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The Role of Hematopoietic Cell Transplantation for Follicular Non-Hodgkin's Lymphoma

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ABSTRACT

The overall survival with follicular lymphoma has not significantly changed over the last few decades, and there is no universal agreement as to the optimal first-line or subsequent therapy. High-dose chemotherapy with autologous hematopoietic cell transplantation (HCT) confers high response rates and improved progression-free survival in advanced-stage disease, and more recent data indicate a positive effect on overall survival. Initial results with myeloablative allogeneic HCT unequivocally demonstrated a reduction in relapse/progression compared with autologous HCT, but it is associated with prohibitive nonrelapse mortality. Nonmyeloablative or reduced-intensity regimens have substantially reduced up-front toxicity, and preliminary data seem highly encouraging with regard to efficacy. Novel strategies include the use of rituximab for *in vivo* purging and maintenance therapy. The incorporation of radioimmunoconjugates into conditioning regimens to deliver targeted radiotherapy also appears promising. This review summarizes current and new developments regarding the role of HCT for patients with follicular lymphoma.

KEY WORDS

Follicular non-Hodgkin's lymphoma • Autologous hematopoietic stem cell transplantation • Allogeneic hematopoietic stem cell transplantation

INTRODUCTION

Although patients with follicular lymphoma (FL) typically experience a relatively indolent disease course, this disease is rarely curable with conventional chemotherapy. Although most patients achieve a remission with initial chemotherapy, subsequent remissions become progressively shorter over time [1,2]. In light of the discouraging results with conventional chemotherapy, autologous and allogeneic hematopoietic cell transplantation (HCT) have been evaluated as alternative approaches. It should be noted, however, that most currently published trials were initiated in the prerituximab era. Therefore, there is still a paucity of data regarding the influence of rituximab on the outcomes in patients undergoing HCT.

AUTOLOGOUS HCT

Relapsed Follicular Non-Hodgkin's Lymphoma

For patients with relapsed follicular non-Hodgkin's lymphoma (NHL) undergoing autologous HCT (AHCT), several studies have consistently shown improved disease-free survival (DFS) after salvage therapy but have shown no conclusive benefit in overall survival (OS) until recently (Table 1). A European group of investigators conducted the first randomized trial, the Chemotherapy vs Unpurged arm vs Purged arm (CUP) trial, that prospectively addressed the role of AHCT in this patient population [3]. In this trial, 140 patients with relapsed, chemosensitive follicular NHL were randomized to chemotherapy alone, AHCT with a purged autograft, or AHCT with an unpurged autograft. OS at 4 years for the chemotherapy arm, unpurged AHCT arm, and purged AHCT arm was 46%, 71%, and 77%, respectively. The 2-year progression-free survival (PFS) was 26%, 58%, and 55%, respectively. There was a significant reduction in hazard rates for both PFS and OS when comparing the chemotherapy patients and the combined groups of AHCT patients. There was no difference between the 2 AHCT arms in these end points, although too few patients were accrued in these 2 arms to evaluate the effect of *ex vivo* purging. These results are the first to demonstrate an OS benefit of AHCT for patients with relapsed follicular NHL.

Table 1. *Autologous Hematopoietic Cell Transplantation for Follicular NHL*

Study	n	Preparative Regimen	Stem Cell Source	DFS/PFS (%)	OS (%)	Years	TRM (%)	Incidence of Secondary MDS/AML (%)
First remission								
GOELAMS [7] 2005 (randomized)	82	CHVP + IFN		48	84	5	0	0
	88	VCAP → TBI/CY	Purged PBPC or BM	60*	78†		0	19
GLSG [8] 2004 (randomized)	126	CHOP or MCP + IFN		33	NR	5	<2.5	NR
	114	CHOP → dexa-BEAM	Unpurged PBPC	64‡	NR		<2.5	NR
GITMO [14] 2002	80	High-dose sequential	PBPC	67	84	4	2	4
Stanford/COH [34] 2001	37	TBI/VP/CY	Purged BM	70	86	10	5	5
GOELAMS [35] 2000	27	CY/TBI	Purged BM	55	64	NR	7	NR
Relapsed								
CUP (randomized) [3] 2003	24	CHOP × 6	NA	26	46	4§	0	NR
	33	CHOP × 3, CY/TBI	BM	58	71		9	
	32	CHOP × 3, CY/TBI	Purged BM	55	77		6	
FHCRC [5] 2003	27	Tositumomab	Purged BM or PBPC	48	67	5	4	7
Stanford [25] 2001	49	TBI/VP/CY	Purged PBPC	44	60	4	10	7
St. Bartholomew's [10] 2000	99	CY/TBI	Purged BM	63	69	5	4	12
Dana-Farber [12] 1999	153	CY/TBI	Purged BM	42	66	8	1	8
Nebraska [36] 1997	100	CY/TBI, BEAC	BM	44	65	4	8	2

DFS indicates disease-free survival; PFS, progression-free survival; OS, overall survival; TRM, treatment-related mortality; MDS, myelodysplastic syndrome; IFN, interferon; CHVP, cyclosphosphamide, doxorubin, teniposide, and prednisone; MCP, mitoxantrone, chlorambucil, and prednisone; VCAP, vincristine, cyclophosphamide, doxorubicin, prednisone; dexa-BEAM, dexamethasone, carmustine, etoposide, cytarabine, and melphalan; AML, acute myelogenous leukemia; GLSG, German Lymphoma Study Group; GITMO, Gruppo Italiano Trapianto Midollo Ossseo; COH, City of Hope; PBPC, peripheral blood progenitor cell; TBI, total body irradiation; VP, etoposide; CY, cyclophosphamide; BM, bone marrow; FHCRC, Fred Hutchinson Cancer Research Center; BEAC, carmustine, etoposide, cytarabine, and cyclophosphamide; NR, not reported; NA, not applicable; CUP, Chemotherapy vs Unpurged arm vs Purged arm; GOELAMS, French Groupe Ouest-des Leucemies et Autres Maladies du Sang; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone.

*$P = .05$.

†$P = .49$.

‡$P < .0001$.

§For overall survival only.

As a method to augment targeted radiation to lymphomatous sites while reducing toxicity to healthy organs, the Seattle group was the first to explore the feasibility of administering myeloablative doses of radioimmunotherapy (RIT). The iodine I 131–anti-CD20 monoclonal antibody tositumomab, followed by etoposide and cyclophosphamide with AHCT, was administered to 52 relapsed NHL patients, including 38 FL patients [4]. The combined RIT/high-dose chemotherapy regimen was well tolerated and yielded a 2-year PFS and OS of 68% and 83%, respectively. This compared favorably to survival in a nonrandomized control group. Only 1 case of myelodysplastic syndrome was seen in the 2-year follow-up. This same group of investigators subsequently published a multivariable cohort analysis of 125 patients with FL treated either with single-agent high-dose tositumomab with autologous stem cell rescue or with conventional AHCT [5]. The RIT group experienced significantly superior PFS and OS compared with the historical high-dose chemotherapy patients (PFS, 48% versus 29%; OS, 67% versus 53%, respectively). The treatment-related mortality (TRM) risk of 3.7% compared favorably with the 11% TRM observed in the historical high-dose chemotherapy group. The Nebraska transplantation team combined conventional-dose tositumomab with BEAM (carmustine, etoposide, cytarabine, and melphalan) in the AHCT setting in 23 patients with relapsed NHL, including 4 FL patients. With a median follow-up of 38 months, the event-free survival (EFS) and OS were 39% and 55%, respectively, and reported toxicities were comparable to those in historical control patients who received BEAM alone [6].

First Remission

Early intensive therapy in patients with newly diagnosed FL or patients in first remission has yielded high response rates, but the role of high-dose chemotherapy with AHCT in this setting is controversial. Several published series have evaluated the efficacy of this approach, but only recently has this question been addressed in a prospective randomized manner. The French Group Ouest-der Leucemies et Autres Maladies du Sang (GOELAMS) group randomized 172 patients with newly diagnosed FL to either an immunochemotherapy regimen (a cyclophosphamide, doxorubicin, vincristine, predisone (CHOP)-like regimen plus interferon) or AHCT with a purged graft after patients attained at least a partial remission to induction chemotherapy [7]. After a median follow-up of 5 years, the transplantation group experienced a significantly higher response rate and longer EFS. The median EFS was 45 months in the chemotherapy group, whereas this end point had not yet been reached in the transplantation recipients. However, these observations did not translate into a superior OS for the transplantation group because of an excessive 19% actuarial risk of secondary malignancies in this group, versus 0% in the chemotherapy recipients. It is interesting to note that when patients were subdivided by risk category according to the Follicular Lymphoma International Prognostic Index, the superiority in EFS among the transplant recipients was seen only in the poor-risk group. The good- and intermediate-risk patients in both treatment groups had comparable outcomes. These results suggest that patients with poor prognostic factors at diagnosis, such as a poor Follicular Lymphoma International Prognostic Index, may benefit from early intensive therapy. The German Low Grade Lymphoma Study Group also recently reported the results of their randomized trial that involved 240 patients with FL [8]. All patients initially received 2 cycles of an anthracycline-based regimen and then were randomized to either AHCT or interferon maintenance therapy until progression. The 5-year PFS favored the transplantation group (64% versus 33%; $P < .0001$), but the results were not sufficiently mature to report OS. As seen in the GOELAMS trial, a significantly increased risk of secondary malignancies was observed in the transplantation group after a preliminary analysis; this risk may negate the benefit of AHCT. On the basis of these results, AHCT cannot be recommended for patients with newly diagnosed FL.

Mounting evidence has confirmed the prognostic relevance of molecular monitoring of minimal residual disease (MRD) in patients with indolent lymphoma who are known to express the *bcl-2*/immunoglobulin H rearrangement. The attainment of polymerase chain reaction (PCR) negativity after transplantation seems to be highly predictive of continued complete remission, as shown in trials from St. Bartholomew's, the University of Heidelberg, and an Italian multicenter group [9-11]. In the Italian trial, with a median follow-up of 75 months, an 88% incidence of relapse was observed among patients who never attained a molecular remission, compared with only 8% among patients who were PCR negative after transplantation.

Graft Purging

Contamination of the hematopoietic stem cell graft by tumor cells is thought to be a major factor that contributes to relapse after AHCT. Reducing the rate of relapse may be achieved by pre-HCT purging of the hematopoietic stem cell product. Although no randomized trials to date strongly support the use of purging, several studies suggest a clinical benefit. The Dana-Farber group demonstrated the effect of successful *in vitro* graft purging: the 8-year freedom from relapse was 83% in the patients who received PCR-negative grafts, compared with 19% in patients who

received PCR-positive grafts [12]. In a large retrospective analysis of 904 FL patients by the International Bone Marrow Transplantation Registry (IBMTR), multivariate analysis revealed that stem cell purging was an independent predictor of relapse and OS [13].

Various *in vitro* purging methods are typically expensive and labor intensive and can be associated with substantial cell losses. Thus, *in vivo* purging via intensive induction therapy or with a single agent such as rituximab may be a more attractive strategy. The multicenter Gruppo Italiano Trapianto Midollo Osseo study administered high-dose sequential therapy at diagnosis with the goal of harvesting stem cells after intensified chemotherapeutic debulking [14]. Nearly half of the patients (47%) had PCR-negative grafts, and 65% of patients achieved clinical and molecular remission. At 4 years, the projected DFS and OS were 67% and 85%, respectively, with an 85% DFS among the patients who achieved a molecular remission.

For the purpose of *in vivo* purging, rituximab has recently emerged as a promising agent for this purpose when given concurrently with chemotherapy. Three recent studies have evaluated the effectiveness of the addition of rituximab to mobilization chemotherapy and yielded stem cell harvests with no PCR-detectable disease in the graft [15-17]. One such study, by Magni et al. [16], evaluated 15 patients with mantle cell lymphoma or FL who were given 2 cycles of intensive chemotherapy with 2 doses of rituximab. Ninety-three percent of the patents who received rituximab had PCR-negative harvests, compared with only 40% of patients who had received the identical chemotherapeutic regimen but without rituximab. The effect of *in vivo* purging on clinical outcome is still unclear but should become more evident as the data matures.

Histologic Transformation

Histologic transformation (HT) occurs in up to 70% of low-grade lymphoma patients and carries a median survival of ≤1 year after transformation with conventional chemotherapy [18-20]. However, this adverse prognosis may be modified by high-dose chemotherapy with AHCT, although this is controversial. Initial reports from Nebraska and the European Group for Blood and Marrow Transplantation (EBMT) reported poor outcomes after AHCT for this subset of patients [21,22]. A more recent update from the EBMT found similar outcomes after AHCT for transformed patients compared with case-matched controls with low-grade disease or *de novo* high- or intermediate-grade disease [23]. Increased lactate dehydrogenase at the time of transformation was the only adverse predictive factor for both OS and PFS. However, a TRM of 18% was observed, which was similar to the 20% TRM reported from the Princess Margaret Hospital in another retrospective analysis in which TRM was closely linked to advanced age. In the Princess Margaret study, the median OS for the 35 transformed patients was a notable 58 months from the time of transformation; the best outcomes were seen in patients who attained a complete remission before transplantation [24]. The Stanford group published a 4-year DFS of 49% and an OS of 50% in 17 patients with HT, which was similar to the updated EBMT study [25]. Comparable outcomes after transplantation were also reported by Corradini et al. [11], with a 10-year projected EFS of 54% for HT patients compared with 65% for patients who retained low-grade histological characteristics. Together, these data suggest that patients with HT may benefit from dose-intensive chemotherapy, especially patients with chemosensitive disease, and that HT does not necessarily portend a poor outcome.

ALLOGENEIC HCT

High-dose chemoradiotherapy with allogeneic HCT has also been offered to patients with recurrent follicular NHL to harness a graft-versus-lymphoma effect and to circumvent the tumor cell contamination associated with autologous hematopoietic stem cell harvests. Although no randomized trials have been performed, several studies have consistently reported a lower risk of relapse compared with AHCT. However, this benefit has been invariably offset by the TRM associated with myeloablative allogeneic HCT. An updated analysis from the IBMTR compared the outcomes of 904 patients with follicular NHL who underwent myeloablative allogeneic HCT (n = 176), purged AHCT (n = 131), or unpurged AHCT (n = 597). The risk for relapse was 54% lower in the allogeneic recipients ($P < .001$) and was 26% lower in recipients of purged autografts ($P = .04$) than in recipients of unpurged autografts [13]. Few relapses occurred in the allogeneic group after 1 year, as opposed to a continuous pattern of treatment failure in the autologous group. However, in a multivariate analysis, the risk of TRM was 4.4 times higher after allogeneic than after autologous transplantation ($P < .001$); this resulted in comparable 5-year probabilities of OS (52% after allogeneic, 62% after purged autologous, and 55% after unpurged autologous transplantation). The use of total body irradiation and receipt of a purged graft were associated with a lower risk of recurrence by multivariate analysis. In another large registry series, the EBMT analyzed the outcomes of 1185 patients with NHL who underwent myeloablative HCT, including 231 patients with low-grade NHL, and compared the results with those of 14 687 AHCT recipients [26]. As in the IBMTR study, the

relapse risk was significantly lower among the allogeneic recipients, but OS was not superior in this group because of the prohibitive TRM of 38% at 4 years. A higher proportion of the allogeneic group, however, was more heavily pretreated and underwent transplantation with more advanced disease. Two single-institution retrospective analyses with myeloablative allogeneic HCT from the Vancouver group and M.D. Anderson demonstrated that long-term DFS can be attained even in FL patients with chemoresistant disease [27,28]. In the M.D. Anderson report, plateaus were observed for both DFS and OS (24 and 44 months, respectively) even though nearly half of the patients had chemoresistant disease before transplantation [28].

Nonmyeloablative HCT

Nonmyeloablative allogeneic HCT incorporates a less intensive preparative regimen and relies primarily on the immunotherapeutic effects of the allograft to confer antitumor activity rather than the cytoreductive effects of high-dose chemotherapy (Table 2). The therapeutic benefit of allogeneic HCT is derived from donor-immunocompetent T cells that mediate an important graft-versus-malignancy effect. Some of the most promising data with nonmyeloablative allogeneic HCT in follicular NHL patients originated from the M.D. Anderson Cancer Center [29]. Twenty patients with relapsed indolent NHL, including 18 FL patients, received a conditioning regimen of fludarabine and cyclophosphamide with or without rituximab. All had received salvage chemotherapy, and 12 were in second or greater complete remission at the time of transplantation. The complete response rate was 100% after transplantation, with no recurrences at a median follow-up of 21 months. DFS and OS at 2 years were both approximately 84%. The incidence of grade II to IV acute graft-versus-host disease (GVHD) was 20%, and the cumulative incidence of chronic GVHD was 64%. Only 1 patient died from a treatment-related complication. These highly encouraging data clearly support the existence of a graft-versus-lymphoma effect, although longer follow-up is necessary to confirm a true plateau in survival. Kusumi et al. [30] demonstrated the efficacy of reduced-intensity conditioning in 45 patients with indolent NHL, including patients with chemoresistant disease. This was a heavily pretreated group; the median number of prior regimens was 4, and some patients had experienced prior treatment failure with AHCT. Patients received a fludarabine-based regimen or low-dose total body irradiation. The 3-year OS was 79%, and 3-year PFS was 83% and 64% for the chemosensitive and chemoresistant patients, respectively. The nonrelapse mortality was 18%, which was much lower than in the

Table 2. *Allogeneic Nonmyeloablative/Reduced-Intensity Transplantation for Follicular NHL*

Study	n	Preparative Regimen	Stem Cell Donor	DFS/PFS (%)	OS (%)	Followup (y)	Acute GVHD Grades II to IV	Chronic GVHD	Relapse (%)	TRM (%)
Japanese multicenter [30] 2005	45 (indolent)	Fludarabine based or low-dose TBI	MRD, MMRD, URD	83 sens 64 res	79	2	49%	59%	3	18
UK multicenter [32] 2004	41 (low grade)	Alemtuzumab, fludarabine, melphalan	MRD, URD	65	73	3	15%	7%	44	11 at 3 y
UK multicenter [31] 2004	28 (low grade)	Alemtuzumab-BEAM	MRD, URD	69	74	1.4	17%*	17%	10	13 at 2 y
M.D. Anderson [29] 2001	20 (indolent)	Fludarabine, rituximab, cyclophosphamide	MRD	84	84	<2	20%	64%	0	10 at 100 d

DFS indicates disease-free survival; PFS, progression-free survival; OS, overall survival; TBI, total body irradiation; MRD, matched related donor; MMRD, mismatched related donor; URD, unrelated donor; BEAM, carmustine, etoposide, cytarabine, and melphalan; TRM, treatment-related mortality; GVHD, graft-versus-host disease; sens, chemosensitive disease at the time of transplantation; res, chemoresistant disease at the time of transplantation.

*Grade I or II GVHD only.

previously mentioned studies that used ablative regimens. The occurrence of acute GVHD was associated with a lower progression rate, although it had no effect on PFS.

Although preliminary evidence demonstrates that TRM is reduced with nonmyeloablative HCT, GVHD still remains a leading cause of mortality. Thus, there have been studies that incorporated alemtuzumab (anti–CD-52 humanized monoclonal antibody) into the preparative regimen to ameliorate acute GVHD via *in vivo* donor T-cell depletion. Graft rejection is also reduced because recipient T cells are also affected. Two separate groups from the United Kingdom have reported remarkably low acute GVHD rates in this setting; grade III and IV acute GVHD was completely eliminated in the study by Faulkner et al. [31]. In that study, 65 patients, including 28 patients with low-grade NHL, received a BEAM/alemtuzumab conditioning regimen. Estimated 1-year TRM was only 8%, and relapse/progression was the major cause of treatment failure. Similar to the above-mentioned Japanese study, relapse did not occur in any patient who developed acute or chronic GVHD, although this association did not reach statistical significance. The other series from the United Kingdom, which also used an alemtuzumab-containing regimen, reported only a 15% incidence of grade II to IV acute GVHD [32].

The EBMT described the use of reduced-intensity conditioning for 188 patients with low-grade lymphoma, including 52 patients with follicular and small lymphocytic NHL. Twenty-nine percent had previously received an AHCT. Most patients received a fludarabine-based preparative regimen, and 10% of patients received BEAM, a more intensive and ablative regimen. The 2-year PFS and OS were 54% and 65%, respectively, with a 21% progression rate. TRM was 31%. The use of a more intensive conditioning regimen most likely contributed to the higher-than-expected TRM [33]. An ongoing trial conducted by the North American Clinical Trials Network is prospectively comparing AHCT with nonmyeloablative allogeneic HCT for patients with chemosensitive relapsed FL. Patients are assigned to a treatment strategy on the basis of the availability of an HLA-matched sibling. This protocol attempts to preemptively address relapse in the autologous arm by incorporating rituximab into the mobilization regimen for *in vivo* graft purging and by administering rituximab after transplantation for maintenance therapy to eradicate MRD. The allogeneic arm uses fludarabine, cyclophosphamide, and rituximab during conditioning and relies on the graft-versus-lymphoma effect for both antitumor efficacy and the reduction of MRD.

SUMMARY

The role of allogeneic HCT and AHCT in follicular NHL has shown considerable progress over the past decade. Regarding AHCT, there are now recent data demonstrating an OS benefit in patients with relapsed FL with chemosensitive disease. An abundance of previous trials have clearly shown improved DFS. With the recent incorporation of radioimmunoconjugates such as tositumomab and monoclonal antibodies such as rituximab into conditioning and mobilization regimens, the role and efficacy of AHCT will continue to evolve and, it is hoped, improve over time for FL patients. The incidence of secondary malignancies, especially myelodysplastic syndrome, however, remains a troubling complication after AHCT.

Although relapse and progression occur significantly less often after myeloablative allogeneic HCT, this modality cannot be recommended because of its prohibitive TRM. Nonmyeloablative or reduced-intensity regimens have shown highly encouraging results and unequivocally induce less upfront toxicity. Longer follow-up, however, is necessary to fully evaluate the long-term effect on the natural history of FL.

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