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Follicular Lymphoma: Prognostic Factors, Conventional Therapies, and Hematopoietic Cell Transplantation

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INTRODUCTION

Follicular lymphoma (FL), commonly referred to as an *indolent lymphoma*, is the second most common type of non-Hodgkin lymphoma (NHL). FL has an incidence of ~15,000 new cases/year in the United States, and the median age is 60 years old at diagnosis [1]. Median survival rates have historically reported to be in the range of 8 to 10 years. Although the availability of newer agents, including the monoclonal antibody rituximab, has dramatically improved outcome and survival, FL remains incurable with standard therapy [2]. Moreover, clinical behavior is markedly heterogeneous with some patients developing progressive or transformed disease early and 15% dying within 2 years from diagnosis, whereas others remain alive for decades without need for treatment. With more available treatment options, including novel agents and hematopoietic cell transplantation (HCT), improved prognostication and identification of predictive markers of response are necessary to facilitate individualized risk-adapted therapy.

The hallmark genetic abnormality associated with FL is the presence of a chromosomal translocation, t(14;18)(q32;q21) or variant in 85% of the cases, which juxtaposes the immunoglobulin heavy chain gene on chromosome 14 with the *BCL2* oncogene on chromosome 18 leading to constitutive expression of the BCL2 protein. Although critical for lymphomagenesis, this early molecular event is by itself insufficient to produce FL. Overexpression of *BCL2* confers relative resistance to apoptosis, thus allowing the cells a survival advantage and facilitating the acquisition and retention of secondary genetic abnormalities that likely determines the clinical phenotype. Whereas the underlying biology of the malignant cell is a key component contributing to clinical behavior, it has become increasingly recognized that outcome in FL is influenced by a complex interplay between the malignant cell, immune cells of the microenvironment, and host constitutional genetics (Figure 1) [3].

Clinical Prognostic Factors

The International Prognostic Index (IPI) developed for aggressive lymphoma also reliably identifies risk groups in FL, however, it only classifies a small proportion of patients into the highest-risk category and, therefore, has limited utility [4,5]. In 2004, the Follicular Lymphoma International Prognostic Index (FLIPI) was published resulting from a multicenter effort [6]. It includes five adverse parameters: age >60 years, stage III to IV, hemoglobin <120 g/L, number of involved nodal areas >4, and elevated serum lactate dehydrogenase, and classifies patients into three groups with 10-year overall survival (OS) rates of 71%, 51%, and 36%, respectively. The FLIPI was subsequently shown to be predictive in patients treated with immunochemotherapy, patients in first relapse, and to correlate with the risk of transformation [7-9]. More recently, the FLIPI-2 index was published, incorporating ß2-microglobulin, lymph node size >6 cm, bone marrow involvement, anemia, and age over 60 years [10]. The majority of patients in the FLIPI-2 study cohort had received immunochemotherapy, and the 3-year progression-free survival (PFS) rates ranged from 51% to 91% (Table 1). The FLIPI and FLIPI-2 indices are useful in clinical practice and valuable for stratification in clinical trials. However, they remain a clinical surrogate for biologic heterogeneity, and marked variations in outcome remain within each risk group. In addition, they have limited ability to identify a subgroup of patients with

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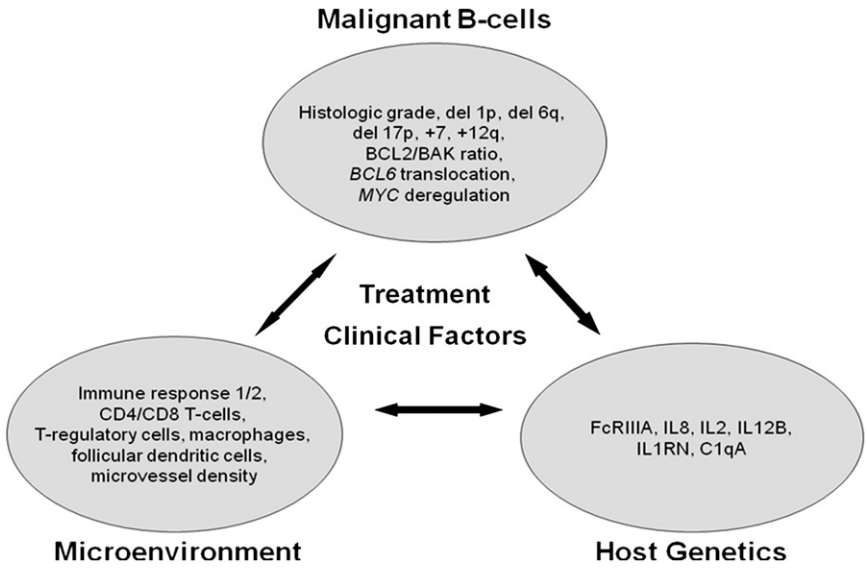

Figure 1. Factors influencing outcome in follicular lymphoma.

sufficiently poor outcomes to warrant initial intensive or alternative treatment approaches.

Histologic Grade

Three grades of FL are recognized by the World Health Organization based on the proportion of centroblasts seen in neoplastic follicles. Grade 3 has been further subclassified into grade 3a with centrocytes present, and grade 3b contains solid sheets of centroblasts. The correlation of clinical grade to clinical outcome is an unresolved debate. There is general consensus that patients with FL grades 1 and 2 behave indolently, and these entities have been merged in the recent edition of the World Health Organization [11]. FL grade 3 seems to behave more aggressively, but reports have been conflicting regarding its potential curability with anthracycline-based therapy [12,13]. It has been suggested that FL grade 3a forms part of a spectrum of indolent lymphoma with grades 1 and 2, and grade 3b may be similar to diffuse large B-cell lymphoma (DLBCL), but several reports have found no difference in outcome between FL grades 3a and 3b when treated with anthracycline-based therapy [12-14]. Grade 3 FL has historically been treated similarly to DLBCL, and any area of DLBCL within a follicular lymphoma should be diagnosed and treated like a DLBCL, according to the National Comprehensive Center Network guidelines.

Molecular Prognostic Factors

Cytogenetics

In addition to the t(14,18) translocation, the majority of patients with FL harbor additional karyotypic abnormalities at diagnosis. The mean number of alterations is highly variable, with higher numbers of alterations tending to correlate with a higher grade of FL. Recurring secondary cytogenetic events include gains of chromosome 1q, 2p, 6p, 7, 8, 12q, 18, X, and der18q, and losses of 1p, 6q, 10q, 13q, and 17p [15-19]. The genetic alterations most strongly associated with a poor prognosis have also been correlated with a higher risk of transformation and include deletions of 1p, 6q, and 17p, and gains of 7 and 12q [20]. In contrast, some studies have failed to show a link between these secondary cytogenetic changes and outcome [21]. Translocations involving *BCL6* occur infrequently in FL grades 1 and 2 but were noted in 18% of cases of FL grade 3a and 44% of FL grade 3b and have been shown to correlate with a risk of transformation [22].

Gene-expression profiling

Various studies have used gene expression profiling (GEP) to elucidate prognostic variables in FL, which highlights the major role of immune cells in

Table 1. Clinical Prognostic Indices in Follicular Lymphoma

FLIPI [6][a] (n = 1,795, patients not treated with rituximab)

Risk group	No. of Factors	% Patients	5-yr OS (%)	10-yr OS (%)
Low	0-1	36	91	71
Intermediate	2	37	78	51
High	≥3	27	53	36

FLIPI-2 [10][b] (n = 832, 68% treated with rituximab)

Risk group	No. of Factors	% Patients	3-yr PFS (%)	5-yr PFS (%)
Low	0	20	91	80
Intermediate	1-2	53	69	51
High	≥3	27	51	19

FLIPI indicates Follicular Lymphoma International Prognostic Index; OS, overall survival; PFS, progression-free survival.
[a]Adverse risk factors: age >60 yr, stage III/IV, hemoglobin <120 g/L, elevated serum lactate dehydrogenase, number of nodal sites >4.
[b]Adverse risk factors: age >60 yr, hemoglobin <120 g/L, elevated ß2-microglobulin, bone marrow involvement, nodal size >6 cm.

determining outcome [23-26]. A landmark study of GEP was performed by the Leukemia Lymphoma Molecular Profiling Project using whole biopsy specimens from 191 patients with untreated FL [24]. Two signatures of gene expression were identified that best correlated with survival prediction. The "immune-response 1" signature included genes encoding for T cell markers and genes that are highly expressed in macrophages and predicted a favorable outcome. The "immune-response 2" signature included genes that are preferentially expressed in macrophages, dendritic cells, or both, and predicted an unfavorable outcome. When patients were grouped into quartiles based on their survival-predictor scores, which reflected the signature expression levels within their biopsies, median survival ranged from 3.9 years to 13.6 years. The predictive capacity of the gene expression model was independent of the IPI and, interestingly, the gene expression signatures reflected the biologic characteristics of the nonmalignant cells within the tumor. Given the complexities of this technique, lack of validated commercially available platforms, and the requirement for fresh tissue, GEP is not yet ready for routine clinical use.

Microenvironment

Follicular lymphoma cells reside within a microenvironment that closely resembles the normal germinal center and are intimately associated with follicular dendritic cells, T cells, histiocytes, and macrophages. It is believed that interactions between these cells modulate the growth and survival of FL cells, as was suggested by GEP studies [23-25,27]. Immunohistochemistry (IHC) studies have explored the correlation between nonneoplastic cells and outcome. Conflicting results have emerged, likely due to small study cohorts, variable treatments received, and poor reproducibility of IHC methodology [28].

Tumor-associated macrophages have been evaluated using IHC for CD68. Increased macrophage content has been associated with inferior survival independent of the IPI in patients treated with chemotherapy [29]. In more recent trials, the negative impact of high macrophage content was no longer evident in patients receiving immunochemotherapy. Various subsets of T cells within the nonneoplastic cells in FL biopsies have also been found to affect prognosis. Such subsets include helper $CD4^+$ T cells, cytotoxic $CD8^+$ T cells, and immunosuppressive T-regulatory cells ($CD4^+$, $CD25^+$, and $FOXP3^+$), but the exact role exerted by these subsets is not completely understood.

Host Constitutional Genetics

In view of the prominent role played by host immune cells, the potential for host genetic factors to predict FL treatment response and prognosis has been explored [30]. Single nucleotide polymorphisms (SNPs) are changes in the DNA sequence by 1 base pair. SNPs in the *FcγR* genes may significantly alter the binding affinity between the Fc portion of rituximab and the Fc receptors on macrophages. Several studies have reported a correlation between the *FcRIIIA* genotype and outcome after single-agent rituximab in patients with FL [31,32]. Patients homozygous for 158VV *FcRIIIA* polymorphism did significantly better than the heterozygotes, 158VF. A study of patients with recurrent FL confirmed these findings and identified a second polymorphic site related to the duration of response (*FcRIIA* 131 histidine/arginine) [33]. In contrast, studies of patients with FL treated with cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP), and rituximab did not find that *FcRIIIA* or *RIIA* polymorphisms correlated with outcome [34,35].

The impact of immune response SNPs in FL was analyzed resulting in identification of a final set of four prognostically relevant immune response SNPs (*IL-8*, *IL-2*, *IL-12B*, and *IL-1RN* [30]). An outcome predictor was built using clinical and demographic factors combined with the four deleterious SNPs, which identified three risk groups with 5-year OS estimates of 96%, 72%, and 58%, respectively. These patients were treated in an era before the use of rituximab. Although these four genes strongly predicted outcome in patients with FL, none was associated with the risk of developing FL [30,36]. These results suggest that the composition and functional status of the immune cells in the tumor microenvironment of FL may be driven by the genetics of the host.

Improved biologic insight into the pathogenesis of FL highlights the complex interaction between the malignant tumor cell, nonmalignant cells of the microenvironment, and host genetic factors that ultimately help determine outcome. Although many biologic correlates have been linked to prognosis, inconsistencies in the literature and lack of validation currently limit the value of molecular prognostic indicators. Furthermore, the impact of molecular factors may vary depending on the treatment received and thus should be evaluated in the context of specific therapeutic approaches. The FLIPI and FLIPI-2 are useful clinical tools but do not provide biologic insight or identify patients with sufficiently poor outcomes to warrant alternative therapy and, thus, are of limited value in guiding the choice of initial treatment.

Treatment for FL

Conventional therapy

Although FL can undergo histologic transformation, the disease usually follows an indolent clinical course. Because most patients have advanced-stage disease, this section focuses on the treatment of advanced-stage, low-grade (grade 1-2) FL.

With a newly diagnosed patient, the first decision is whether immediate treatment is required. A "watch-and-wait" approach is appropriate in asymptomatic patients with low disease burden, such as those with no site of disease of ≥7 cm and no more than three sites of disease between 3 to 7 cm. In addition to disease burden, other indications for treatment include symptomatic extranodal disease, "B" symptoms, massive or symptomatic splenomegaly, cytopenias from extensive bone marrow involvement, or threatened end-organ function. Patients who do not require immediate treatment should be assessed periodically to determine whether treatment is indicated. In addition, a steady progression of disease over 6 months is also an indication for treatment [37].

When treatment is indicated, options include single-agent rituximab or a rituximab-chemotherapy combination. For patients with a low disease burden, or who are elderly or frail, single-agent rituximab may be effective, with more than 50% of patients responding [38,39]. Other frontline options for frail or low-disease-burden patients include chlorambucil (with or without rituximab) or radioimmunotherapy (RIT). An American intergroup trial randomized 554 newly diagnosed patients with FL to either rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone (R-CHOP) vs CHOP plus iodine-131 tositumumab [40]. With a median follow-up of 5 years, there was no difference between the two arms in terms of OS, PFS, or serious adverse events.

For patients with high disease burden or severe symptoms, a rituximab/chemotherapy combination is generally used. In several studies, the addition of rituximab to various chemotherapy regimens improves PFS and even OS in some studies [41-43]. Between 2004 and 2007, in the United States, R-CHOP was the most commonly used initial regimen in patients with FL [44]. Rituximab, cyclophosphamide, vincristine, and prednisone (R-CVP) are also frequently used. Compared to R-CHOP, R-CVP is somewhat less active, but also less toxic [43]. More recently, bendamustine plus rituximab has become a popular frontline regimen based on preliminary data showing improved efficacy and reduced toxicity vs R-CHOP [45].

After first-line chemoimmunotherapy, patients may undergo observation, "maintenance" rituximab, or consolidation with RIT. The Primary Rituximab and Maintenance (PRIMA) phase 3 randomized trial studied the impact of maintenance rituximab after frontline rituximab/chemotherapy treatment [46]. An improved 3-year PFS was reported in favor of rituximab maintenance, although no difference in OS was seen. Other studies in the frontline setting have similarly shown a benefit to maintenance rituximab after induction therapy with rituximab or CVP [47,48]. ^{98}Y-ibritumomab tiuxetan has been studied as consolidation after frontline chemotherapy (+/− rituximab). Patients receiving RIT consolidation have improved PFS compared to those observed after frontline therapy. However, interpretation of these data is limited because the majority of patients did not receive rituximab with induction [49].

There are many potential treatment options to consider for recurrent FL. When possible, patients should be enrolled on a clinical trial. Off-protocol options include (1) single-agent rituximab with or without maintenance rituximab, (2) various chemotherapy regimens (+/− rituximab) including bendamustine, CHOP, chlorambucil, fludarabine, or platinum-based regimens, (3) RIT, or (4) external-beam radiation therapy [37]. In general, for patients previously exposed to (or resistant to) rituximab, these approaches are associated with a median PFS in the 6- to 18-month range. Such treatments may also be used as cytoreductive strategies before HCT. In selecting treatment, one needs to consider which therapies have been previously administered, prior response, number of relapses, and patient factors such as age, comorbidities, and the patient's goals of therapy. For example, with an early relapse (<12 months), a non-cross-resistant regimen is suggested (eg, bendamustine if R-CHOP was used previously). Additionally, adding rituximab may be beneficial if the patient previously had a response to a rituximab-containing regimen that lasted at least 6 months.

Novel Agents

A wide variety of commercially available novel agents show promise in FL. These include the proteosome inhibitor, bortezomib, the fully humanized anti-CD20 antibody, ofatumumab, the mammalian target of rapamycin (mTOR) inhibitors, everolimus and temsirolimus, and the histone deacetylase inhibitor, vorinostat.

Bortezomib, a selective inhibitor of the 26S proteasome, has been studied in both the relapsed/refractory and frontline treatment of FL. In a large randomized phase 3 trial of relapsed rituximab-naïve or rituximab-sensitive FL, single-agent rituximab was compared to the combination of bortezomib and rituximab. The bortezomib plus rituximab arm had a median PFS of 12.8 months vs 11.0 months in the rituximab alone arm [50]. The combination of bendamustine, bortezomib, and rituximab showed an 88% overall response rate (including 53% complete response) in 63 patients with relapsed/refractory FL. PFS was 14.9 months [51]. Due to the high activity of this regimen, bendamustine, bortezomib, and rituximab are now being tested in the frontline setting as one arm of the ongoing Eastern Cooperative Oncology Group 2408 protocol. Adding bortezomib to R-CVP is also feasible and well tolerated with a complete response rate comparing favorably to historical controls [52].

The immunomodulatory agent, lenalidomide, was tested as a single agent in relapsed or refractory

indolent NHL, with a 27% overall response rate in patients with FL. Median duration of response was longer than 16.5 months [53].

A large number of monoclonal antibodies are undergoing evaluation for B cell NHL, including FL. These novel antibodies target distinct CD20 epitopes, or non-CD20 surface markers. These agents may offer therapeutic advantages such as higher potency for antibody-dependent or complement-mediated cytotoxicity and may overcome rituximab resistance or lead to additive/synergistic effects when combined with other therapeutic agents. Ofatumumab is a fully humanized monoclonal antibody that targets a distinct epitope on the CD20 molecule. In relapsed/refractory FL, an overall response rate of 42% was seen, with a median duration of response 29.9 months [54]. However, in a separate study of ofatumumab in rituximab-refractory patients, a response rate of only 11% was seen [55]. In previously untreated patients, ofatumumab was combined with CHOP chemotherapy with complete responses seen in 69% and an overall response rate up to 100%, with favorable toxicity profiles [56].

The PI3K/Akt/mTOR signaling pathway is activated in many lymphoid malignancies and is therefore an attractive target for therapy. Everolimus and temsirolimus are first-generation mTOR inhibitors that are Food & Drug Administration-approved for the treatment of renal cell carcinoma. Everolimus as a single agent produced a 50% response rate in 16 patients with FL [57]. Temsirolimus also shows promising activity in patients with relapsed FL, with an overall response rate of 35% [58].

The histone deacetylase inhibitor, vorinostat, has been evaluated in patients with relapsed/refractory indolent lymphoma. Of the 17 patients with FL, a 47% overall response rate was reported, with a median PFS of 15.6 months [59].

In addition to the current commercially available agents discussed previously, a large number of other novel agents are under development. These include novel monoclonal antibodies, antibody/toxin conjugates, as well as agents which target B cell receptor signaling (fostamatinib, PCI-32765), protein kinase C (enzastaurin), PI3K (CAL-101), the proteosome, HDACs, and others [60].

HCT

For patients with FL with advanced disease, HCT has been used as an alternative approach, especially to younger patients but typically was offered late in their course because of the long natural history inherent to this disease and the nonrelapse mortality (NRM) associated with HCT. However, refinements in HCT including improved donor selection, better supportive care, and allogeneic reduced-intensity conditioning regimens have lowered NRM and thus broadened eligibility.

Autologous HCT

Several trials have unequivocally reported improved disease-free survival (DFS) with one randomized trial showing an OS benefit in patients with chemosensitive relapsed FL [61,62]. The European Blood and Marrow Transplant (EBMT) conducted the CUP trial (chemotherapy vs unpurged arm vs purged arm) that prospectively addressed the role of autologous HCT in 140 patients with relapsed FL [63]. There was a significant reduction in hazard rates for both PFS and OS when comparing the chemotherapy- only patients and the combined groups of patients with autologous HCT. The 4-year OS was 46% for the chemotherapy arm, 71% for the unpurged arms, and 77% for the HCT purged arms. The sample sizes in the two HCT arms were too small to measure the effect of ex vivo purging. Unfortunately, this trial closed early due to slow accrual and was also conducted in the pre-rituximab era, which limits the relevance of the previously mentioned findings. The Groupe d'Etude des Lymphomes de l'Adulte/Group Ouest-Est des Leucemies et des Autres Maladies du Sang (GELA/GOELAMS) groups retrospectively examined the impact of autologous HCT in patients with FL at first relapse [64]. In this series of 175 patients, the 3-year OS was significantly higher in patients who proceeded to HCT vs patients who did not undergo HCT (92% vs 63%; $P = .0003$). This study included patients who received prior rituximab. However, as this was a retrospective study, the favorable impact of HCT may have been affected by selection bias because only patients responding to salvage therapy proceeded to HCT. The addition of radioimmunoconjugates to high-dose chemotherapy has also been explored in this setting [65,66].

Autologous HCT as consolidation in first complete remission has not shown an OS benefit compared to conventional chemotherapy alone based on four large randomized European trials and thus cannot be recommended as part of frontline therapy [67-70]. Three of the four trials showed a higher event-free survival (EFS) or PFS in the HCT arms compared to conventional chemotherapy, but there was no advantage in OS in all four trials. Additionally, the cumulative incidence of secondary malignancies was notably higher in the HCT arms in three of the trials.

Myeloablative Allogeneic HCT

Allogeneic HCT (alloHCT) is the only treatment modality with curative potential for patients with advanced FL. In contrast to autologous HCT, alloHCT uses the graft-vs-lymphoma (GVL) effect mediated by donor T cells to eradicate minimal residual disease and circumvents potential tumor cell contamination in the graft. Despite the lower relapse risk associated with myeloablative alloHCT, this benefit has been offset

Table 2. Prospective Trials of Reduced-Intensity Allogeneic HCT for Relapsed Follicular Lymphoma

	No. of Patients	Median Age (range)	% Prior AutoHCT	Preparation Regimen	Donor Type	DFS/EFS	OS	TRM	Median Follow-up
CALGB [85] 2011	44 (16 with FL)	53 (39-68)	0	Flu/Cy	MRD	75%	81%	9%	4.6 yr
United Kingdom [77] 2010	82	45 (26-65)	26	Flu/Mel/Alem	MRD URD	76%	76%	15%	43 mo
GELTAMO [81] 2010	37	50 (34-62)	46	Flu/Mel	MRD	57%	54%	37%	52 mo
FHCRC [84] 2008	62 (54 with FL)	54 (33-66)	32	TBI +/− Flu	MRD URD	43%	52%	42%	36 mo
MD Anderson [80] 2008	47	53 (33-68)	19	Flu/Cy/RTX	MRD URD	83%	85%	15%	60 mo

HCT indicates hematopoietic cell transplantation; autoHCT, autologous hematopoietic cell transplantation; DFS/EFS, disease-free survival/event-free survival; OS, overall survival; TRM, treatment-related mortality; CALGB, Cancer and Leukemia Group B; FL, follicular lymphoma; Flu, fludarabine; Cy, cyclophosphamide; MRD, matched related donor; Mel, melphalan; Alem, alemtuzumab; URD, unrelated donor; GELTAMO, Grupo Español de Linfomas/Trasplante Autólogo de Médula Ósea; FHCRC, Fred Hutchinson Cancer Research Center; TBI, total body irradiation; RTX, rituximab.

by the NRM associated with the intensive preparative regimen. An analysis from the Center for International Blood and Marrow Transplant Research (CIBMTR) compared the outcomes of 904 patients with FL who underwent myeloablative alloHCT, purged autologous HCT, or unpurged autologous HCT [71]. There was a 54% lower risk of relapse in the allogeneic group ($P < .001$) and a 26% reduction in relapse in the purged autograft group compared to the recipients of unpurged grafts. After 1 year, a plateau in relapse risk was observed in the allogeneic recipients as opposed to a continuous pattern of treatment failure in the autologous group. The EBMT reported the outcomes of 1,185 patients with NHL including 231 patients with low-grade NHL who underwent myeloablative alloHCT and compared the results with 14,687 autologous HCT recipients [72]. Although relapse risk was significantly lower among the allogeneic recipients, OS was comparable between the autologous and allogeneic recipients due to the prohibitive 4-year treatment-related mortality (TRM) of 38%. Three single-institution retrospective analyses have shown long-term DFS in patients with FL including patients with chemoresistant disease after myeloablative allogeneic HCT. The 5-year EFS from these three series ranged from 45% to 75%, and outcomes varied depending on chemosensitivity at the time of HCT [73-75].

Allogeneic Reduced-Intensity HCT

Reduced-intensity conditioning (RIC) incorporates a less intensive preparative regimen and relies more on the immunotherapeutic effects of the allograft to confer antitumor activity rather than the cytoreduction of high-dose chemotherapy. The goal of RIC is to adequately immunosuppress the recipient to allow engraftment of donor cells with a minimal to moderate amount of cytoreduction. RIC regimens are being increasingly used, and results have been highly encouraging. Such regimens are associated with a lower risk of NRM and can be offered to older patients in contrast to ablative regimens. Among the various NHL histologies, the GVL effect seems to be the most potent against the indolent histologies, especially in patients with FL [76].

Table 2 provides details on five selected prospective trials of patients with FL undergoing RIC alloHCT with four of the five trials including patients who had failed a prior autologous HCT. The largest prospective series originates from the United Kingdom in which 82 patients with FL (21 patients had failed a prior autologous HCT) underwent a conditioning regimen of fludarabine, melphalan, and alemtuzumab [77]. The alemtuzumab was administered for the main purpose of in vivo T cell depletion (TCD). Grade 2 to 3 acute graft-versus-host disease (GVHD) was seen in only 13% of patients, and the 4-year cumulative incidence of extensive chronic GVHD was 18%. The 4-year PFS was 76% for all patients, but when analyzed by donor type, the PFS increased to 90% for recipients of matched sibling donors and was 64% for recipients of unrelated donor grafts. Relapse risk was 26% and was significantly higher in patients with persistently mixed donor chimerism vs patients who achieved full donor chimerism (relapse incidence: 40% vs 14%, respectively; $P = .01$). Additionally, 13 patients who relapsed received donor lymphocyte infusion with nine patients experiencing a sustained remission, which lends further support to the GVL effect against FL.

A retrospective series from the EBMT group aimed to assess the impact of in vivo TCD in patients with advanced FL undergoing RIC alloHCT from matched sibling donors [78]. For analytical purposes, patients were divided into groups who received antithymocyte globulin (n = 46), patients who received alemtuzumab (n = 42), and patients who received neither agent in the preparative regimen (n = 76). The incidences of acute and chronic GVHD were significantly lower in the in vivo TCD group compared with patients not receiving a TCD agent (acute, 17% vs 31%, respectively; $P = .04$; and chronic 33% vs

73%, respectively; $P < .01$). However, the use of a TCD agent did not affect NRM despite the lower incidence of GVHD. Disease status at HCT was the only factor that emerged as a true predictor of outcome. The French Society of Bone Marrow Graft Transplantation and Cellular Therapy retrospectively reported the outcomes of 73 patients with FL after RIC alloHCT [79]. The 3-year OS and EFS were 56% and 51%, respectively, with a relapse rate of 9.6%. As with the EBMT series, chemosensitivity was predictive of OS and EFS.

Some of the most encouraging data originated from the MD Anderson Group in which 47 patients (n = 45 matched related donor; n = 2 unrelated donor) with relapsed FL underwent alloHCT using the fludarabine, cyclophosphamide, rituximab conditioning regimen [80]. The complete remission rate after alloHCT was 100%. With a median follow-up of 60 months, the OS and PFS were 85% and 83%, respectively. The incidence of grade 2 to 4 acute GVHD was only 11% with a 36% incidence of extensive chronic GVHD. One distinctive feature of this study was the use of high-dose rituximab in which three of the four planned doses of rituximab were given at 1,000 mg/m^2. In contrast to the previously mentioned study from the United Kingdom, the depth of donor chimerism did not affect relapse risk. In light of these impressive results, the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) has embarked on a phase II multicenter trial for relapsed patients with FL with the goal to validate the highly promising results using the fludarabine, cyclophosphamide, rituximab regimen in the setting of RIC alloHCT. The Grupo de Espanol de Linfomas/Transplante Autologo de Medula Osea (GELTAMO) group reported the results of 37 patients with matched sibling donors who received fludarabine and melphalan as the conditioning regimen [81]. The 4-year DFS was 55% with a relapse rate of 8%, which is notable considering that 46% of patients had failed a prior autologous HCT.

The CIBMTR performed retrospective analyses to compare outcomes of patients with FL who received a myeloablative regimen (n = 120) vs an RIC regimen (n = 88) [82]. The type of conditioning regimen did not have an impact on PFS, OS, and TRM but did affect progression. In multivariate analysis, there was a significantly higher risk of progression with RIC alloHCT (RR,2.97; 95% confidence interval, 1.03-8.55; $P = .044$). The 3-year progression rate was 8% in the ablative group vs 17% in the RIC group. It should be noted that the RIC recipients were older than the ablative recipients (median age, 51 years vs 44 years, respectively), had a longer time from diagnosis to HCT (36 vs 25 months, respectively), and a higher incidence of comorbid conditions. Chemosensitivity and recipient performance status were better predictors of outcome rather than conditioning regimen used. There are no prospective randomized trials comparing outcomes between autologous HCT vs RIC alloHCT for patients with relapsed FL. The Blood and Marrow Transplant Clinical Trials Network embarked on a biological assignment trial to address this question, but the trial closed prematurely due to poor accrual [83]. A total of 30 patients were accrued with eight patients in the alloHCT arm and 22 patients proceeding to autologous HCT. With a median follow-up of 36 months, the OS was 73% vs 100%, and the PFS was 63% vs 86% in the autologous and RIC alloHCT arms, respectively, with TRM at 1 year being 15% and 0%, respectively. Due to the small sample sizes, statistical comparisons were not possible.

In summary, both autologous and alloHCT can confer long-term survival in patients with relapsed FL. HCT should be offered to patients who have progressed after one to two prior regimens if they have a good performance status and can tolerate an aggressive approach. For patients who are not heavily pretreated and who are chemosensitive at the time of relapse, autologous HCT is a reasonable approach. However, numerous allogeneic HCT trials have shown the existence of robust graft-vs-lymphoma effect in FL, and prolonged DFS has been shown in several studies. The NRM associated with myeloablative regimens remains prohibitive, and thus RIC allogeneic HCT has become the de facto standard in alloHCT for patients with FL. The CIBMTR reported that the number of RIC regimens increased from <10% of transplantations in 1997 to >80% in 2002 [82]. Risk factors for relapse after RIC regimens include chemorefractory disease and transformed disease, and thus chemosensitivity should be established before alloHCT [84]. The optimal choice between proceeding to autologous HCT or RIC alloHCT for a chemosensitive relapsed patient with FL is not definitive, but the advent of RIC allogeneic HCT and associated promising results has led to a major shift in practice in increased utilization of RIC regimens.

CONCLUSION

The definitive management of patients with advanced follicular NHL remains under considerable debate due to the numerous treatment options available. Fortunately, response rates are increasing, and recent results show that OS seems to be improving. The goal of treatment is to alleviate symptoms of the disease and to emphasize quality of life. HCT should be offered. The greater availability of treatment options further emphasizes the utility of predictive biomarkers and prognostic indices to guide risk-adapted therapies with the ultimate goals of increasing survival with less toxicities.

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