improved PFS and EFS, but improved OS has not yet been demonstrated. The role of auto-SCT in this setting is controversial.

Allogeneic Transplant

In patients with advanced follicular lymphoma, allo-SCT may offer a potential cure. Also there is an increased incidence of late relapse following auto-SCT, which has led to further investigations utilizing allogeneic transplant for follicular lymphoma. Several retrospective studies that have demonstrated a lower risk of relapse following allo-SCT, but the incidence of TRM and acute and chronic GVHD has offset any significant difference in overall outcomes.

The IBMTR/ABMTR compared the outcomes of 904 patients undergoing transplantation for follicular lymphoma. A total of 176 patients received HLA-identical sibling allo-SCT and 728 (131 purged, 597 unpurged) received auto-SCT.⁶⁴ At 5 years, the recurrence rates were

significantly lower in the allogeneic group compared to the purged and unpurged auto-SCT groups (21%, 43%, and 58%, respectively), but the TRM rates were higher in the allogeneic group (30%, 14%, and 8%, respectively). This resulted in similar 5-year probabilities of survival among the three groups (51%, 62%, and 55%, respectively). In this study, there were few late recurrences beyond 1 year of transplantation, which supports the curative potential of allo-SCT in patients with follicular lymphoma.

A study from the University of Nebraska showed similar results. Deshpande and colleagues⁶⁵ compared long-term outcomes of 204 follicular lymphoma patients who received either allo- or auto-SCTs. Allo-SCT patients had a significantly greater 5-year PFS compared to auto-SCT patients (76% vs 41%; $P=.034$) but no significant difference in OS (76% vs 61%; $P=.18$).

Because the high TRM rates offset any difference in OS, several groups have utilized nonmyeloablative or RIC SCT. RIC is a less intensive preparative regimen that relies on the immunotherapeutic effects of the allograft and has lower TRM compared to myeloablative conditioning.

Khoury and colleagues⁶⁶ reported on 20 patients (18 with follicular lymphoma and 2 with chronic lymphocytic leukemia) who received an RIC regimen of fludarabine and cyclophosphamide; 9 patients received rituximab in addition to chemotherapy. All patients had a CR with no relapse at a median follow-up of 21 months. The 2-year actuarial DFS rate was 84%; the rate of acute grade II–IV GVHD was 20%, but the cumulative incidence rate of chronic GVHD was 64%. These results are promising; however, 12 patients were in CR at the time of transplantation and the median follow-up was short (21 months). Longer follow-up is needed to confirm the plateau in survival.

These studies demonstrate that allogeneic transplantation after either myeloablative or nonmyeloablative conditioning has lower relapse rates than autologous transplantation and a possible plateau in the survival curves after the initial posttransplant period, but is associated with a higher rate of morbidity and mortality.

Currently there are no prospective randomized studies comparing auto-SCT and allo-SCT for follicular lymphoma.

Mantle Cell Lymphoma

Mantle cell lymphoma is a newly recognized disease and accounts for only about 6% of cases of adult NHL.⁶⁷ The median age of onset is 65 years, and the disease predominates in men. Mantle cell lymphoma has poor response rates to therapy and poor OS. It responds well to initial chemotherapy, but remissions are short, with a median survival of 3–4 years.^{67,68} No chemotherapeutic regimen

has been shown to be curative,⁶⁹⁻⁷⁶ thus leading to further investigations of high-dose chemotherapy followed by either auto- or allo-SCT. In the absence of clinical trials, the exact role of SCT in mantle cell lymphoma has not been clearly established. Options include auto-SCT at relapse, auto-SCT in first remission, full-intensity allo-SCT, or RIC allo-SCT.

Autologous Transplantation

There have been a number of single-center trials evaluating auto-SCT in first and subsequent remissions.⁷⁷⁻⁷⁹ At the University of Nebraska, we evaluated clinical outcomes and prognostic factors in 40 patients who underwent high-dose chemotherapy and auto-SCT for mantle cell lymphoma between 1991 and 1998.⁷⁸ With a median follow-up of 24 months, the 2-year EFS was 36%, and the OS was 65%. After a multivariate analysis, the only factor associated with poor EFS rate was the number of prior chemotherapy regimens. Those who had received 3 or more prior therapies had a 2-year EFS of 0% as compared to 45% for those who had received fewer than 3 therapies ($P=.004$).

A retrospective analysis was performed on pooled data from the EBMT and ABMTR registries on the outcome of 195 mantle cell lymphoma patients who had received an auto-SCT from 1988 to 1998.⁸⁰ After a median follow-up of 3.9 years, the 2-year and 5-year PFS rates were 55% and 33%, respectively, and OS rates were 76% and 50%, respectively. Multivariate analysis showed that patients with chemosensitive disease not in first CR were 2.99 times more likely to die over time than patients transplanted in first CR ($P<.001$). Hence, patients treated with auto-SCT in first CR have better results than patients receiving auto-SCT in subsequent relapses.

The European Mantle Cell Lymphoma Network performed the only prospective randomized trial comparing myeloablative radiochemotherapy followed by auto-SCT to an interferon- α maintenance program in patients in first CR.⁸¹ In total, 122 patients were assessable; 62 proceeded to auto-SCT and 60 received interferon- α . The patients in the transplantation arm experienced a significantly longer PFS with a median of 39 months compared to 17 months in the interferon arm ($P=.01$). However, the 3-year OS rates were not significantly different between the two arms: 83% in the auto-SCT group and 77% in the interferon group ($P=.18$). In a subset analysis, patients undergoing transplantation in CR had the greatest benefit. Longer follow-up is needed to determine if there is any difference in OS. These data suggest that auto-SCT may improve prognosis when performed as part of first-line treatment. However, most patients continue to relapse and as a result auto-SCT does not appear to be curative in the majority of patients.

A number of strategies have been employed for increasing the success of auto-SCT in mantle cell lymphoma, including the use of rituximab^{82,83} and RIT. Gopal and colleagues⁸⁴ used high-dose I-131 tositumomab, etoposide, and cyclophosphamide with stem cell support in 16 patients with relapsed mantle cell lymphoma. At 3 years, patients had a 93% survival rate and 61% remained progression-free. The utilization of alternative induction therapy with hyperCVAD (cyclophosphamide, vincristine, doxorubicin, decadron, methotrexate, cytarabine) and SCT improved the remission rate.^{85,86} Vose and colleagues⁸⁷ utilized hyperCVAD with or without rituximab followed by auto-SCT in patients with mantle cell lymphoma in either first CR or partial remission (PR). Between June 1991 and November 2005, 80 patients received an auto-SCT in first CR (n=47) or first PR (n=33). A standard anthracycline-based CHOP-like (\pm rituximab) induction regimen was given to 48 patients and 32 patients received hyperCVAD (\pm rituximab) prior to transplant. After a median follow-up of 38 months, there was a significant advantage for the hyperCVAD regimen over the CHOP-like regimen in regard to PFS and OS. The PFS rates at 1 and 3 years were 97% and 78%, respectively, in the hyperCVAD group compared to 76% and 55%, respectively, in the CHOP-like group. The OS rates at 1 and 3 years were 97% and 97% in the hyperCVAD group compared to 94% and 68% in the CHOP-like group, respectively. HyperCVAD (\pm rituximab) induction therapy should be given to eligible patients with auto-SCT in first CR.

Allogeneic Transplantation

There is a paucity of data with respect to the use of allogeneic transplantation in mantle cell lymphoma. Given that the average age at diagnosis is 65, allogeneic transplant is unsuitable for most patients. There have been limited studies with few patients. Two studies are from the IBMTR and EBMT. In the IBMTR study,⁸⁸ 212 patients with a median age of 50 received allogeneic transplants. The OS rate at 2 years was only 40%. In the EBMT study, Vandenberghe and coworkers⁸⁹ evaluated 22 allogeneic transplant recipients and found EFS and OS rates of 50% and 62%, respectively, but the median follow-up was too short. Other studies in the literature have included a limited number of patients.

There have been several studies in the literature regarding RIC allo-SCT. In a report by Khouri and coauthors,⁹⁰ allo-SCT with reduced-intensity conditioning proved to be favorable in 18 patients with advanced or recurrent mantle cell lymphoma. The day-100 mortality was 0% and, after a median follow-up of 26 months, the actuarial probability of EFS was 82% at 3 years. The group at the Fred Hutchinson Cancer Research Center evaluated RIC

allo-SCT in 33 patients (16 HLA-matched, 17 unrelated) with relapsed and refractory mantle cell lymphoma.⁹¹ At 2 years, the relapse and nonrelapse mortality rates were 9% and 24%, respectively; the OS and DFS rates were 65% and 60%, respectively.

Currently there is no conclusive evidence that allo-SCT is curative for mantle cell lymphoma. Further studies comparing auto- versus allo-SCT are needed. New therapeutic strategies are warranted to further improve the prognosis of mantle cell lymphoma.

Conclusions

Hematopoietic SCT has become an increasingly important treatment modality for hematologic malignancies since its introduction into clinical practice. The use of either autologous or allogeneic transplantation has proven to be beneficial in certain subsets of patients with NHL. The addition of novel agents, including monoclonal antibodies, RIT, and vaccines, to transplantation may improve the DFS and OS. Continued exploration of novel chemotherapeutics is also needed. The use of the nonmyeloablative transplant has the promise to extend the benefits of transplant to a wider range of patients. Nonmyeloablative transplantation can decrease morbidity and mortality compared to full-intensity transplantation and needs to be further investigated, especially in patients in whom allogeneic transplantation may be appropriate.

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