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Review Article

Hematopoietic Stem Cell Transplantation for Follicular Lymphoma : Optimal Timing and Indication

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The definitive management of advanced follicular lymphoma (FL) remains controversial due to various treatment options, including watchful waiting, single-agent or combination chemotherapy, monoclonal antibody, and radioimmunotherapy. These options can provide prolonged progression-free survival. However, they cannot cure advanced FL. Allogeneic hematopoietic stem cell transplantation (allo-SCT) remains the sole curative therapy for FL. Allo-SCT has had a major impact with the use of reduced-intensity conditioning regimens because of its lower associated nonrelapse mortality compared with myeloablative regimens. Autologous SCT (auto-SCT) shows high response rates and extends progression-free survival in patients with chemosensitive relapse. In the rituximab era, however, associated comorbidities, risk of secondary cancers, and presence of refractory disease have become problematic in the auto-SCT population. On the basis of results from large-scale randomized trials, upfront auto-SCT is not recommended. Novel conditioning regimens including radioimmunotherapy followed by either auto-SCT or allo-SCT are likely to show efficacy even in chemorefractory disease. Consequently, the optimal timing for SCT remains a matter of opinion, except for patients in first remission. However, the outcomes of allo-SCT and auto-SCT keep on improving. Physicians should note that there is no therapy with a track record equivalent to that of SCT for relapsed or refractory FL. 〔*J Clin Exp Hematop 54(1): 39-47, 2014*〕

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INTRODUCTION

The median overall survival (OS) of patients with follicular lymphoma (FL) was approximately 10 years. However, the availability of the chimeric anti-CD20 monoclonal antibody (mAb) rituximab has demonstrated survival benefits.[1] Nonetheless, FL remains incurable regardless of the use of rituximab in combination with chemotherapy and as maintenance therapy, or radioimmunotherapy with an anti-CD20 antibody linked to yttrium-90 (ibritumomab tiuxetan) or to iodine-131 (tositumomab). Some patients develop progressive or transformed disease at an early stage, with 15% dying within 2 years of diagnosis, whereas others remain alive for decades without requiring treatment.[2] Despite the development of numerous treatment strategies to reduce the risk of progression, optimal therapeutic strategies for patients with FL remain undefined.

The role and timing of hematopoietic stem cell transplantation (SCT) in the management of FL are controversial. While high-dose therapy (HDT) with autologous SCT (auto-SCT) has low treatment-related mortality (TRM) and morbidity, disease relapse remains a major concern. Myeloablative (MA) allogeneic SCT (allo-SCT) is a potentially curative modality ; however, it is often associated with prohibitive TRM, particularly in frailer patients. This treatment modality has typically been offered to younger patients later in the course of their disease due to the long natural history of this disease and the higher risk associated with this procedure. However, improved supportive care, more accurate donor selection, and reduced-intensity conditioning (RIC) regimens have lowered nonrelapse mortality (NRM) and broadened eligibility for allo-SCT. Here, the available published data pertaining to the role and optimal timing of SCT in patients with FL are reviewed.

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AUTO-SCT

Upfront setting

Auto-SCT has been extensively studied in FL as a consolidation strategy for chemosensitive indolent disease.[3-14] Many of these studies demonstrated a significant improvement in PFS compared with historical controls. In the pre-rituximab era, 3 randomized controlled trials conducted by European groups compared the efficacy of auto-SCT with that of conventional therapy followed by interferon maintenance (Table 1).[11,13,14] Progression-free survival (PFS) was significantly higher in the SCT arms in 2 of the 3 trials, but the two arms showed no difference in OS among all 3 trials. In the SCT arms, the incidences of therapy-related malignancies were significantly increased. In the rituximab era, an Italian group conducted a randomized controlled trial comparing standard therapy with auto-SCT in patients with high-risk FL. Enrolled patients (n = 134) were randomized to receive CHOP followed by rituximab or rituximab-supplemented high-dose sequential chemotherapy with auto-SCT.[15] With a median follow-up of 51 months, the 4-year event-free survival (EFS) was significantly higher in the SCT arm (61% vs. 28%, $P < 0.001$), but the two arms showed no difference in OS. The molecular remission (MR) rates were 44% in the standard therapy arm and 80% in the SCT arm ($P = 0.002$). Patients in MR had a better PFS than those without MR ($P < 0.001$). Interestingly, patients in the conventional chemotherapy arm who relapsed were crossed over to the SCT arm, which resulted in a 3-year EFS of 68% after a median follow-up of 30 months. These results suggest that administering rituximab with induction and salvage chemotherapy may overcome HDT and auto-SCT. The above 4 trials demonstrated a significant improvement in PFS, but no impact on OS.

One reason for the lack of impact on OS has been the excess number of second malignancies, that is, myelodysplastic syndrome (MDS), acute myelogenous leukemia (AML), and solid tumors. The cumulative incidence of developing therapy-related MDS/AML after auto-SCT ranges from 4% to 20%, as reported in the literature, and occurs at a median of 2.5-7 years after auto-SCT.[12,16,17] Risk factors of therapy-related MDS/AML include receipt of alkylator, fludarabine (Flu), and total-body irradiation (TBI)-based conditioning regimens, especially TBI doses of 13.2 Gy.[10,17,18] The use of a TBI-containing regimen was associated with a higher risk of developing therapy-related MDS/AML in a retrospective study of FL patients from the European Blood and Marrow Transplant Group (EBMT).[12] The cumulative incidence of developing solid tumors after auto-SCT in patients with non-Hodgkin lymphoma (NHL) who received a TBI-based regimen was 10% at 10 years, at the Dana-Farber Cancer Institute.[19] Subsequently, their long-term results showed that the cumulative incidence of second malignancy, with death without second malignancy a competing risk, was 16% at 10 years and was estimated to be 38% at 15 years.[20] In the upfront auto-SCT cohort, 9.4% of patients died of secondary malignancy (8 MDS/AML and 1 metastatic breast cancer). Therefore, auto-SCT as consolidation therapy in first remission (CR1) patients is not recommended.

Salvage setting for relapsed disease

Auto-SCT for patients with relapsed disease plays a more important role in managing FL than for patients in CR1. Several studies including prospective trials reported high response rates, with 5-year PFS ranging from 40% to 50%.[12,18,21-24] Combined data from St. Bartholomew's Hospital and the Dana-Farber Cancer Institute showed 10-year freedom from progression of 48%.[18] On the subject of prognostic factors, patients with chemosensitive disease, those not heavily pretreated, and those having a lower-risk Follicular Lymphoma International Prognostic Index (FLIPI) score at auto-SCT had improved OS.[21,25] The impact of histological grade on outcome is controversial. A Seattle group indicated no effect of having a higher grade (grade 3 vs. grades 1-2) of FL at auto-SCT, whereas a Nebraska group showed inferior outcomes of patients with grade 3 FL.[21,26]

In the pre-rituximab era, EBMT reported the outcomes of

Table 1. Randomized prospective trials addressing the role of auto-SCT for FL in first remission

Study group (year)	N	Median age in Auto vs CT	Conditioning	Median follow-up (months)	OS in Auto vs CT	PFS in Auto vs CT	TRM in Auto vs CT	Secondary malignancy with Auto vs CT
GLSG (2004)[13]	307	49 vs 49	TBI/Cy	50	Not reported	65% vs 33% (5 yrs)	< 2.5% in both arms	3.5% vs 0% (MDS/AML)
GELA (2006)[11]	401	49 vs 49	TBI/Cy/VP-16	92	76% vs 71% (7 yrs)	38% vs 28% (7 yrs)	Not reported	n = 11 vs n = 14
GOELAMS (2009)[14]	166	51 vs 50	TBI/Cy	108	76% vs 80% (9 yrs)	64% vs 39% (9 yrs)	Not reported	n = 12 vs n = 1
GITMO (2008)[15]	136	51 vs 51	MITO/MEL	51	81% vs 80% (4 yrs)	61% vs 28% (4 yrs)	n = 3 vs n = 2 (100 days)	6.6% vs 1.7% (4-yr MDS/AML)

auto-SCT, autologous hematopoietic stem cell transplantation; FL, follicular lymphoma; GLSG, German Low Grade Lymphoma Study Group; GELA, groupe d' etude des lymphomes de l'adulte; GOELAMS, groupe ouest-est des leucemies et autres maladies du sang; GITMO, gruppo italiano trapianto di midollo osseo; TBI, total body irradiation; Cy, cyclophosphamide; VP-16, etoposide; MITO, mitoxantrone; MEL, melphalan; OS, overall survival; Auto, high-dose therapy and auto-SCT; CT, chemotherapy; PFS, progression-free survival; TRM, treatment-related mortality; MDS, myelodysplastic syndrome; AML, acute myelogenous leukemia

693 FL patients who underwent auto-SCT using registry data.[12] Four-fifths of the patients received auto-SCT in a disease status other than CR1. The 10-year PFS and OS for patients who were not in CR1 at auto-SCT were 28% and 48%, respectively. For the overall series, 54% developed recurrent disease at a median of 1.5 years after auto-SCT (range, 1 month to 13.5 years). The 5-year NRM was 9%. Older age, chemoresistant disease status, use of bone marrow + peripheral stem cells (PBSC) as sources of stem cells, and use of a TBI-based conditioning regimen were associated with shorter OS on multivariate analysis. Sixty-four patients (9%) developed a second malignancy at a median of 7 years after SCT (range, 1-17). A German group also reported retrospective data of 241 FL patients who underwent auto-SCT including salvage setting (36%) and prior rituximab (14%).[23] The 10-year OS and PFS were 75% and 49%, respectively. The 10-year relapse probability was 47%, with a median time to relapse of 20 months (range, 2-128). Five secondary malignancies were observed. EBMT also conducted the CUP (chemotherapy vs. unpurged auto-SCT vs. purged auto-SCT) trial, which was the only prospective randomized study comparing auto-SCT and chemotherapy in relapsed FL patients.[22] A total of 140 patients were registered, and 89 with chemosensitive disease after 3 cycles of salvage chemotherapy were randomly assigned. The 4-year OS was 46% for the chemotherapy arm, 71% for the unpurged auto-SCT arm, and 77% for the purged auto-SCT arm. This trial was closed early because of slow accrual. Notwithstanding the small number of patients, the trial showed significant PFS and OS benefits following auto-SCT. There was no reported difference in outcomes of purged compared to unpurged auto-SCT. However, since this trial was conducted in the pre-rituximab era, its significance and clinical relevance to contemporary clinical practice were questioned. The Groupe d'Etude des Lymphomes de l'Adulte/Groupe Ouest Est d'Etude des Leucémies et Autres Maladies du Sang (GELA/GOELAMS) investigated the impact of auto-SCT compared with conventional salvage chemotherapy in 175 FL patients at first relapse.[24] Seventy patients (40%) had chemotherapy with rituximab as first-line therapy, 112 (64%) had rituximab at first relapse, and 42 (24%) underwent auto-SCT. There was a significant difference in 3-year OS between patients who received auto-SCT and those who did not (92% vs. 63%, respectively; $P = 0.0003$). Frontline rituximab exposure did not affect outcome. Although auto-SCT affected event-free survival and OS in multivariate analysis, this retrospective study may have been affected by selection bias since only patients responding to salvage therapy proceeded to auto-SCT. Whether post-auto-SCT rituximab maintenance will improve clinical outcomes is an area of active investigation but, at the moment, it cannot be considered a standard option.[27-30]

On the basis of a search of the literature, patients who are chemoresistant, had 3 or more prior chemotherapy regimens, have a poor performance status, and are older than 70 years of age should not receive auto-SCT. In other words, good candidates for auto-SCT are patients who are in second CR or partial remission (PR), do not have BM involvement, have a good performance status, and who are not candidates for curative therapies, namely, allo-SCT, because of donor unavailability, associated comorbidities, or patient preference. Heavily pretreated patients with refractory disease are unlikely to benefit from HDT and should be considered for participation in clinical trials. Auto-SCT can be considered for patients who are medically unfit for RIC allo-SCT or those without even an alternative donor, with the understanding that a cure may not be achievable. For patients with limited stage at the time of relapse, thoughtful consideration should include offering nontransplant treatment, namely, radiotherapy and/or conventional chemotherapy.

In vivo *autograft purging*

To eliminate autograft contamination and obtain molecular remission after SCT, *in vivo* methods of graft purging have been explored. After rituximab became available, *in vitro* graft purging procedures were mostly replaced by *in vivo* purging. A Pavia group demonstrated that the concurrent administration of rituximab and HD-cytarabine (AraC) was a safe and efficient method to obtain *in vivo* purged polymerase chain reaction (PCR)-negative PBSC in patients with indolent lymphoma (14 relapsed/refractory FL and 2 refractory mantle cell lymphoma [MCL]).[31] A Milan group reported an early trial of intensive rituximab-based salvage chemotherapy and mobilization chemotherapy for 36 patients with relapsed/refractory FL.[32] All patients were successfully mobilized after HD-cyclophosphamide (Cy) with rituximab (primary harvest) and HD-AraC with rituximab (secondary harvest). After HD-Cy, a PCR-negative graft was collected in 68% of patients, while after HD-AraC, it was collected in 97%. The 12-year OS and PFS were 70% and 76%, respectively, with a plateau starting at 6 years. An Italian group conducted a prospective phase II trial that comprised a sequence of immunochemotherapy, *in vivo* purging using rituximab with HD-AraC and HDT with BEAM, followed by auto-SCT, in 64 patients with advanced relapsed or refractory FL.[27] Two consolidation doses of rituximab were given on days +14 and +21 after auto-SCT. In this study, durable negativity for IGH-BCL2 rearrangement after SCT was associated with long-term PFS. In contrast, patients with loss of IGH-BCL2 negativity invariably experienced PD. This may lend additional support to the concept that persistent molecular negativity is the principal determinant of long PFS in patients with FL undergoing auto-SCT.

The lack of randomized data to prove the curative potential of purged auto-SCT has prevented the uniform acceptance

of this modality. For candidates of auto-SCT, however, *in vivo* graft purging with rituximab is recommended in view of the data showing that rituximab can render PCR-negative autografts and that achievement of MR after auto-SCT is a predictor of prolonged clinical remission.

Conditioning regimens

From a global perspective, the most frequently used conditioning regimens (HDT regimens) for FL patients undergoing auto-SCT include BEAM (carmustine, etoposide [VP-16], AraC, melphalan [Mel]), BEAC (carmustine, VP-16, AraC, Cy), and CBV (Cy, carmustine, VP-16). In Japan where carmustine is not available, MCEC (ranimustine, carboplatin, VP-16, Cy), LEED (Mel, Cy, VP-16, dexamethasone), and MEAM (ranimustine, VP-16, AraC, Mel) are apparently frequently used. The combination of TBI with Cy and/or VP-16 is infrequently used since the use of TBI was associated with a higher risk of developing therapy-related MDS/AML after auto-SCT.[12,16,17]

Radiolabeled monoclonal antibodies, yttrium-90 ibritumomab tiuxetan and iodine-131 tositumomab, have been utilized as single agents or combined with high-dose chemotherapy (i. e. BEAM) as conditioning regimens before auto-SCT.[33-35] Although these treatment strategies are well tolerated and adverse events are comparable to those with chemotherapy-alone regimens, these agents are currently not routinely used with auto-SCT in view of their high price and the complicated logistical steps needed to administer them. Furthermore, radioimmunoconjugate-containing regimens do not appear to increase efficacy compared with chemotherapy-alone regimens. On the basis of these data, chemotherapy-alone conditioning regimens are favored. Other regimens should only be used within the context of a clinical trial.

ALLO-SCT

Myeloablative allo-SCT

MA allo-SCT for patients with FL was primarily offered and yielded low relapse rates and high TRM rates.[36-38] Two registry studies from the Center for International Blood and Marrow Transplant Research (CIBMTR) and the EBMT reported the outcomes of relapsed FL patients who underwent either auto-SCT or MA allo-SCT.[36,39] In both studies, the relapse risk was significantly lower in the allo-SCT group than in the auto-SCT recipients. Relapse after allo-SCT was noted within 2-5 years, while continuous relapse occurred in the auto-SCT patents. In both studies, however, no difference in OS was seen between MA allo-SCT and auto-SCT groups (approximately 50-60%), primarily due to unacceptably high rates of TRM after MA allo-SCT (approximately 35-40% vs. 8-15% after auto-SCT). A nationwide survey in Japan for MA allo-SCT in NHL (n = 233) reported durable remissions in relapsed or refractory FL patients (n = 37), with 2-year OS of 57%.[40] TRM was observed in 98 NHL patients (42%), and 68% of them were related to GVHD. In a multivariate analysis, chemoresistance at allo-SCT, prior autograft, and chronic GVHD were identified as adverse prognostic factors for TRM. Relapse or progression of FL after allo-SCT was observed in only 5 patients (13%). The University of British Columbia reported NRM of 24% and 5-year OS of 58% after typically TBI-based allo-SCT for advanced-stage FL (n = 29), including 9 chemosensitive patients.[41] The Princess Margaret Hospital reported notably low TRM of 15% and 5-year OS of 79% after non-TBI allo-SCT (n = 33) or syngeneic SCT (n = 4) typically utilizing busulfan (Bu)-Cy conditioning for chemosensitive FL.[42]

A serious late complication of allo-SCT is the occurrence of secondary malignant neoplasms. The Fred Hutchinson Cancer Research Center (FHCRC) reported that the 20-year cumulative incidences of basal cell cancer (BCC) and squamous cell cancer (SCC) were 6.5% and 3.4%, respectively.[43] TBI was a significant risk factor for BCC, most strongly among patients younger than 18 years old at allo-SCT. Chronic GVHD increased the risk of both BCC and SCC. A multi-institutional cohort showed that TBI exposure was associated with nonsquamous cell cancers, especially breast, thyroid, bone, and brain cancers, as well as malignant melanoma.[44] The risk of secondary solid cancers reached 3-fold among patients followed for 15 years or more after allo-SCT.

Reduced-intensity conditioning allo-SCT

RIC regimens were developed to improve the applicability of allo-SCT to older, heavily pretreated patients, particularly those with associated medical comorbidities. These regimens confer adequate immunosuppression to facilitate engraftment with a minimal to moderate amount of cytoreduction, aim at reducing transplant-related toxicities, and rely more heavily on the donor-mediated GVL effects rather than the cytoreduction due to HDT. Table 2 provides outcomes of recent studies of relapsed or refractory FL patients undergoing allo-SCT. All 12 studies mainly included patients who had received RIC or nonmyeloablative (NMA). Seven of 12 studies were conducted as prospective phase I or II trials. All of these 7 prospective trials looked into the feasibility and efficacy of RIC or NMA conditioning allo-SCT.

A report from the M. D. Anderson Cancer Center attracted attention due to its excellent long-term outcomes (the longest follow-up of 107 months).[45] Forty-seven patients with relapsed FL received the FCR (Flu, Cy and rituximab) conditioning regimen that uniquely incorporated a high dose of rituximab, in which 3 of the 4 planned doses were given at 1,000 mg/m^2 (days −6, +1, +8). The 11-year EFS and OS in

Table 2. Studies of allo-SCT in relapsed or refractory FL since 2008

Author (year)	N	Age (range)	Conditioning	Chemo-refractory	Prior CT regimens > 3	Related donor	Unrelated donor	PBSC	BM	Median follow-up (months)	OS	PFS	NRM	RI
Khouri *et al*. (2012)[49,a]	47	53 (33-68)	NMA (Flu/Cy/R)	0%	36%	96%	4%	96%	4%	107	78% (11 yrs)	72% (11 yrs)	13% (1 yr)	6%
Rezvani *et al*. (2008)[50,a]	54 (62[c])	54 (33-66)[c]	NMA	37%	6 (1-19)[d]	55%	45%	100%	0%	37	52% (3 yrs)	43% (3 yrs)	42% (3 yrs)	14% (3 yrs)
Hari *et al*. (2008)[57,b]	120	44 (27-70)	MA	28%	32%	100%	0%	37%	63%	50	71% (3 yrs)	67% (3 yrs)	25% (3 yrs)	8% (3 yrs)
	88	51 (27-70)	RIC	32%	43%			9%	91%	35	62% (3 yrs)	55% (3 yrs)	28% (3 yrs)	17% (3 yrs)
Avivi *et al*. (2009)[58,b]	44	42 (30 –55)	MA	34%	46%	0%	100%	55%	45%	36	47% (3 yrs)	43% (3 yrs)	37% (3 yrs)	20% (3 yrs)
	87	51 (30 –66)	RIC	23%	63%			69%	31%		53% (3 yrs)	49% (3 yrs)	33% (3 yrs)	
Thomson *et al*. (2010)[55,a]	82	45 (26-65)	RIC (Flu/Mel/Alem)	9%	4 (1-8)[d]	48%	52%	87%	13%	43	76% (4 yrs)	76% (4 yrs)	15% (4 yrs)	26% (4 yrs)
Pinana *et al*. (2010)[51,a]	37	50 (34-62)	RIC (Flu/Mel)	18%	27%	100%	0%	100%	0%	52	54% (4 yrs)	57% (4 yrs)	35%	8%
Bethge *et al*. (2010)[59,a]	17 (40[c])	55 (34-68)[c]	RIC (^{90}Y/Flu/2 Gy TBI)	15%[c]	4 (2-8)[c,d]	33%[c]	67%[c]	100%	0%	22[c]	67% (2 yrs)	57% (2 yrs)	45% (2 yrs)[c]	36%[c]
Abou-Nassar et al. (2011)[60,b]	12	55 (40-66)	RIC (^{90}Y/Flu/Bu)	42%	5 (2-10)[d]	25%	75%	92%	0%	31	83% (2 yrs)	74% (2 yrs)	18% (1 yr)	8%
Shea *et al*. (2011)[52,a]	16 (44[c])	53 (39-68)[c]	NMA (Flu/Cy)	0%	2 (1-3)[d]	100%	0%	100%	0%	55	81% (3 yrs)	75% (3 yrs)	9% (3 yrs)[c]	19%
Khouri *et al*. (2012)[49,a]	26	55 (29-66)	RIC (^{90}Y/Flu/Cy)	38%	3 (2-7)[d]	62%	38%	96%	4%	33	88% (3 yrs)	83% (3 yrs)	8% (1 yr)	8%
Ono *et al*. (2012)[53,b]	19	47 (34-58)	RIC (Flu/Mel)	68%	37%	32%	68%	11%	89%	75	84% (5 yrs)	84% (5 yrs)	16%	0%
Tada *et al*. (2012)[54,b]	46	50 (31-67)	RIC (Flu/Bu-based, 85%), MA (15%)	63%	52%	50%	50%	50%	46%	66	77% (5 yrs)	70% (5 yrs)	16% (5 yrs)	15% (5 yrs)

allo-SCT, allogeneic hematopoietic stem cell transplantation; FL, follicular lymphoma; NMA, nonmyeloablative conditioning; MA, myeloablative conditioning; RIC, reduced-intensity conditioning; Flu, fludarabine; Cy, cyclophosphamide; R, rituximab; Mel, melphalan; Alem, alemtuzumab; ^{90}Y, ibritumomab tiuxetan; TBI, total body irradiation; Bu, busulfan; CT, chemotherapy; PBSC, peripheral blood stem cell; BM, bone marrow; OS, overall survival; PFS, progression-free survival; NRM, nonrelapse mortality; RI, relapse incidence

a, Prospective study; b, Retrospective study; c, For the whole indolent B-NHL cohort; d, The median number of prior chemotherapy regimen (range)

that study were 72% and 78%, respectively, with only 3 relapses observed. On the basis of these impressive results, the Blood and Marrow Transplant Clinical Trials Network is conducting a multicenter phase II trial using the same FCR regimen in chemosensitive relapsed FL patients who have either a matched related or unrelated donor. Since accrual has been completed, we have to wait until the results are released. However, care should be taken when interpreting the outcomes of the above 2 trials on the FCR regimen because only chemosensitive patients were enrolled. The FHCRC reported the results of a prospective study of NMA (2 Gy TBI with or without Flu) allo-SCT in relapsed or refractory indolent NHL (n = 62).[46] The majority of patients (87%) had a diagnosis of FL, including 14 patients with follicular large-cell lymphoma or FL grade IIIA. Disease transformation to a diffuse aggressive histology was documented in 16 patients (26%). At the time of SCT, 16 patients were in CR, 23 in PR, 14 (23%) with refractory disease, and 9 (14%) with relapsed disease (untreated in the 2 months before SCT). The 3-year OS and PFS rates were 52% and 43%, respectively, for patients with indolent disease. The 3-year NRM was 42% for the overall series. Two Spanish prospective multicenter trials included 37 patients with FL who underwent RIC (Flu and Mel) allo-SCT.[47] At the time of SCT, 14 patients were in CR, 16 in partial remission, and 7 (19%) had refractory or progressive disease after salvage chemotherapy. The 4-year OS rates for patients in CR, PR, or with refractory or progressive disease were 71%, 48%, and 29% (P = 0.09), whereas the 4-year NRM were 26%, 33%, and 71%, respectively. The incidence of relapse for the whole group was only 8%. Cancer and Leukemia Group B conducted a phase II study to evaluate the safety and efficacy of an RIC regimen with allo-SCT for recurrent low-grade B-cell malignancies.[48] Sixteen patients (36%) had FL. The 3-year OS and EFS rates were 81% and 75% for the FL patients. The 3-year TRM was 9%.

By contrast, in 2 retrospective studies of allo-SCT for relapsed or refractory FL from Japan, using FM (Flu and Mel)-based or FB (Flu and Bu)-based RIC in a majority of cases,[49,50] the percentages of patients who had chemoresistant disease at allo-SCT were notably higher (63%-68%) than from other series from North America or Europe (Table 2). Nevertheless, the 5-year PFS and OS in those studies were 70%-84% and 77%-84%, respectively, with low NRM (16% for each study). To confirm these excellent data, conducting a multicenter prospective study of FB-based or FM-based conditioning regimens for heavily treated, chemoresistant patients with FL would be a direction in the development of allo-SCT for FL.

A British group conducted a large prospective study of RIC allo-SCT for FL and employed *in vivo* T-cell depletion (TCD) with alemtuzumab.[51] In this study, 43 of 82 enrolled patients (52%) underwent unrelated donor SCT. Ten percent of patients had refractory disease. The 4-year PFS, OS, and TRM rates were 76%, 76%, and 15%, respectively. The incidence of grade 2-3 acute GVHD was 13% and the 4-year cumulative incidence of extensive chronic GVHD was only 18%. The relapse rate was slightly high (26%) and donor lymphocyte infusion was frequently needed, likely because of the use of TCD.

To assess the role of *in vivo* TCD in patients with advanced FL undergoing RIC allo-SCT, the EBMT retrospectively analyzed the outcomes of 164 patients who had a

matched sibling donor and were conditioned with Flu plus an alkylating agent.[52] For the purpose of this study, patients were divided into 3 groups: the first group received rabbit antithymocyte globulin (ATG; n = 46), the second group received alemtuzumab (n = 42), and the third group received neither agent (n = 76). Although the patients in the TCD group experienced significantly lower incidences of acute and chronic GVHD than the non-TCD group, there was no difference in NRM between the two groups; however, the use of TCD was associated with a significantly higher 3-year relapse rate (28% vs. 14%, $P = 0.05$). The most noticeable predictor of all outcomes (relapse, NRM, PFS, and OS) was disease status at allo-SCT.

Two retrospective studies using registry data compared traditional MA conditioning regimens to RIC in FL. The CIBMTR reported the outcomes of allo-SCT only from HLA-identical siblings (n = 208).[53] There was no difference in PFS and OS based on conditioning regimen. However, the risk of disease progression was significantly higher in the RIC group (relative risk = 2.97, $P = 0.04$). The EBMT reported the outcomes only from HLA-matched unrelated donors (n = 131).[54] Contrary to the CIBMTR study, RIC regimens were associated with a lower NRM (relative risk = 2.5, $P = 0.01$) and significantly longer PFS and OS (relative risk = 2.2, $P = 0.01$), and relapse was comparable between the two groups. In both the CIBMTR and the EBMT studies, chemoresistance and a lower performance status were found to affect TRM, OS, and PFS. In view of the increased risk of progression that the CIBMTR observed, further validation is recommended in a larger dataset with a longer follow-up or a prospective cohort.

The indications for MA regimen rather than RIC regimen are rarely discussed since evidence in these studies has showed that chemosensitivity at allo-SCT rather than conditioning intensity is the most trustworthy predictor of outcome. Therefore, an MA regimen should not be recommended for FL patients, besides in a clinical trial, even for patients with stable or progressive disease at the time of allo-SCT. In addition, at the moment, it is difficult for physicians practically to decide the timing of RIC allo-SCT for FL having a generally prolonged course because no clinical trials have directly examined the optimal timing of SCT. On an individual basis, conducting multicenter phase II studies of third- or fourth-line chemotherapy (or chemoimmunotherapy) followed by RIC allo-SCT for FL is warranted. Well-designed and feasible prospective clinical trials should be conducted.

Novel conditioning regimens

RIC allo-SCT is a potentially curative therapeutic option for patients with advanced FL, but disease relapse remains a cause of treatment failure. Radioimmunoconjugates administered before RIC allo-SCT may enhance cytoreduction and allow more time for the GVL effect to develop without the associated toxicity of MA allo-SCT. The M. D. Anderson group published the results of a prospective clinical trial of RIC allo-SCT using a ^{90}YFC (^{90}Y-ibritumomab tiuxetan, Flu, Cy) regimen for advanced FL (n = 26).[45] Ten patients (38%) had chemorefractory disease. With a median follow-up of 33 months, the 3-year PFS rates for patients with chemorefractory and chemosensitive disease were 80% and 87%, respectively ($P = 0.7$). The 1-year TRM was 8%. A German group reported a phase II study combining radioimmunotherapy (RIT) using ^{90}Y-ibritumomab tiuxetan with RIC using Flu and 2 Gy TBI followed by allo-SCT from related (n = 13) or unrelated donors (n = 27) for advanced NHL (17 FL, 13 chronic lymphocytic leukemia, 8 MCL, and 2 other histologies).[55] Disease status at SCT was CR in 7 patients, PR in 27 patients, and SD in 6 patients (i. e. 15% of chemorefractory disease). The 2-year OS and EFS for patients with FL were 67% and 57%, respectively. However, the 2-year NRM was 45% for all patients. NRM for patients transplanted from an HLA-matched related donor was 16% versus 58% from an unrelated donor ($P = 0.073$). Causes of deaths were infections (n = 8; 6 sepsis, 1 aspergillosis, and 1 viral encephalitis), GVHD (n = 7), and cerebral bleeding (n = 1). The Dana-Farber Cancer Institute retrospectively described the outcomes of 12 patients with FL who received ^{90}Y-ibritumomab tiuxetan followed by RIC (Flu + Bu) allo-SCT.[56] Two patients (17%) had transformed to a more aggressive histology and 5 (42%) had chemorefractory FL. The 2-year OS, PFS, and NRM were 83%, 74%, and 18%, respectively. On the basis of the results of these studies, RIT-containing RIC allo-SCT is a promising modality in patients with chemorefractory FL. However, for auto-SCT, these agents are currently not routinely offered with allo-SCT due to their high cost and the complex logistical steps needed to administer them. On the basis of the current data, chemotherapy-only conditioning regimens, with or without low-dose TBI to enhance stem cell engraftment, are favored.

The use of tandem auto-SCT followed by allo-SCT has also been studied. A Montreal group reported the outcomes of tandem BEAM or BEAC auto-SCT/NMA (Flu and Cy) allo-SCT for 27 patients with FL.[57] Five patients (19%) demonstrated histological progression toward an aggressive lymphoma. Disease status before auto-SCT included 8 patients (30%) in CR, 14 (52%) in PR, and 5 (19%) refractory. OS and PFS rates at 3 years after NMA allo-SCT were both 96%. Only 1 patient died from GVHD-related complications, at 7 months after allo-SCT. Marseille and Milan groups reported the results of 34 high-risk relapsed NHL patients, including 14 patients with FL, who underwent tandem BEAM or high-dose Mel auto-SCT followed by RIC (Flu + Bu + ATG or Flu + Cy with or without thiotepa) allo-SCT.[58] The 5-year OS and PFS were 77% and 68%, respectively, with a 2-year TRM of 6%. The clinical implications of preceding

auto-SCT before RIC allo-SCT should be confirmed by further large-scale studies.

CONCLUSIONS

The optimal timing and optimal conditioning regimen of SCT for FL remain controversial, except for in patients in first remission. On the basis of results from large-scale randomized trials, upfront auto-SCT is not recommended. Patients with relapsed FL who are auto-SCT candidates (non-allo-SCT candidates) should be guided to SCT before they are thought to be "heavily pretreated." A few studies have demonstrated that outcomes are more favorable if patients have received fewer than 3 prior regimens. The relapse rate is notably lower with allo-SCT than with auto-SCT. Fortunately, the NRM associated with allo-SCT has declined with the use of RIC regimens, and clear plateaus in survival and relapse are now frequently observed after RIC allo-SCT for FL. However, subsequent relapsed disease may not respond to further salvage therapy, which greatly diminishes the potential efficacy of RIC allo-SCT. If a patient has compromised cardiac or pulmonary function, then high-dose chemotherapy may not be feasible and RIC allo-SCT should be offered. In addition, for FL patients who failed a prior auto-SCT, RIC allo-SCT should be offered. For patients who are allo-SCT candidates, chemosensitivity is the most robust prognostic factor for outcomes after SCT, regardless of conditioning intensity. By contrast, some recent retrospective studies using RIC (FB-based or FM-based) regimens have demonstrated that chemosensitivity at allo-SCT was not a prognostic factor because the outcomes of FL patients with chemorefractory disease at SCT have been favorable. In our group, for patients who have received more than 3 lines of prior chemotherapy regimens and demonstrate any chemosensitivity, we favor proceeding to RIC allo-SCT if a suitable donor (matched or one-locus mismatched related or unrelated donor) can be found in a timely manner. Physicians should note that there is no therapy with an equivalent track record to that of SCT for relapsed or refractory FL.

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