

# Hematopoietic stem cell transplantation for the management of follicular lymphoma

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**Abstract:** Although much has been published on the application of autologous and allogeneic hematopoietic stem cell transplantation in patients with follicular lymphoma (FL), no uniform consensus exists among physicians on when to use this strategy. Three large randomized trials failed to show a survival benefit using autologous transplantation for FL patients in first complete remission. Similarly, many Phase II or registry-based studies have also failed to show a survival benefit with autologous transplantation in relapsed or refractory FL patients, although the progression-free survival seems to be prolonged in transplant recipients. Allogeneic stem cell transplantation can cure a subset of patients with FL, but high nonrelapse mortality and morbidity remain a concern. No consensus exists on what conditioning regimen should be used, or how the newer monoclonal antibodies should be incorporated into the transplant paradigm. Here we present a review of the role of autologous and allogeneic hematopoietic stem cell transplantation in patients with FL.

**Keywords:** review, follicular lymphoma, allogeneic transplantation, autologous transplantation

## Background

With approximately 15,000 new cases each year in the US, follicular lymphoma (FL) is the second most common subtype of non-Hodgkin's lymphoma (NHL).<sup>1</sup> Advanced FL has traditionally been considered incurable with conventional treatment.<sup>2</sup> In most cases, FL is characterized by a long median survival but a continuous pattern of relapse.<sup>3</sup> Eventually the lymphoma becomes resistant to chemotherapy or undergoes transformation to the more aggressive large-cell histology.

In the last five years, several institutions in the US have reported an improvement in the survival of FL patients.<sup>4,5</sup> This improvement is due in part to the availability of drugs like rituximab<sup>6,7</sup> and to radioimmunoconjugates,<sup>8</sup> which have resulted in higher response rates, longer times to disease progression, and due to better supportive care.

High-dose chemotherapy (HDT) supported by both autologous and allogeneic hematopoietic stem cell transplantation (HSCT) has been studied extensively in patients with FL. However, at present, there is no consensus among physicians on when to use this strategy. Considerable evidence suggests that HDT alone may not be effective in eradicating FL. However, in some studies, a plateau in progression-free survival (PFS) has been observed which could suggest that a subgroup of patients with FL might be cured by autologous HSCT.<sup>9</sup> Addition of monoclonal antibodies like rituximab and radioimmunoconjugates to the transplant regimen may further improve

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the outcomes.<sup>10,11</sup> Monoclonal antibodies have also been used during hematopoietic stem cell mobilization to obtain “tumor-free” grafts.<sup>12</sup>

In allogeneic HSCT, donor cells repopulate the marrow, and a graft-versus-lymphoma (GVL) effect may also play an important role in preventing relapses.<sup>13–15</sup> Observations that support the presence of a GVL effect are the induction of complete remission (CR) by modulating immunosuppressive therapy and by infusing donor lymphocytes into patients whose FL relapses after allogeneic HSCT.<sup>16–18</sup>

Observations in FL patients that autologous HSCT is associated with a low transplant-related mortality (TRM) but with higher relapse rates compared with allogeneic HSCT<sup>19,20</sup> led to the concept of using nonmyeloablative or reduced-intensity conditioning regimens (RIC, also called minitransplants) for allogeneic transplantation.<sup>21</sup> The preparative regimen itself is not effective in eradicating FL, but it is immunosuppressive enough to allow engraftment of allogeneic peripheral blood stem cells (PBSC) or a bone marrow graft. *In vivo* expansion of immunocompetent cells after successful engraftment is responsible for the GVL effect. The less intensive preparative regimen is associated with a lower TRM and can be used in FL patients who are not suitable for myeloablative regimens because of advanced age or comorbidities. Also, the risk of acute severe graft-versus-host disease (GVHD) may be lower in these patients because development of GVHD is related in part to the toxicity of the conditioning regimen and subsequent cytokine production.<sup>22,23</sup> The GVL effect may be augmented by the infusion of additional donor lymphocytes in FL patients who achieve successful engraftment.<sup>24</sup>

In recent years, allogeneic transplants have become safer, with TRM reduced from 40% to 10% or less at one year posttransplant.<sup>25,26</sup> These improvements are attributable to better patient selection, better supportive care measures, improved human leukocyte antigen typing, advances in prevention and management of acute and chronic GVHD, and introduction of RIC and nonmyeloablative transplant regimens.

Although several published trials have evaluated the role of HDT and allogeneic or autologous HSCT in NHL, interpretation of these results is hindered by low patient enrolments, differences between the trials in selection criteria and transplant regimens used, and relatively short follow-up. It is also important to remember that the patient populations studied in these trials were a highly selected group and thus the results may not be applicable to all patients with FL.<sup>27</sup>

## Autologous transplantation

HDT with autologous bone marrow or PBSC transplantation for patients with relapsed or recurrent FL has produced disease-free survival (DFS) rates from 31% to 63% and overall survival (OS) rates from 50% to 69% at two to eight years of follow-up.<sup>28–30</sup> For patients who underwent transplant in first remission, DFS rates vary from 38% to 65%, and OS rates of up to 75% at three to 10 years of follow-up have been reported (Table 1).<sup>9,31,32</sup> The differences in outcomes may be related to various factors, including the small number of patients in each study, selection criteria, patient characteristics, source of stem cells, purging, preparative regimen used, timing of transplantation, and posttransplant maintenance. Many of these studies included patients with indolent lymphoma histologies rather than only patients with FL histology.

## Autologous transplantation for relapsed or refractory FL

Numerous Phase II studies have evaluated the role of autologous HSCT in patients with relapsed or refractory FL.<sup>28–30,33</sup> Rohatiner et al published mature data from a retrospective analysis of HDT supported by autologous bone marrow transplantation as consolidation therapy for second or subsequent remission in patients with FL.<sup>28</sup> A total of 121 patients received cyclophosphamide and total body irradiation (TBI) supported by autologous bone marrow transplantation. The graft mononuclear cell fraction was treated *ex vivo* with anti-CD20 monoclonal antibodies and complement. Of interest was an apparent plateau in the remission duration curve of 48% at 12 years. The 10-year OS and PFS rates were 54% and 48%, respectively. Both remission and OS durations were significantly longer in patients treated in a second remission than in an age-matched, remission-matched group of patients who had been treated at the same institution before the introduction of autologous HSCT. However, the development of secondary myelodysplasia (s-MDS) and secondary acute myeloblastic leukemia (s-AML) resulted in 15 deaths (12.4%) in the transplanted patients.<sup>28</sup>

A retrospective study by Montoto et al evaluated the outcomes of 693 patients with FL who had undergone HDT.<sup>33</sup> Of the 693 patients, 131 were in first CR. Median follow-up was 10.3 years. The 10- and 15-year PFS for the entire series were 31% and 27%, respectively. On multivariate analysis, younger age and disease status at the time of HSCT correlated with longer PFS. Ten-year and 15-year OS rates with HDT were 52% and 47%, respectively. On multivariate analysis, shorter OS was associated with older

**Table I** Autologous hematopoietic stem cell transplantation for follicular lymphoma

Trial	Patients (n)	Preparatory regimen	Follow-up (years)	PFS/EFS (%)	OS (%)
Relapsed/recurrent disease/primary induction failure					
Rohatiner <sup>28</sup>	121	Cy/TBI	9	48 at 10 y	54 at 10 y
Freedman <sup>29</sup>	153	Cy/TBI	5	42 at 8 y	66 at 8 y
Bierman <sup>30</sup>	100	TBI 77	2.6	44 at 4 y	65 at 4 y
		Non-TBI 23			
Apostolidis <sup>36</sup>	99	Cy/TBI	5.5	63 at 5 y	69 at 5 y
Cao <sup>37</sup>	49 (FLGL)	TBI 60	—	44 at 4 y	60 at 4 y
	26 (FLCL)	Non-TBI 32		51 at 4 y	58 at 4 y
	17 (TFL)			49 at 4 y	50 at 4 y
First remission (randomized)					
Lenz <sup>32</sup>	240	HSCT chemo	4.2	65 at 5 y 33 at 5 y ( <i>P</i> < 0.0001)	84 at 5 y overall
Gyan <sup>9</sup>	172	HSCT chemo	9	64 at 9 y 39 at 9 y ( <i>P</i> = 0.004)	76 at 9 y 80 at 9 y ( <i>P</i> = NS)
Sebban <sup>40</sup>	401	HSCT chemo	7.5	38 at 7 y 28 at 7 y ( <i>P</i> = NS)	71 at 7 y 76 at 7 y ( <i>P</i> = NS)
First remission and relapsed refractory					
Montoto <sup>33</sup>	CR1 131	TBI-based 401	10.3	27 at 15 y	47 at 15 y
	Beyond CR1 562	Chemo-based 289			

**Abbreviations:** HSCT, hematopoietic stem cell transplantation; Cy/TBI, cyclophosphamide/total body irradiation; PFS, progression-free survival; EFS, event-free survival; OS, overall survival; FLGL, follicular low-grade lymphoma; FLCL, follicular large cell lymphoma; TFL, transformed follicular lymphoma; TBI, total body irradiation; NS, not significant; CR, complete remission; y, years.

age, chemoresistant disease, stem cells derived from bone marrow, and TBI-containing regimens. Thirty-nine patients developed s-MDS/s-AML, and 34 of these 39 patients had received TBI as the conditioning regimen. The 10-year non-relapse mortality (NRM) was 6% for those who received non-TBI-based regimens and 16% for those receiving TBI-based regimens. On multivariate analysis, older age, chemoresistant disease, and TBI were associated with a higher NRM. As in the previous study, there was a plateau in the PFS curve, again suggesting that a select group of patients might be cured with HDT. In this analysis, TBI-containing regimens were associated with a negative impact on survival.<sup>33</sup>

In a different study from the Dana Farber Cancer Institute, 153 patients with relapsed FL received monoclonal antibody-purged autologous bone marrow transplantation and showed DFS and OS rates at eight years of 42% and 66%, respectively.<sup>29</sup> Patients whose bone marrow was negative as assessed by polymerase chain reaction (PCR) for bcl-2/IgH gene rearrangement after purging experienced longer freedom from recurrence than did those whose bone marrow remained PCR-positive (*P* < 0.0001). Continued PCR negativity in follow-up bone marrow samples was also strongly predictive of continued CR. The 12-year survival from diagnosis for these 153 patients was an impressive 69%.<sup>29</sup> Bierman et al presented a retrospective analysis of 100 patients who had undergone

autologous HSCT for FL at their institution between 1983 and 1993.<sup>30</sup> The median follow-up duration of surviving patients was 2.6 years (range 1.0–11.7). The OS rate at four years was 65% and the relapse-free survival (RFS) rate was estimated to be 44%. Bierman et al did not observe a definite plateau in the RFS curve. The only factor that was significantly associated with OS and RFS was the number of chemotherapy regimens administered prior to transplantation.<sup>30</sup>

The prospective CUP trial was initiated to analyze the value of *ex vivo* purging in patients with relapsed chemosensitive FL who were undergoing HDT and autologous HSCT.<sup>34,35</sup> After three cycles of chemotherapy, responsive patients were randomized to three more cycles of the same chemotherapy (C), or HDT followed by autologous unpurged (U) or purged (P) HSCT. Purging was performed using a cocktail of monoclonal antibodies. Of the 140 patients registered, 89 fulfilled the criteria for randomization (C: 24, U: 33, and P: 32). Median follow-up time was 69 months in surviving patients. Patients in the U and P arms had higher PFS/RFS rates. Kaplan–Meier estimates of two-year PFS for C, U, and P were 26%, 58%, and 55%, respectively (hazards ratio for C versus U + P was 0.3, *P* = 0.0009). OS rates at four years for C, U, and P were 46%, 71%, and 77%, respectively (hazards ratio for C versus U + P was 0.4, *P* = 0.026). Unfortunately, the trial was terminated early due to slow patient

accrual, and therefore the role of *ex vivo* purging could not be evaluated.<sup>34,35</sup>

To evaluate the long-term results of HDT in FL with specific emphasis on the prognostic significance of PCR-detectable Bcl-2/IgH rearrangements, Apostolidis et al treated 99 FL patients with HDT as consolidation therapy for second or subsequent remission.<sup>36</sup> *In vitro* purging of the bone marrow graft was accomplished by treatment with anti-B-cell antibodies and complement. Median follow-up was 5.5 years (range 1.5–12.5). Overall, 12% of patients developed s-MDS or s-AML. Kaplan–Meier estimates of freedom from recurrence and survival rates at five years were 63% and 69%, respectively. Multivariate analysis showed that absence of the Bcl-2/IgH rearrangement at the time of diagnosis and three or fewer treatment episodes before HDT were significant prognostic factors for improved survival. For patients bearing Bcl-2/IgH rearrangements in univariate and multivariate analyses, absence of a PCR-detectable Bcl-2/IgH rearrangement during follow-up was associated with a significantly lower risk of recurrence ( $P < 0.001$ ) and death ( $P = 0.02$ ), whereas the PCR status of the reinfused bone marrow graft did not correlate with outcome.<sup>36</sup>

In another retrospective analysis, Cao et al investigated the outcome of HDT and autologous HSCT in patients with FL beyond first remission.<sup>37</sup> Ninety-two patients with primary induction failure or with relapsed FL were treated with myeloablative therapy followed by transplantation of purged autologous bone marrow or PBSC. The four-year estimate of OS was 60% and of DFS was 44% in patients with follicular low-grade histology. A TBI-containing HDT regimen was associated with significantly longer DFS and OS in multivariate analysis, and OS was also significantly longer among those who had received three or fewer chemotherapy regimens prior to transplantation. In a subset analysis of 17 patients with transformed FL, the four-year estimated rate of OS was 50% and of DFS was 49%. There were three occurrences of s-MDS that yielded an estimated incidence rate of 7% at 56 months. Contrary to the results obtained by Montoto et al in this study, the TBI-containing regimen appeared to be superior to the BCNU (carmustine)-based regimen for relapsed FL, although late effects could not be ascertained because of the short duration of follow-up.<sup>33,37</sup>

With the availability of rituximab, *in vivo* purging strategies have largely replaced *in vitro* purging methods.<sup>11,38,39</sup> Using rituximab and high-dose cytarabine followed by granulocyte-colony stimulating factor in 14 patients with

relapsed or refractory FL or mantle cell lymphoma enrolled in a program of HDT and autologous HSCT allowed for the collection of a PBSC graft that was free of monoclonal B-cells and contained an adequate cell dose. Of nine patients PCR-positive for bcl-2 or bcl-1 in blood and marrow at the start of immunochemotherapy, all showed PCR-negative PBSC grafts. The widespread use of immunochemotherapy administered prior to mobilization also produces B-cell depletion and may also play a role in the collection of tumor-free grafts. Tarella et al reported on the impact of adding rituximab to a modified high-dose sequential chemotherapy regimen in patients with NHL.<sup>11</sup> Included in the study were 223 patients with FL who received the original or a modified high-dose sequential chemotherapy regimen. Two parameters significantly influenced the outcome of multivariate analysis, ie, disease status at HDT and the addition of rituximab. In those who received rituximab and those who did not receive it, the five-year OS rates were 82% and 68% ( $P = 0.01$ ) and event-free survival (EFS) rates were 66% and 46% ( $P = 0.001$ ), respectively.<sup>11</sup>

Sebban et al evaluated the impact of HDT and HSCT and rituximab on the outcome for patients with relapsed FL. Two cohorts of patients treated in two successive randomized Groupe d'Etude des Lymphomes de l'Adulte (GELA) studies, (Groupe d'Etude des Lymphomes Folliculaires [GELF] GELF-86 and GELF-94) with the same chemotherapy regimen were studied.<sup>40,41</sup> Of the 364 patients included in these two studies, 254 had FL that progressed or relapsed and were included in the analysis. Of the 254 patients, 98 were treated with HDT, including 33 with a rituximab-containing salvage regimen and 69 with rituximab alone or combined with chemotherapy but without HDT. Patient characteristics at diagnosis were similar in all subgroups. HDT was associated with a statistically significant benefit of EFS for relapse and survival after relapse. Rituximab was associated with a greater benefit than HDT for these two endpoints. When both treatments were combined, patients treated with the rituximab-containing salvage regimen followed by HDT after relapse had a five-year survival rate of more than 90%.<sup>40,41</sup>

Some of the factors that have been found to be statistically significant for DFS rate and/or OS after autologous HSCT for relapsed or refractory FL are patient age at the time of transplantation,<sup>30,33</sup> presence of minimal residual disease before and after transplantation,<sup>29,36</sup> chemotherapy-resistant versus chemotherapy-sensitive disease at the time of transplantation,<sup>30,33</sup> number of chemotherapy regimens or



treatment episodes prior to transplantation,<sup>33,37,42</sup> and the type of conditioning regimen.<sup>33,37</sup>

## Autologous transplantation in first complete remission of FL

Good results have also been reported with HDT and autologous HSCT in patients with FL in first remission (Table 1).<sup>9,32,40</sup> The German Low-Grade Lymphoma Study Group (GLSG) initiated a randomized trial to compare the effect of myeloablative radiochemotherapy followed by autologous HSCT with interferon-alpha (IFN- $\alpha$ ) maintenance therapy for patients with FL in first remission.<sup>32</sup> A total of 307 patients were enrolled. After two cycles of induction chemotherapy, patients were randomly assigned to either the HSCT or the IFN- $\alpha$  group. Two hundred and forty patients were evaluable for the comparison of HSCT and IFN- $\alpha$ . The five-year PFS rate was significantly longer in the HSCT arm (65% versus 33% in the HSCT and IFN- $\alpha$  arms, respectively,  $P < 0.0001$ ). Because of the short follow-up, the impact on OS could not be determined.<sup>32</sup>

The Groupe Ouest Est d'Etude des Leucémies et Autres Maladies du Sang (GOELAMS) multicenter study randomized 172 patients with untreated FL to either immunochemotherapy or HDT followed by purged HSCT.<sup>9</sup> The conditioning regimen for HSCT was TBI and cyclophosphamide. The nine-year OS was similar in the HDT and conventional chemotherapy groups (76% and 80%, respectively). Again the PFS was significantly higher in the HSCT than in the chemotherapy group (nine-year PFS 64% versus 39%;  $P = 0.004$ ). A PFS plateau was observed in the HDT group after seven years. On multivariate analysis, OS and PFS were affected independently by performance status score, number of nodal areas involved, and treatment group. Secondary malignancies occurred more frequently in the HDT group than in the chemotherapy group. The occurrence of a PFS plateau is encouraging and may suggest that a subgroup of patients with FL might be cured with HSCT.<sup>9</sup>

Sebban et al compared a standard chemotherapy regimen + interferon with standard chemotherapy followed by HDT + ASCT in treatment-naïve patients with advanced FL.<sup>40</sup> Of a total of 401 patients were enrolled, 209 patients received chemotherapy and IFN- $\alpha$  for 18 months and 192 received chemotherapy followed by HDT and autologous HSCT with a TBI-containing regimen. Overall response rates were similar in both groups (79% and 78% after induction chemotherapy). Of the 150 patients eligible for HDT, 131 underwent transplantation. Intent-to-treat analysis after a median follow-up of 7.5 years showed no difference

between the two arms for OS ( $P = 0.53$ ) or EFS ( $P = 0.11$ ). Patients with a complete response at the end of the induction therapy had a statistically longer EFS and OS ( $P = 0.02$  and  $P < 0.001$ , respectively).<sup>40</sup>

In a randomized, multicenter study by Ledatto et al patients received chemotherapy followed by rituximab or rituximab-supplemented high-dose sequential chemotherapy with autologous HSCT to assess the value of intensified chemotherapy as a first-line treatment for high-risk FL.<sup>43</sup> After a median follow-up of 51 months, the four-year EFS was 28% and 61%, respectively, in the chemotherapy versus HSCT arm ( $P < 0.001$ ), with no difference in OS. Molecular remission was achieved in 44% of chemotherapy patients and in 80% of patients receiving HSCT ( $P < 0.001$ ) and was the strongest independent outcome predictor.<sup>43</sup>

With the exception of the study by Ledatto et al all studies mentioned were conducted in the pre-rituximab era. Therefore, the impact of rituximab cannot be fully evaluated in patients undergoing autologous HSCT. Two recent abstracts have addressed the role of autologous HSCT in patients with FL who have received front-line rituximab therapy.<sup>44,45</sup> Hiddemann et al conducted a retrospective analysis of two GLSG studies, which showed that rituximab-cyclophosphamide/doxorubicin/vincristine/prednisone (R-CHOP) followed by IFN maintenance achieved a five-year PFS of 67% and was comparable with CHOP followed by autologous HSCT.<sup>45</sup> R-CHOP followed by HSCT, however, revealed a five-year PFS of 79%, with only one relapse after 24 months. This study suggested that autologous HSCT may have a role in the era of front-line R-CHOP therapy, particularly for intermediate- or high-risk patients with advanced stage FL.<sup>44</sup>

Because of the long natural history of FL, lack of survival benefit in most studies, and concern regarding the development of secondary malignancies, autologous HSCT for high-risk patients with FL in first CR remains investigational.

## Allogeneic transplantation Myeloablative regimens

Several studies have suggested that allogeneic transplantation for FL may improve the DFS when compared with autologous transplantation because of the presence of the GVL effect. The probability of relapse after allogeneic transplantation has ranged from 10% to 15%.<sup>26</sup> In the past, the low relapse rate observed after allogeneic transplantation has not translated into an improvement in OS because of the high TRM associated with the use of HDT (Table 2).<sup>26,46</sup> For example, in a study of 113 patients published by the International Bone Marrow Transplant Registry in 1998, the probability of DFS

**Table 2** Allogeneic hematopoietic stem cell transplantation for follicular lymphomas: Myeloablative conditioning regimen

Trial	N <sup>a</sup>	Preparatory regimen	Follow-up (months)	EFS/PFS (%)	OS (%)	NRM (%)	Relapse (%)
van Besien <sup>26</sup>	113	TBI 84% Non-TBI 16%	25	49	49	40	16
Kuruville <sup>47</sup>	37	Bu/Cy	65	79	76	16	3

three years after myeloablative allogeneic transplantation was 49%, but the recurrence rate was only 16%. However, the NRM was 40%.<sup>26</sup> Factors associated with improved survival were age <40 years, improved performance status at the time of transplantation, chemosensitive disease, and use of TBI-based conditioning regimens.<sup>26,47</sup>

In a report by Kuruville et al, 37 patients with indolent FL underwent allogeneic HSCT.<sup>47</sup> With a median follow-up duration of 63.5 months in survivors, the five-year OS was 79% and TRM was 15%. The median age of patients in this study was only 45 years (range 24–58).<sup>47</sup>

Although data are limited on the use of unrelated versus related donors, a recent analysis from the National Marrow Donor Program included 52 patients with FL who had received myeloablative allogeneic HSCT between 1991 and 2004. The one-year TRM was 42% and the two-year PFS was 42%.<sup>48</sup>

## Allogeneic versus autologous transplantation in FL

Most of the published studies comparing allogeneic and autologous transplantation are retrospective or registry-based (Table 3). A prospective study by the Bone Marrow Transplant-Clinical Trials Network was closed early due to slow accrual, thus highlighting a commonly encountered problem in conducting prospective studies.<sup>49</sup>

Van Besien et al reported on 904 patients who had undergone HSCT for FL.<sup>19</sup> A total of 176 patients had received allogeneic transplants, 131 patients had received purged autologous transplants, and 597 patients had received unpurged autologous transplants. Five-year TRM rates were 30%, 14%, and 8%, and five-year recurrence rates were 21%, 43%, and 58% after allotransplantation, purged autotransplantation, and unpurged autotransplantation, respectively. In multivariate analyses, allotransplantation had higher TRM and lower disease recurrence. Purged autotransplantation had a 26% lower recurrence risk than unpurged autotransplantation. However, five-year probabilities of survival were similar in the three groups (51%, 62%, and 55% after allogeneic, purged autotransplantation, and unpurged autotransplantation, respectively). Advanced age, prolonged interval from diagnosis to transplantation, high lactate dehydrogenase, refractory disease, bone marrow involvement, low performance scores, and transplantation between 1990 and 1993 were associated with adverse outcomes. TBI use was associated with higher TRM but lower recurrence. No association existed between acute or chronic GVHD disease and recurrence after allotransplantation.<sup>19</sup>

In a retrospective study, Verdonck et al compared allogeneic and autologous transplantation in 28 patients with advanced low-grade lymphoma. The probability of disease

**Table 3** Myeloablative allogeneic versus autologous hematopoietic stem cell transplantation

Trial	Preparatory regimen	N	Follow-up (months)	EFS/PFS (%)	OS (%)	NRM (%)	Relapse (%)
Van Besien <sup>19</sup>	Auto unpurged	597	41	31	55	8	58
	Auto purged	131	49	39	62	14	43
	Allo	176	36	45	51	30	21
Verdonck <sup>50</sup>	Auto	18 <sup>a</sup>	–	22	same	0	83
	Allo	10 <sup>a</sup>	41	68		3 patients	0
Hosing <sup>20</sup>	Auto	68	71	17	34	6	74
	Allo	44	53	45	49	34	19
							( <i>P</i> = 0.003)
Stein <sup>46</sup>	Auto	36	–	71	56	–	–
	Allo	15	–	64	15	46	–
				( <i>P</i> = 0.049)	( <i>P</i> = 0.012)		
Ingram <sup>24</sup>	Auto	82	88	56	67	2	43
	Allo	44	34	58	69	20	20
				( <i>P</i> = NS)	( <i>P</i> = NS)	( <i>P</i> = 0.001)	( <i>P</i> = 0.01)

<sup>a</sup>Included other low-grade histologies.

**Abbreviations:** Auto, autologous; allo, allogeneic; PFS, progression-free survival; EFS, event-free survival; OS, overall survival; NRM, nonrelapse mortality; TBI, total body irradiation; NS, not significant; Bu/Cy, busulfan/cyclophosphamide.

progression among patients who had undergone allogeneic HSCT was 0% versus 83% for autologous recipients at 41 months of follow-up ( $P = 0.002$ ). PFS was 68% versus 22% at two years ( $P = 0.049$ ).<sup>50</sup>

Hosing et al retrospectively compared the outcomes of HDT allogeneic versus autologous HSCT in patients with refractory or recurrent indolent NHL.<sup>20</sup> Of 112 patients, 68 patients had undergone autologous HSCT and 44 had undergone allogeneic transplantation. In the allogeneic HSCT group, the median follow-up time was 53 months (range 21–113), and the OS and DFS rates were 49% and 45%, respectively. After a median follow-up time of 71 months (range 22–109) in the autologous HSCT group, the OS and DFS rates were 34% and 17%, respectively. The probability of disease progression was significantly higher in the autologous HSCT group than it was in the allogeneic HSCT group (74% versus 19%;  $P = 0.003$ ).<sup>20</sup>

Ingram et al analyzed 126 patients with relapsed advanced-stage FL who received BCNU, cytarabine, etoposide, melphalan (BEAM)-alemtuzumab allogeneic HSCT ( $n = 44$ ) or BEAM-autologous HSCT (BEAM-auto,  $n = 82$ ).<sup>24</sup> The allogeneic group had a younger median age but had received a higher median number of therapies pretransplant ( $P = 0.015$ ) than had the autologous group. The allogeneic group had a higher NRM than did the autologous group at one year (20% versus 2%;  $P = 0.001$ ). Older age and heavy pretreatment were associated with a high NRM and poor survival in the allogeneic group. Noted again was a significantly lower relapse rate (20% versus 43%;  $P = 0.01$ ) at three years in the allogeneic group, with no relapses after two years compared with a continued pattern of relapse in the autologous group. No difference in OS or DFS was identified at three years, whereas a plateau in OS and DFS with crossing of the survival curves in favor of the allogeneic group was observed.<sup>24</sup>

Using the European Bone Marrow Transplant registry, Peniket et al analyzed 1185 allogeneic transplants for

lymphoma reported to the registry between 1982 and 1998 and compared the results with those of 14,687 autologous procedures performed over the same period.<sup>51</sup> Two hundred and thirty-one patients had low-grade histology, and actuarial OS four years after transplantation was 51% for this subgroup. These outcomes are relatively poor because of the high procedure-related mortality. Multivariate analysis showed that status at transplantation significantly affected outcome. A matched analysis was performed; for all categories of lymphoma, OS was better for autologous than for allogeneic transplantation, and the relapse rate was lower in the allogeneic group.<sup>51</sup>

## Allogeneic nonmyeloablative or reduced-intensity transplantation for FL

Preliminary results using nonmyeloablative preparative regimens for allogeneic transplantation have been very encouraging, with less than 15% TRM (Table 4).<sup>52–56</sup> One of the first reports was published by Khouri et al who treated 20 patients having indolent histology NHL with nonmyeloablative allogeneic HSCT. The day 100 mortality was 10% and, after a median follow-up duration of 21 months (range 5–46), the actuarial probability of being alive and in remission was 84% (95% confidence interval [CI], 53%–84%).<sup>21</sup> In a follow-up report on 47 patients with FL who had received a conditioning regimen of fludarabine, cyclophosphamide, and rituximab followed by allogeneic HSCT, all patients experienced CR posttransplant and only two relapsed.<sup>25</sup> With a median follow-up time of 60 months (range 19–94), the estimated OS and PFS rates of that study were 85% and 83%, respectively. The incidence of Grade II–IV acute GVHD was only 11%.<sup>25</sup>

Rezvani et al studied 62 patients with indolent or transformed NHL who had received allogeneic HSCT from related ( $n = 34$ ) or unrelated ( $n = 28$ ) donors after nonmyeloablative conditioning using 2 Gray of TBI  $\pm$  fludarabine.<sup>52</sup> Of the

**Table 4** Allogeneic hematopoietic stem cell transplantation for follicular lymphomas: Reduced intensity and/or nonmyeloablative conditioning regimen

Trial	N	Preparatory regimen	Follow-up (months)	EFS/PFS (%)	OS (%)	NRM (%)	Relapse (%)
Khouri <sup>25</sup>	47 <sup>a</sup>	FCR	36	83	85	15	4
Morris <sup>57</sup>	41	FM/Campath	36	65	73	11	44
Kusumi <sup>56</sup>	45 <sup>c</sup>	Various	24	83 sens 64 res	79	18	2
Robinson <sup>55</sup>	52 <sup>c</sup>	Various	10	54	65	31	21
Rezvani <sup>52</sup>	62 <sup>b</sup>	TBI $\pm$ Flu	37	43	52	23	14

**Notes:** <sup>a</sup>Patients with follicular lymphoma; <sup>b</sup>included patients with transformed follicular lymphoma; <sup>c</sup>included other low grade histologies.

**Abbreviations:** FCR, fludarabine, cyclophosphamide, rituximab; FM, fludarabine/melphalan; PFS, progression-free survival; EFS, event-free survival; OS, overall survival; NRM, non-relapse mortality; TBI, total body irradiation; NS, not significant; HR, hazards ratio.

62 patients, 54 had FL. Sixteen patients had histologic transformation before HSCT, and median follow-up time after transplant was 36.6 months. At three years, the estimated OS and PFS rates were 52% and 43%, respectively, for patients with indolent disease and 21% and 18%, respectively, for patients with transformed disease. Their study reported that the incidences of Grade II–IV acute GVHD and extensive chronic GVHD were 63% and 47%, respectively. Among survivors, the median Karnofsky performance status at last follow-up was 85%. It is encouraging that long-term survivors reported good overall functional status.<sup>52</sup>

Robinson et al reported the outcome of RIC allogeneic HSCT for 188 patients with lymphoma from the Working Party Lymphoma of the European Group for Blood and Bone Marrow Transplantation.<sup>55</sup> Fifty-two patients had indolent histology. The two-year TRM, OS, and PFS rates for patients with indolent histology were 31%, 65%, and 54%, respectively. Probability of disease recurrence was 21% at two years. For the entire group (including all histologies), age greater than 50 years was a risk factor for increased TRM. Refractory disease at transplant was associated with an increased risk of progression and poor OS.<sup>55</sup>

Kusumi et al conducted a nationwide survey of 112 adult Japanese patients who had undergone RIC allogeneic HSCT for NHL.<sup>56</sup> Included in the study were 45 patients with indolent histology. Cumulative incidences of Grade II–IV acute GVHD and chronic GVHD were 49% and 59%, respectively, for the entire group. With a median follow-up of 23.9 months, three-year OS was 81% in patients with FL. For patients with indolent histology, three-year PFS was 83% for chemosensitive patients and 64% for chemorefractory patients.<sup>56</sup>

Morris et al reported the outcomes of RIC allogeneic HSCT for NHL in 88 patients, 41 of whom had low-grade histology.<sup>57,58</sup> With a median follow-up of 36 months (range 18–60 months), the actuarial OS rates at three years were 73%. The 100-day and three-year TRM rates were 2% and 11%, respectively. The actuarial current PFS rate at three years, including the rate for patients who achieved remission after donor lymphocyte infusion was 65%. Patients with low-grade NHL and chronic lymphocytic leukemia achieved excellent PFS with extremely low TRM and GVHD, even when matched related donors were unavailable.<sup>57,58</sup>

## Myeloablative versus reduced-intensity conditioning regimens

The studies discussed in this section are also retrospective studies and differ in their patient characteristics. In general, patients who received myeloablative regimens were younger, had good performance status, had fewer comorbidities, and were more likely to have refractory disease (Table 5).

Khouri et al compared allogeneic transplantation for indolent NHL using HDT versus nonmyeloablative regimens in patients who had chemosensitive disease at the time of transplantation.<sup>59</sup> OS and DFS were 100% for the nonmyeloablative arm versus 36% for the HDT arm ( $P = 0.004$ ). The median follow-up time in that study was 30 months (range 2–79 months).<sup>59</sup>

In a retrospective analysis of 208 transplants reported to the Center for International Blood and Marrow Transplant Research between 1997 and 2002, Hari et al compared traditional myeloablative conditioning regimens with RIC for FL.<sup>54</sup> Conditioning regimens were categorized as

**Table 5** Allogeneic hematopoietic stem cell transplantation for follicular lymphoma: Reduced intensity and/or nonmyeloablative versus myeloablative conditioning regimen

Trial	N <sup>a</sup>	Preparatory regimen	Follow-up (months)	EFS/PFS (%)	OS (%)	NRM (%)	Relapse (%)
Hari <sup>54</sup>	MA 120	Various	50	67	71	23	17
	RIC 88		35	55 ( $P = 0.07$ )	62 ( $P = 0.15$ )	23 ( $P = \text{NS}$ )	
Rodriguez <sup>53</sup>	MA 18	Cy/TBI or Bu/cy	69	50	56	38	19
	RIC 16	FM	20	49 ( $P = 0.56$ )	68 ( $P = 0.83$ )	28 ( $P = 0.4$ )	
Sorrow <sup>60</sup>	MA 27	Cy/TBI or Bu/cy	61	HR MA versus	HR MA versus	–	–
	RIC 14	TBI ± Flu	44	RIC 3.16 ( $P = 0.02$ )	RIC 2.02 ( $P = 0.07$ )		
Avivi <sup>61</sup>	MA 44	various	38	43	47	37	same
	RIC 87		34	49 ( $P = \text{NS}$ )	53 ( $P = \text{NS}$ )	33 ( $P = \text{NS}$ )	

**Notes:** <sup>a</sup>Patients with follicular lymphoma; <sup>b</sup>included patients with transformed follicular lymphoma; <sup>c</sup>included other low grade histologies.

**Abbreviations:** MA, myeloablative; RIC, reduced intensity conditioning; PFS, progression-free survival; EFS, event-free survival; OS, overall survival; NRM, nonrelapse mortality; NS, not significant; HR, hazards ratio; Cy/TBI, cyclophosphamide/total body irradiation; Bu/Cy, busulfan/cyclophosphamide; FM, fludarabine/melphalan; Flu, fludarabine.



myeloablative ( $n = 120$ ) or RIC ( $n = 88$ ). Patients who had received RIC were older and had had a longer time interval from diagnosis to transplant. Median follow-up of survivors was 50 months (range 4–96) after myeloablative conditioning versus 35 months (range 4–82) after RIC ( $P < 0.001$ ). Surprisingly, the OS, PFS, and TRM did not differ between the two groups. At three years, OS rates for the myeloablative and RIC cohorts were 71% and 62% ( $P = 0.15$ ) and PFS rates were 67% and 55% ( $P = 0.07$ ), respectively. Lower performance score and resistance to chemotherapy were associated with higher TRM and lower OS and PFS rates. On multivariate analysis, an increased risk of lymphoma progression after RIC was observed (relative risk [RR] = 2.97;  $P = 0.04$ ).<sup>54</sup>

Rodriguez et al performed a retrospective analysis of 88 patients who had been conditioned with conventional myeloablative regimens ( $n = 48$ ) or RIC ( $n = 40$ ).<sup>53</sup> Compared with patients who had received myeloablative regimens, those who had received RIC were older, had more often failed autologous transplantation, and had more frequently received peripheral blood and unrelated donor transplants. The relapse rate was significantly lower in the patients receiving myeloablative regimens than it was in those receiving RIC regimens (13% versus 28%;  $P = 0.05$ ). The one-year transplantation-related mortality rate was 33% for myeloablative and 28% for RIC regimens ( $P = 0.40$ ). Kaplan–Meier two-year OS and PFS were 52% and 46% for myeloablative versus 53% and 40% for RIC regimens ( $P =$  not significant). Factors associated with improved survival were chemosensitive disease at transplantation (RR = 57%;  $P = 0.05$ ) and absence of prior autologous HSCT (RR = 37%;  $P = 0.002$ ).<sup>53</sup>

Sorror et al stratified outcomes using the hematopoietic cell transplantation-specific comorbidity index.<sup>60</sup> Patients in the nonmyeloablative group were older, had more previous treatment and more comorbidities, more frequently had unrelated donors, and more often had malignancy in remission than did patients in the myeloablative group. After HSCT, patients without comorbidities both in the nonmyeloablative and myeloablative cohorts had comparable NRM, OS, and PFS. Patients with comorbidities experienced lower NRM and better OS after nonmyeloablative conditioning. Nonmyeloablative transplant recipients with comorbidities had favorable adjusted PFS compared with patients in the myeloablative group.<sup>60</sup>

Avivi et al analyzed the outcomes of patients with FL treated with matched unrelated allogeneic HSCT.<sup>61</sup> A total of 131 patients had been treated with RIC ( $n = 87$ ) or conventional myeloablative ( $n = 44$ ) regimens between 2000

and 2005. RIC recipients were significantly older, with a longer interval from diagnosis to transplant, and had failed a previous autograft more often than patients treated with a conventional myeloablative regimen. NRM was 30% at one year. After a median follow-up of 36 months, the three-year PFS was 47%. The three-year OS rate for the whole series was 51%. On multivariate analysis, RIC regimens were associated with a lower NRM and a significantly longer PFS and OS.<sup>61</sup>

In recent years, RIC has become the standard for allogeneic HSCT in FL and appears to result in similar long-term outcomes. Although DFS is similar to myeloablative conditioning, some studies have shown an increased risk of late disease progression after RIC, which is concerning. Although some of these patients may be induced back into remission with the judicious use of donor lymphocyte infusion, there is a risk of inducing severe GVHD with repeated donor lymphocyte infusions. Therefore, the impact of dose reduction on relapse and survival needs additional study. Use of monoclonal antibodies and radioimmunoconjugates in the allogeneic transplant regimens may also affect outcomes, and studies are ongoing.<sup>25,62</sup>

## Discussion

Selected patients with FL may benefit from HSCT, but it is still uncertain which subset of patients may receive the most benefit. Patients with relapsed and chemosensitive FL should be considered for autologous HSCT because several Phase II studies have shown survival advantage and prolonged remissions.<sup>28,33</sup> Although data are limited, it is reasonable to expect that the addition of monoclonal antibodies like rituximab during stem cell collection for *in vivo* purging will reduce tumor contamination of the graft and therefore reduce relapse rates. The role of autologous HSCT for FL in the rituximab era has been questioned by some, but preliminary data suggest that HDT-autologous HSCT is still beneficial in patients with FL who relapse following rituximab-containing regimens.<sup>45,63</sup> Similarly, incorporation of monoclonal antibodies or radioimmunoconjugates during HDT is feasible and may improve the long-term outcomes, and studies are ongoing. Concern remains, however, regarding the increased risk of s-MDS/s-AML observed by most investigators. The patients who appear to benefit most from this strategy are those with chemosensitive disease, who have received less than three chemotherapy regimens, and do not have high-risk FL international prognostic index scores.<sup>64</sup> Addition of TBI has been shown to increase the risk of developing s-MDS/s-AML in some studies and

therefore non-TBI-based regimens should be used when feasible.<sup>33</sup> Maintenance therapy after transplantation may also be considered in a subset of patients, although data is lacking in those with FL.

Despite four large randomized studies comparing upfront autologous HSCT with standard chemotherapy in FL, no survival advantage was noted for the HSCT arms. Two of these studies, GOELAMS<sup>9</sup> and GLSG,<sup>32</sup> reported a longer PFS in the transplant arms without survival advantage in GOELAMS, and the OS is not yet reported for GLSG. Only one upfront randomized study included rituximab in the treatment regimen, and that study also failed to show a survival advantage for HSCT despite longer EFS.<sup>43</sup> Thus, upfront autologous HSCT for FL should only be done in clinical trials.

Allogeneic HSCT has been shown to cure patients with FL. Allogeneic transplants should be offered to patients who are young, have a matched donor, and are beyond first CR. Myeloablative regimens are associated with significant TRM. Use of nonmyeloablative or RIC regimens appears very promising, but more studies and longer follow-up is needed before definite treatment recommendations can be made. There is concern regarding higher relapse rates after nonmyeloablative or RIC regimens. At our institution we offer allogeneic HSCT to younger FL patients who have good performance status, are beyond first remission, and who have a matched human leukocyte antigen donor available. These patients should be enrolled in clinical trials whenever possible.

## Disclosures

The author reports no conflict of interest in this work.

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