Published in final edited form as:

Oncologist. 2009 July ; 14(7): 726–738. doi:10.1634/theoncologist.2009-0045.

Role of Hematopoietic Stem Cell Transplant in the Management of Follicular Lymphoma

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Abstract

Despite decades of published data regarding the application of autologous and allogeneic stem cell transplant in patients with follicular lymphoma, there remain no uniform indications for its use in this disease. Autologous transplant has been shown to lead to longer progression-free survival times in randomized trials when compared with postremission interferon-based chemo-immunotherapy. However, the development of rituximab and its use in frontline, salvage, and maintenance therapy complicates the decision to pursue autologous transplant, a modality developed prior to the advent of anti-CD20 monoclonal antibodies. Allogeneic transplant offers the advantages of lymphoma-free grafts and the immunologic graft-versus-lymphoma effect. These factors may confer the possibility of long-term remission, though historically they have been accompanied by high rates of upfront morbidity and mortality, especially in heavily pretreated patients with a poor performance status or chemotherapy-refractory disease. Advances in patient selection, human leukocyte antigen (HLA) matching, conditioning regimens, and supportive care have reduced transplant-related mortality and the incidence of graft-versus-host disease.

Recently published data focus on the incorporation of rituximab and radioimmunoconjugates prior to, during, and following autologous transplant. Furthermore, reduced-intensity allogeneic stem cell transplantation has increasingly been used for relapsed follicular lymphoma patients with comorbidities or advanced age. Several recent reports suggest that reduced-intensity regimens may provide a high likelihood of long-term disease-free survival for patients up to 70 years of age with

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Disclosures

Matthew Foster: *Consultant/advisory role:* Genzyme; **Don A. Gabriel:** *Intellectual property rights/inventor or patent holder:* Patents provisionally filed; *Honoraria:* Speakers' bureau for Millennium, Novo Nordisk, Talecris; *Research funding/contracted research:* GlaxoSmithKline; *Ownership interest:* Invitro; **Thomas Shea:** *Consultant/advisory role:* Board of Directors, CALGB; CIBMTR Scientific Advisors, president-elect; *Honoraria:* Speakers' bureau for Schering Plough, Genentech, Bristol-Myers Squibb, Novartis; *Research funding/contracted research:* Genzyme.

Section editor **George P. Canellos** has disclosed no financial relationships relevant to the content of this article.

The article discusses unlabeled, investigational, or alternative use(s) of a product, device, or technique—alemtuzumab (Campath®; Genzyme), rituximab (Rituxan®; Genentech), iodine-131 tositumomab (Bexxar®; Corixa Corporation and GlaxoSmithKline), yttrium-90 ibritumomab tiuxetan (Zevalin®; Spectrum Pharmaceuticals, Inc.)—for conditioning regimens for HSCT.

The content of this article has been reviewed by independent peer reviewers to ensure that it is balanced, objective, and free from commercial bias.

AUTHOR CONTRIBUTIONS

Conception/Design: Matthew Foster, Don A. Gabriel, Thomas Shea

Collection/assembly of data: Matthew Foster, Thomas Shea

Data analysis: Matthew Foster, Thomas Shea

Manuscript writing: Matthew Foster, Don A. Gabriel, Thomas Shea

Final approval of manuscript: Matthew Foster, Don A. Gabriel, Thomas Shea

a good performance status, chemotherapy-sensitive disease, and HLA-matched sibling donors. Such patients with relapsed disease should be referred to a transplant center that can enroll them in one of the forthcoming clinical trials that aim to confirm these outcomes.

Keywords

Lymphoma; Follicular lymphoma; Non-Hodgkin's; Hematopoietic stem cell transplantation; Transplantation conditioning; Bone marrow purging; Rituximab

INTRODUCTION

Follicular lymphoma (FL) has historically been considered incurable in its advanced stages. Typically, initial chemosensitivity is followed by progressively shorter remissions, poorer response rates, and frequent transformation into aggressive lymphoma [1]. In past decades, advances in chemotherapy and radiation had not impacted the natural history of the disease, but data now suggest that recent advances have improved survival [2–4]. Hematopoietic stem cell transplant (HSCT) was first used for FL in the 1980s [5]. Although improvements in patient selection, conditioning regimens, and supportive care have resulted in less morbidity and mortality [6], and superior outcomes are achieved when transplant is applied in FL prior to histologic transformation [7], there are no uniform guidelines for the incorporation of transplant into the management of FL. Furthermore, the advent of chemoimmunotherapy and radioimmunotherapy has changed the therapeutic landscape, making older transplant data less applicable to today's patients.

Rituximab (Rituxan®; IDEC Pharmaceuticals, San Diego, and Genentech, Inc, San Francisco, CA) has improved response rates and time to progression in patients with advanced FL, without significant increases in toxicity [8]. Thus, for rituximab-naïve relapsed patients, the use of this anti-CD20 monoclonal antibody either alone or with chemotherapy is an attractive option. Even for heavily pretreated patients, the anti-CD20 radioimmunoconjugates iodine-131 tositumomab (Bexxar®; Corixa Corporation, South San Francisco, CA and GlaxoSmithKline, Philadelphia) and yttrium-90 ibritumomab tiuxetan (Zevalin®; Spectrum Pharmaceuticals, Inc., Irvine, CA) have induced complete and durable responses [9,10]. With these expanding options, the optimal time and indication for transplant remains unclear despite the potential for long-term remission and cure with these approaches.

The menu of options available to the transplant specialist is also complex. In prior decades, transplant-related mortality (TRM) rates of up to 40% [11] made myeloablative allogeneic HSCT practicable only for the youngest, fittest patients with human leukocyte antigen (HLA)-matched donors. Subsequent advances in HLA matching, supportive care, and prevention and treatment of graft-versus-host disease (GVHD) have lowered TRM rates considerably [6,12, 13]. Autologous transplant has long been available for patients who are not candidates for allografts, though the high rate of bone marrow involvement in advanced FL makes stem cell product contamination a concern. Ex vivo and in vivo stem cell purging and the wide array of conditioning regimens complicate the approach to autologous transplant. Long-term follow-up of autologous HSCT studies has also demonstrated rates of second hematologic malignancies and solid tumors in the range of 3%–12.4% [14–16] and 1.6%–8.3% [17–20], respectively. Mortality from these second malignancies partially negates the lower short-term TRM rate of this approach.

These findings complicate the decision to pursue any transplant, even more so the choice between autologous and allogeneic HSCT. Other variables include donor selection, intensity

of the conditioning regimen, stem cell source, and GVHD prophylaxis. This review aims to clarify recently published data on the application of HSCT in advanced FL.

AUTOLOGOUS TRANSPLANT

It has been nearly three decades since the first published series of patients who received autologous bone marrow transplant for FL [5]. In the 1990s, a nonrandomized series reported 8-year disease-free survival rates of up to 42% [21]. More recently, the European Blood and Marrow Transplantation (EBMT) group registry reported long-term outcomes of 693 FL patients [22]. With a median follow-up of 10.3 years, the 10-year progression-free survival (PFS) rate was 31% and the 10-year overall survival (OS) rate was 52%. Nine percent developed second malignancies at a median of 7 years post-transplant.

Mature follow-up of patients ($n = 121$) in second or subsequent remission conditioned with cyclophosphamide plus total body irradiation (TBI) was also reported recently in a two-institution series [16]. With a median follow-up of 13.5 years, the 10-year PFS rate was 48% and the 10-year OS rate was 54%. Though the PFS Kaplan-Meier curve achieved a plateau beyond 8 years, the curve for OS did not, resulting, in part, from the 12.4% of patients succumbing to treatment-related myelodysplastic syndrome (MDS) or acute myelogenous leukemia (AML).

In attempts to solve the problem of product contamination by lymphoma, ex vivo purging of autologous stem cell products using combinations of anti B-cell antigen monoclonal antibodies and complement have been employed, with encouraging results [23]. In a nonrandomized case series, patients who received purged stem cell infusions free from minimal residual disease by polymerase chain reaction (PCR) had a higher 8-year freedom-from-relapse rate (83%, compared with 19% for PCR⁺ patients; $p = .0001$) [21].

More recently, rituximab-containing mobilization regimens have been employed as in vivo purging strategies [24,25]. Such approaches have yielded stem cell products apparently free from residual lymphoma, and encouraging post-transplant outcomes have been attributed to rituximab use in patients previously naïve to immunotherapy. An Italian group compared high-dose sequential (HDS) therapy with or without rituximab incorporation during mobilization [26]. When compared with historical controls treated with HDS without rituximab, those treated with HDS plus rituximab had a superior 5-year projected OS rate (82% versus 68%; $p = .011$) and event-free survival (EFS) rate (66% versus 46%; $p = .001$). Others have compared such in vivo purging strategies with ex vivo CD34⁺ cell-enrichment techniques [27]. Both approaches yielded B cell-free grafts but were associated with delayed hematologic recovery in CD34⁺ cell-selected patients and delayed immunoglobulin reconstitution in rituximab-purged patients. Although infectious complications did not appear frequent in this analysis, other studies have shown a higher risk for serious infections with thoroughly purged products [28,29].

In an attempt to definitively assess the benefit of ex vivo purging, the Chemotherapy Unpurged or Purged (CUP) trial [30] randomized 89 patients with chemotherapy-sensitive, relapsed FL to three cycles of chemotherapy or high-dose therapy (HDT) with either unpurged or immunomagnetically purged autologous stem cells. That trial suffered slow accrual and was discontinued at a sample size that only allowed comparison of chemotherapy with transplant. Despite the failure of the CUP trial to address ex vivo purging, it remains the only randomized trial comparing chemotherapy with HDT in relapsed FL. At a median follow-up of 69 months, the hazard ratio (HR) for PFS was 0.30 ($p = .0009$) in favor of HDT. Furthermore, the HR for OS also favored HDT over chemotherapy (HR, 0.40; $p = .026$).

Autologous HSCT for FL in first remission was studied in three European multicenter, randomized trials in the prerituximab era. These clinical trials, conducted by the German Low-Grade Lymphoma Study Group (GLSG) [31] and the French cooperative groups Groupe Ouest Est d'Etude des Leucémies et Autres Maladies du Sang (GOELAMS) [32] and Groupe d'Etude des Lymphomes de l'Adulte (GELA) [33], enrolled untreated patients aged <59–61 with symptomatic, bulky, or progressive disease. Patients received cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP)-like induction regimens and were randomized to either 1 year of interferon-based maintenance therapy or cyclophosphamide plus TBI-based HDT with autologous HSCT. The trials generally suggested an EFS difference in favor of autologous transplant (Table 1), although the largest of the three trials, the GELA-sponsored Groupe d'Etude des Lymphomes Folliculaires (GELF)-94 study, failed to reach statistical significance with regard to disease-free survival. With the longest randomized follow-up data published to date (9 years), a recent update of the GOELAMS trial showed longer disease-free survival in the autologous HSCT group, along with a 16% incidence of late second cancers in the transplant group at 10 years that resulted in a similar OS rate between groups [32].

Although the randomized trials consistently suggested longer disease-free survival times, autologous SCT for FL has not achieved widespread application for three reasons. First, none of the trials of autologous SCT in patients in first remission demonstrated an OS benefit. It is thus uncertain whether autologous transplant merely delays inevitable relapse or changes the ultimate course of disease. Second, the early benefit of a disease-free interval is partially offset by the incidence of therapy-related MDS (tMDS) and secondary AML (sAML), previously estimated to be between 4.3% [34] and 12.3% [35]. The GLSG trial estimated the 5-year risk for tMDS or sAML to be 3.5% in the transplant group and 0% in the chemotherapy plus interferon group ($p = .0248$) [15]. Because of the high mortality from sAML and tMDS, even low rates of these complications may off-set early benefits of autologous transplant. Second solid and hematologic malignancies occurred at a particularly high rate in the transplant arm of the GOELAMS trial (16%), especially in patients whose stem cell product underwent positive selection for CD34⁺ cells (33%). The authors postulate that such purging techniques remove immunocompetent cells from the bone marrow that later participate in antitumor activity [32]. Finally, the publication of most randomized data for autologous transplant coincided with advances in the use of rituximab in frontline, salvage, and maintenance therapy for FL [8,36]. The ensuing widespread use of rituximab has supplanted interferon-based chemoimmunotherapy and made the comparator groups in these randomized trials less germane to modern patients.

AUTOLOGOUS TRANSPLANT IN PATIENTS PREVIOUSLY TREATED WITH RITUXIMAB

Initially, single-center retrospective series suggested that rituximab therapy prior to autologous SCT may not benefit patients with relapsed FL. When 56 subsequently transplanted low-grade lymphoma patients treated initially with rituximab-containing therapy were compared with 55 rituximab-naïve patients at Washington University, no differences in disease-free survival or OS emerged [37]. A similar retrospective analysis of rituximab-pretreated versus rituximab-naïve FL patients transplanted at the Cleveland Clinic showed no difference in disease-free survival between the groups, although the median OS was not reached [38]. Cox multivariable models suggested trends for shorter OS and DFS times in rituximab-pretreated patients, but these trends did not reach statistical significance.

A large secondary analysis with mature follow-up was recently reported by GELA. The study included FL patients treated in two prospective trials (GELF-94 and GELF-86) who did not receive HDT or rituximab as part of their initial therapy [39]. Patients were combined for this analysis because they received identical frontline chemoimmunotherapy with CVHP

(cyclophosphamide, doxorubicin, teniposide/VP16, and prednisone) plus interferon followed by bimonthly maintenance. The authors analyzed 254 patients age <61 who subsequently relapsed. The 5-year EFS rate was greatest (67%) when patients received both rituximab-containing salvage therapy and autologous SCT, and lowest (19%) when patients received neither rituximab nor HSCT. Rituximab resulted in both a greater 5-year EFS rate after relapse (patients not transplanted, 39% with rituximab versus 19% without, $p = .0002$; patients transplanted, 67% versus 46%, $p = .0532$) and a greater 5-year OS rate after relapse regardless of transplant status (patients not transplanted, 70% with rituximab versus 33% without, $p < .0001$; transplanted patients, 93% versus 63%, $p = .0071$). Although demonstrating a trend favoring rituximab plus SCT, the benefit of SCT in patients who received rituximab-based salvage regimens did not reach statistical significance (EFS rate for SCT versus non-SCT patients, 67% versus 39%, $p = .16$; OS for SCT versus non-SCT patients, 93% versus 70%, $p = .13$). Because the choice of salvage therapy and SCT was at the discretion of physicians, selection bias prevents definitive conclusions about the superiority of the various approaches.

Two recent abstracts from Germany also address the issue of autologous transplant in FL patients who received first-line rituximab plus CHOP (R-CHOP). A retrospective study combined patients enrolled in the CHOP-containing arms of two GLSG trials, '96 (CHOP versus mitoxantrone, chlorambucil, and prednisone followed by randomization to interferon maintenance versus autologous SCT) and '00 (CHOP versus R-CHOP followed in responding patients aged <60 years by randomization to interferon maintenance versus autologous SCT). Patients who received R-CHOP followed by autologous SCT in first complete remission (5-year PFS rate, 79%) fared better than those receiving CHOP with interferon maintenance (27%), CHOP with autologous SCT (66%), or R-CHOP with interferon maintenance (67%) [40]. However, in a comparison of transplanted patients in the '00 trial, no significant benefit emerged for frontline R-CHOP (5-year PFS, 78%) over CHOP (66%; $p = .43$). An insufficient number of events at a median follow-up of 58 months of these groups makes further follow-up necessary [41].

More recently, the Italian cooperative group published data at a median follow-up of 51 months from the Gruppo Italiano Trapianto di Midollo Osseo/Intergruppo Italiano Linfomi (IIL) randomized trial of 136 patients with high-risk, untreated stage III or IV FL [42]. High-risk disease status was defined as an age-adjusted International Prognostic Index (IPI) score [43] ≥ 2 or an IIL score [44] ≥ 3 . Patients were randomized to either six courses of CHOP-21 followed by four doses of rituximab or the HDS regimen (sequential doxorubicin, vincristine, and prednisone followed by 2 g/m² etoposide and subsequently 7 g/m² cyclophosphamide for mobilization) with rituximab incorporated both prior to and following cyclophosphamide as an in vivo purging strategy (R-HDS regimen) prior to autograft conditioned with mitoxantrone and melphalan. Similar to the randomized trials conducted prior to the widespread use of rituximab, the EFS rate was superior in the transplanted arm (4-year projected EFS rate, 61% versus 28%; $p < .001$) without any impact on the OS rate (CHOP-R, 80%; R-HDS, 81%; $p = .96$). Partly responsible for the similar OS data was a trend toward higher a 4-year cumulative incidence of second hematologic cancer (AML/MDS) that was seen in the R-HDS group (6.6%, versus 1.7% with CHOP-R; $p = .111$). However, another explanation for the similar survival rates in the two groups remains the fact that patients with relapsed or refractory lymphoma after CHOP-R had 3-year EFS and OS rates of 64% and 73%, respectively, and 3-year EFS and OS rates of 68% and 81%, respectively, if salvaged with R-HDS. Furthermore, using bone marrow PCR for molecular monitoring, the authors found that patients in molecular remission had similar EFS rates regardless of treatment arm, and patients not in molecular remission likewise had similar outcomes. Such patterns in the data suggest that upfront autologous transplant may result in more durable remissions than conventional chemoimmunotherapy but not alter the ultimate course of disease.

COMPARISONS BETWEEN AUTOLOGOUS AND ALLOGENEIC SCT

The theoretical advantages of allogeneic transplant lie in immunologic graft-versus-tumor effects and the use of cell products devoid of tumor cells and prior chemotherapy-induced DNA damage. These advantages should lead to lower rates of relapse and second hematologic malignancies. Clinical evidence of a graft-versus-lymphoma (GVLy) effect is suggested by a late plateau in the rates of relapse seen in allogeneic HSCT recipients, whereas patients receiving autologous transplants relapse continuously [45]. Evidence in support of the GVLy effect in FL has been demonstrated by molecular responses after tapered immunosuppression and donor lymphocyte infusion in patients who relapse after allograft [46,47].

A retrospective analysis of non-Hodgkin's lymphoma (NHL) patients in the International Bone Marrow Transplant Registry and the EBMT registry called the GVLy phenomenon into question by demonstrating equally low rates of relapse in syngeneic and full-intensity allogeneic transplant recipients [48]. Importantly, chemosensitivity was inversely related to relapse on multivariate analysis, and fewer allograft recipients demonstrated chemosensitivity prior to transplant than did syngeneic graft recipients. This discrepancy, along with the retrospective nature of the study, suggests that unmeasured differences between patient groups may have existed. The inclusion of diverse NHL histologies also precludes specific conclusions regarding FL.

The only prospective comparison between autologous and allogeneic HSCT for relapsed FL closed early as a result of poor accrual [49]. The largest published retrospective study included 904 patients who underwent autologous or HLA-matched, sibling donor allogeneic HSCT at member institutions of two registries between 1990 and 1999 [6]. At baseline, the group receiving allogeneic transplants was younger and more likely to have a poor performance status, an elevated lactate dehydrogenase level, bone marrow involvement, and chemotherapy-resistant disease. The 5-year estimates of disease-free survival (45% versus 39% versus 31%) and OS (51% versus 62% versus 55%) were similar among the allogeneic, purged autologous, and unpurged autologous groups, respectively. Although relapse rates in allogeneic HSCT recipients demonstrated a plateau at 21% between 3 and 5 years post-transplant, relapses continued in autologous HSCT patients beyond 3 years. This difference in relapse rates was offset in the OS analysis by a higher TRM rate in the allogeneic group (24% at 1 year versus 4%–8% at 1 year for autologous SCT recipients).

Similar patterns of lower relapse rates but a higher nonrelapse mortality (NRM) rate with allogeneic SCT were observed in recent retrospective studies of allogeneic versus autologous SCT in FL [50,51]. The EBMT compared registry patients receiving autologous SCT for relapsed FL ($n = 1,394$) with those receiving reduced-intensity allogeneic SCT ($n = 110$) [50]. The risk for NRM was higher in allograft patients (risk ratio [RR], 3.5; $p < .001$), but the risk for relapse was greater in autografted patients (RR, 2.8; $p < .001$).

A two-center British study reported on 126 patients who underwent either unpurged autologous transplant with BCNU, etoposide, cytarabine, and melphalan (BEAM) or allogeneic HSCT after conditioning with BEAM plus alemtuzumab. Again, significant differences were seen in terms of the TRM rate (20% for allogeneic SCT, 2% for autologous SCT; $p = .001$) and relapse rate at 3 years (20% in the allogeneic group, 43% in the autologous group; $p = .01$). However, the 3-year disease-free survival rates (allogeneic, 58%; autologous, 56%; $p = .9$) and OS rates (allogeneic, 69%; autologous, 67%; $p = .99$) were indistinguishable. In patients followed beyond 3 years, a trend is emerging for a plateau in terms of both OS and disease-free survival in allogeneic HSCT recipients, but autologous SCT patients suffer both late relapses and second malignancies. Efforts to refine patient selection, supportive care, and treatment of GVHD may eventually result in a survival benefit for allogeneic over autologous HSCT. At the same time,

the use of reduced-intensity allografts following failed autotransplants has resulted in encouraging results that suggest that such an approach may lead to effective salvage of patients initially treated with an autologous transplant [52]. Nevertheless, without prospective, randomized comparisons between autologous and allogeneic transplants, the decision to pursue autograft or allograft for an individual patient must involve a balanced discussion of the risks of early mortality and late second malignancies, along with an acknowledgment of the limitations of the currently available retrospective data.

REDUCED-INTENSITY ALLOGENEIC TRANSPLANT

With the goal of making allogeneic transplant feasible for older, heavily pretreated patients, reduced-intensity conditioning (RIC) regimens were first reported in relapsed lymphoma patients almost 10 years ago [53]. The bulk of the experience with RIC regimens is published in the form of single-arm case series of relapsed NHL patients (Table 2). The earliest retrospective studies of RIC reported data from multicenter registries. The EBMT reported 188 patients from 51 centers, with only 52 low-grade lymphoma patients [54]. Follow-up was limited (median, 283 days), and patients were treated with 17 different conditioning regimens. Sixteen percent of patients either had chemotherapy-resistant disease or were in untreated relapse prior to transplant. Despite a disappointing 2-year estimated TRM rate of 30.9%, the PFS rate (54%), OS rate (65%), and incidences of both acute (24%) and extensive chronic (9%) GVHD were considered acceptable. On multivariate analysis, age >50 years predicted TRM (RR, 2.02; 95% confidence interval [CI], 1.03–4.0; $p = .041$), and the presence of chemosensitivity prior to transplant predicted favorable PFS and OS times (RR, 2.3; 95% CI, 1.4–3.7; $p = .007$ and RR, 2.4; 95% CI, 1.4–4.2; $p = .002$, respectively).

Retrospective surveys conducted in Japan [55] and France [13] also evaluated patients, with varied NHL histology at multiple centers, who underwent heterogeneous conditioning regimens. Follow-up was limited in the Japanese study (median, 23.9 months), and only 3-year survival estimates are reported for the indolent lymphoma subgroup, with a PFS rate of 77% and an OS rate of 79%. Multivariate analysis identified that indolent histology, methotrexate-containing GVHD prophylaxis, performance status score of 0–1, and a long interval from diagnosis to transplant had a favorable effect on PFS (all $p < .05$). With the longest median follow-up (37 months) of all retrospective studies, the French series showed disappointing rates of PFS (51%; 95% CI, 40%–64%) and OS (56%; 95% CI, 45%–69%). Furthermore, the reported TRM rate of 40% was similar to that reported using myeloablative regimens [11]. The reasons for poor outcomes in these heterogeneous groups is unclear, but may be related to lack of standardized GVHD prophylaxis and a significant incidence of GVHD. Furthermore, 16.4% of the French patients had chemotherapy-resistant lymphoma prior to transplant, a factor previously identified to predict poor outcome [54].

Reflecting an aggressive application of RIC allogeneic SCT for FL, 37% of 54 patients transplanted within the Seattle-based consortium had progressive disease or untreated relapse prior to transplant [56]. Accordingly, the entire cohort, 26% of whom had transformed disease, experienced rates of TRM (42%), PFS (38%), and OS (43%) that were generally inferior to those reported in other retrospective series. Additionally, the frequency of matched-unrelated donor transplants (31%) and HLA-mismatched allografts (22%) was likely responsible for the high incidences of acute (63%) and extensive chronic (47%) GVHD.

In general, three prospective studies of RIC in FL have reported the most favorable outcomes with regard to TRM, incidence of GVHD, and survival (Table 2). Such outcomes are likely the result of selective inclusion criteria inherent to prospective trials. For instance, neither the phase II MD Anderson trial incorporating rituximab into RIC [57] nor the Cancer and Leukemia Group B (CALGB) 109901 trial [58] enrolled patients with chemotherapy-refractory disease.

Only 2.4% of the patients in a British study of alemtuzumab added to a fludarabine–melphalan conditioning regimen had refractory disease prior to transplant [59]. Requirements for HLA matching were also strict in these prospective studies, with no mismatched grafts in either the CALGB or MD Anderson studies. Unrelated donors were rare, at 0%, 4%, and 26% in the CALGB, MD Anderson, and U.K. studies, respectively. Accordingly, rates of GVHD, TRM, PFS, and OS were generally more favorable in those trials than in the retrospective studies.

With a median follow-up of 60 months, the MD Anderson series nearly doubles the maturity of other reports. This considerable experience with a single rituximab, fludarabine, and cyclophosphamide-containing regimen over 8 years has yielded impressive PFS (83%; 95% CI, 69%–91%) and OS (85%; 95% CI, 71%–93%) rates. Furthermore, only six of the 47 patients suffered infection-related death after a regimen that targeted both cellular and humoral immunity. These promising results deserve further investigation in a prospective, multicenter fashion such as is currently available through the Blood and Marrow Transplant Clinical Trials Network (BMT CTN).

COMPARISONS BETWEEN MYELOABLATIVE CONDITIONING AND RIC

The limited data comparing myeloablative conditioning with RIC allogeneic SCT in FL are summarized in Table 3. Prior to 2008, the only published comparison of the two approaches came from a City of Hope report that included small numbers of FL patients among patients of varied NHL histologies [60]. Although there were no differences with regard to survival, GVHD, or mortality, the sample was likely underpowered to show such differences.

In 2008, two similar single-institution series were published comparing fully myeloablative allografts with RIC allografts in relapsed FL. A report from the University of Minnesota described small numbers of indolent lymphoma patients who were treated with varied conditioning regimens and cell products including bone marrow, peripheral blood stem cells (PBSCs), and umbilical cord blood (UCB) [61]. With 3 years of follow-up, no differences with regard to OS, PFS, or GVHD were detected. However, there was a significantly lower TRM rate in the RIC group (17%, versus 43% in the myeloablative transplant recipients; $p = .05$). There was no subgroup analysis for indolent lymphoma patients.

In Seattle, 41 FL patients were included in RIC and myeloablative cohorts [62]. The two groups were treated with standardized institutional conditioning protocols. Within the low-grade lymphoma subgroup, patients had a trend toward a lower risk for relapse with myeloablative conditioning, but these patients had a higher risk for TRM (3.16; $p = .02$). When analyzed according to the previously validated [63] HCT-specific comorbidity index (HCT-CI), which approximates a patient's cumulative burden of mild, moderate, and severe organ impairment, patients without comorbidities had similar TRM and OS rates regardless of conditioning intensity, whereas patients with high comorbidity scores fared better with RIC (HR for TRM, 0.47; $p = .009$; HR for OS, 0.63; $p = .04$).

The largest published retrospective analysis of RIC versus myeloablative conditioning regimens for FL patients was conducted by the international registry Center for International Bone Marrow Transplant Research [12]. The study included 120 patients who received matched sibling allografts after myeloablative conditioning and 88 who underwent RIC between 1997 and 2002. RIC patients were older, more likely to be in or beyond second remission, more likely to have received prior rituximab, and more likely to receive PBSCs rather than marrow-derived stem cells (all $p < .05$). As expected in a registry population, individual conditioning regimens varied considerably. Despite the larger population studied, no statistically significant differences in PFS, OS, or TRM emerged. There was a trend toward a greater PFS rate in the myeloablative group (67%, versus 55%; $p = .07$). On multivariate analysis, there were significantly higher rates of treatment failure and TRM, with a lower OS

rate in patients with Karnofsky Performance Status scores <90 or chemotherapy-refractory disease. Rates of acute GVHD were similar between the groups, though chronic GVHD was more common in those receiving RIC, perhaps because of the more frequent use of PBSCs in this group.

Despite the similar survival rates reported in these large cohorts, the probability of progression 3 years post-transplant was higher in RIC patients (17%, versus 8% for myeloablative patients), a difference that persisted in a multivariate analysis (RR for progression in RIC patients, 2.97; 95% CI, 1.03– 8.55; $p = .044$). The differences in baseline age and disease history between groups in this study reflect improvements in patient selection for the two approaches. There were likely unmeasured variables such as organ dysfunction and comorbidities that led to differences in patient selection for RIC over myeloablative regimens. Such variables could obscure differences in outcomes that may become apparent in prospective evaluations of well-matched patients.

A similar analysis restricted to recipients of matched unrelated donor allografts was presented by the EBMT [52]. The 93 patients who underwent RIC transplants had a higher 3-year NRM rate (34%, versus 46%; $p < .001$), PFS rate (43%, versus 35%; $p = .004$), and OS rate (49%, versus 40%; $p = .001$) when compared with the 51 patients who received conventional myeloablative conditioning. RIC patients were older and were more likely to have failed a prior autograft than myeloablative patients. Taken together, these results suggest that RIC transplants may offer equivalent or superior survival for patients aged >50 or those with significant comorbidities, when compared with the use of fully ablative transplants in such patients.

NOVEL DIRECTIONS

Despite encouraging results, neither autologous nor allogeneic transplant has been widely adopted in FL. Autograft tumor contamination and late development of secondary AML/MDS after HDT remain barriers to the widespread application of these approaches, as do advances in competing nontransplant therapies. The application of allotransplant remains limited as a result of TRM, GVHD, and the availability of HLA-matched donors. UCB transplants have the advantages of increasing the donor pool for patients without an HLA-compatible donor and rapid procurement of stem cells. Despite the promise of UCB, there is limited published experience regarding its use in adults with NHL [61,64,65].

In attempts to deliver therapeutic radiation doses without the toxicity of TBI, radioimmunotherapy (RIT) has been employed in autologous transplant regimens for FL. The radioimmunoconjugate yttrium-90 ibritumomab tiuxetan has been added to HDT in phase II studies of relapsed B-cell lymphomas (with small subsets of FL patients) [66,67]. Toxicity appears to be acceptable, with median times to engraftment of 10–12 days and low TRM rates (0%–3%). Furthermore, a retrospective comparison suggests longer survival with yttrium-90-based RIT HDT than with TBI-based autologous HSCT [68]. Emerging evidence also suggests that RIT-based RIC allogeneic HSCT can be accomplished with acceptable morbidity and TRM [69].

A chemotherapy-free regimen of high-dose ^{131}I -tositumomab has been used with favorable results in patients aged >60 [70], even when compared with historical controls who received conventional HDT [71]. To date, no prospective studies have compared RIT-based autologous transplant with conventional HDT for FL.

CONCLUSIONS

Despite much published experience in the application of SCT in FL, there remains no consensus on the timing, patient selection, conditioning regimen, or stem cell source. The expanding menu

of nontransplant therapies makes the risk for TRM unattractive to many patients and physicians. Many transplant studies are retrospective analyses of patients with varied lymphoma histologies who received diverse conditioning regimens. Comparisons between older and newer therapeutic strategies suffer from disparate durations of follow-up. The fact that much of the transplant data was collected in the prirituximab era also hinders comparison of transplant and nontransplant outcomes for patients diagnosed and treated within the last 10 years. Nevertheless, for a disease that has traditionally been considered incurable in its advanced stages, optimism about the plateau of relapse curves in allogeneic transplant studies is appropriate.

Studies have uniformly shown inferior transplant outcomes for patients with chemotherapy-refractory disease, poor performance status, and comorbidities [72]. These consistencies suggest that early identification and referral of high-risk, fit patients with chemotherapy-sensitive disease may be the optimal transplant strategy. Based on published experience with performance status [72], the Follicular Lymphoma IPI [73], the HCT-CI [63], and the risk for late relapse and second malignancies in long-term survivors of autologous transplant [22,45], a reasonable strategy might include early autologous transplantation for otherwise healthy high-risk patients in first or second remission. Patients who relapse later could be treated with a RIC allogeneic transplant. At our own center, we have felt that the availability of antibody-based and other effective therapies can often lead to clinically meaningful remissions without including transplantation. As a result, and because of the risks of second tumors and late relapses, we have generally preferred allogeneic to autologous transplants. We recommend them for patients with HLA-matched donors who have less than a near complete initial remission or remission duration of <2 years. We also limit this strategy to those patients with good organ function, a good performance status, and chemotherapy-sensitive disease. Such an approach may provide long-term survival for selected patients, but additional follow-up and enrollment of both related and unrelated transplant recipients in multicenter trials such as that from CALGB and a forthcoming BMT CTN trial will be imperative in determining the applicability of such strategies.

LEARNING OBJECTIVES

1. Evaluate recent data regarding outcomes of autologous and allogeneic stem cell transplant for follicular lymphoma.
2. Apply patient and disease characteristics to predict favorable post-transplant outcomes for patients with follicular lymphoma.
3. Enumerate the indications for referral of patients with follicular lymphoma to a transplant center.
4. Compare the advantages and disadvantages of allogeneic versus autologous stem cell transplant for follicular lymphoma.

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Table 1

Randomized trials of autologous stem cell transplant for follicular lymphoma in first remission

Trial	n	Therapies	Median follow-up (mos)	EFS (95% CI)			OS (95% CI)		
				Median (mos)	5-/7-/9-Yr estimate	p	Median	5-/7-/9-Yr estimate	p
GLSG	240	CHOP or MCP × 6–8 cycles → IFN- α , 5 × 10 ⁶ units 3 × per week until progression	50.4	NA	5-yr, 36.2% (27.6%–44.8%)	<.001	NA	NA	NA
		CHOP or MCP × 4–6 cycles → Cy, 60 mg/m ² × 2 days and 12 Gy TBI → unpurged PBSCs		NA	5-yr, 62.0% (52.7%–71.4%)		NA	NA	
GOELAMS	166	Monthly CHVP × 6 → every 2-mo CHVP × 6 + IFN- α , 5 × 10 ⁶ units 3 × per wk, mos 1–18	108	NA	9-yr, 56% (45%–67%)	.03	NA	9-yr, 80% (72%–89%)	.55
		VCAP every 3 wks × 2–3 with or without salvage DHAP → Cy, 60 mg/m ² × 2 days and 12 Gy TBI → purged PBSCs		NA	9-yr, 39% (28%–50%)		NA	9-yr, 76% (67%–85%)	
GELA (GELF-94)	401	Monthly CHVP × 6 → every 2-mo CHVP × 6 + IFN- α , 5 × 10 ⁶ units 3 × per wk, mos 1–18	92	33 (29–40)	7-yr, 28% (21%–34%)	.11	NR	7-yr, 71% (65%–71%)	.53
		Every-3-wks CHOP × 4 → Cy, 60 mg/m ² × 2 days + VP-16, 150 mg/m ² × 2 days + 10 Gy TBI → PBSCs		40 (31–64)	7-yr, 38% (31%–45%)		NR	76% (69%–82%)	

Abbreviations: CHOP, cyclophosphamide (750 mg/m² on day 1), doxorubicin (50 mg/m² on day 1), vincristine (1.4 mg/m² on day 1), and prednisone (100 mg/m² on days 1–5); CHVP, cyclophosphamide (600 mg/m² on day 1), doxorubicin (25 mg/m² on day 1), temiposide (60 mg/m² [or VP-16, 100 mg/m²] on day 1), prednisone (40 mg/m² on days 1–5); Cy, cyclophosphamide; DHAP, dexamethasone (40 mg on days 1–4), cytarabine (2 × 2 g/m² on day 2), and cisplatin (100 mg/m² on day 1); EFS, event-free survival; GELA, Groupe d'Etude des Lymphomes de l'Adulte; GELF, Groupe d'Etude des Lymphomes Folliculaires; GLSG, German Low-Grade Lymphoma Study Group; GOELAMS, Groupe Ouest Est des Leucémies et des Autres Maladies du Sang; IFN- α , interferon 2 α ; MCP, mitoxantrone (8 mg/m² on days 1 and 2), chlorambucil (3 × 3 mg/m² on days 1–5), and prednisone (25 mg/m² on days 1–5); NA, not available; NR, not reached; OS, overall survival; PBSCs, peripheral blood stem cells; TBI, total body irradiation; VCAP, vindesine (3 mg/m² on day 1), cyclophosphamide (1,500 mg/m² on day 2), doxorubicin (80 mg/m² on day 2), and prednisolone (50 mg/m² on days 1–5); VP-16, etoposide.

Single-arm studies of reduced-intensity allogeneic stem cell transplant in follicular lymphoma

Table 2

Study	Setting	n ^a	Conditioning regimen	Median age, yrs (range)	Median follow-up, mos (range)	aGVHD, cGVHD	TRM	PFS, % (95% CI)	OS, % (95% CI)
Prospective studies									
Khoury et al. [57]	Single center (MD Anderson)	47	Flu, 30 mg/m ² × 3 days; Cy, 750 mg/m ² × 3 days; rituximab, 375 mg/m ² , day -13 and 1,000 mg/m ² , days -6, +1, +8	53 (33–68)	60 (19–94)	11%, 36%	15%	83% (69%–91%) ^b	85% (71%–93%) ^c
Shea et al. [58]	CALGB, 11 centers	23	Flu, 20 mg/m ² × 5 days; Cy, 1 g/m ² × 3 days	53	31.2	27%, 18%	7%	2-yr, 71% (54%–82%) ^b	2-yr, 76% (60%–87%)
Morris et al. [59]	U.K. consortium, 10 centers	41	Flu, 30 mg/m ² × 5 days; Mel, 140 mg/m ² ; alemtuzumab, 20 mg × 5 days	51 (18–73)	36 (18–60)	15%, 4.5%	11%	3-yr, 65% (CI not given)	3-yr, 73% (CI not given)
Retrospective studies									
Rezvani et al. [56]	FHCRC, 10 centers	54	2 Gy TBI with or without Flu, 30 mg/m ² × 3 days	54 (33–66)	36.6 (2.3–60)	63%, 47%	42%	38% (CI not given)	43% (CI not given)
Vigouroux et al. [13]	French registry, 19 centers	61	Varied: 59% Flu/Bu/ATG, 28.7% Flu + 2 Gy TBI	51 (33–66)	37 (16–77)	34%, 20%	40%	51% (40%–64%) ^b	56% (45%–69%) ^b
Kusumi et al. [55]	Japan, 32 centers	44	Varied: 36% Flu/Bu, 27% Flu/Cy, 20% Flu/Mel	48 (32–61)	23.9 (3.4–44.5)	49%, 59% (incl. limited)	17.7%	3-yr, 77% (CI not given)	3-yr, 79% (67%–91%)
Robinson et al. [54]	EBMT registry, 51 centers	52	Varied: 34% Flu/Mel with or without alemtuzumab, 22% Flu/Cy, 16% Flu/Bu	46 (27–65)	10	24%, 9%	2-yr, 30.9%	2-yr estimate, 54% (CI not given)	2-yr, 65% (CI not given)

^aNumber of low-grade or follicular lymphoma patients.

^bProgression-free survival at median follow-up.

^cOverall survival at median follow-up.

Abbreviations: aGVHD, incidence of grade 2–4 acute graft-versus-host disease; ATG, antithymocyte globulin; Bu, busulfan; CALGB, Cancer and Leukemia Group B; cGVHD, incidence of extensive chronic graft-versus-host disease; CI, confidence interval; Cy, cyclophosphamide; DFCl, Dana Farber Cancer Institute; EBMT, European Blood and Marrow Transplantation; FHCRC, Fred Hutchinson Cancer Research Center; FL, follicular lymphoma; Flu, fludarabine; LG-NHL, low-grade/indolent non-Hodgkin's lymphoma; Mel, melphalan; OS, overall survival; PFS, progression-free survival; TBI, total body irradiation; TRM, transplant-related/nonrelapse mortality.

Table 3
Retrospective cohort studies comparing myeloablative with reduced-intensity conditioning allogeneic transplant

Study	n ^a	n ^b	Conditioning regimen	Median age, yrs (range)	Median follow-up, mos (range)	aGVHD	cGVHD	TRM	PFS, % (95% CI)	OS, % (95% CI)
CIBMTR (Hari et al. [12])	MA, 120; RIC, 88	MA, 120; RIC, 88	MA, varied: 92% Cy-TBI or Bu-Cy; RIC, varied: 42% Flu-Cy, 25% Flu-Bu, 18% Flu-Mel-ATG	MA, 44 (27–70); RIC, 51 (27–70)	MA, 50 (4–96); RIC, 35 (4–82)	MA, 36% (28–45); RIC, 44% (34%–55%); $p = .26$	MA, 46% (36–52); RIC, 62% (52%–72); $p = .03$	23%, both groups	MA, 67% (58%–75%); RIC, 55% (44%–65%); $p = .07$	MA, 71% (63%–79%); RIC, 62% (51%–72%); $p = .15$
City of Hope (Rodriguez et al. [60])	MA, 48; RIC, 40	MA, 18; RIC, 16	MA, 1,320 cGy TBI + 60 mg/kg Cy (or BuCy without TBI, $n = 7$); RIC, Flu, 25 mg/m ² × 5 days → Mel, 140 mg/m ²	MA, 44 (18–54); RIC, 51 (20–67)	MA, 69 (33–97); RIC, 20 (6–42)	MA, 45%; RIC, 65%	MA, 37%; RIC, 50%; no p -value	MA, 38%; RIC, 28%; $p = .4$	MA, 50%; RIC, 49%; $p = .83$	MA, 56%; RIC, 68%; $p = .56$
FHCRC (Sorrer et al. [62])	MA, 68; RIC, 152	MA, 27; RIC, 14	MA, Cy + either 12 Gy TBI or Bu; RIC, 2 Gy TBI with or without Flu, 90 mg/m ²	MA, 46 (10–59); RIC, 60 (18–70)	MA, 61 (21–97); RIC, 44 (7–90)	NR	NR	HR (MA versus RIC), 3.16; $p = .02$	NR	HR (MA versus RIC), 2.02; $p = .07$
University of Minnesota (Tomblyn et al. [61])	MA, 65; RIC, 76	MA, 11; RIC, 24	MA, Cy, 120 mg/kg over 2 days, 1,320 cGy TBI or Bu, 16mg/kg PO × 4 days; RIC, varied: included Flu, Cy, Bu (PO), 2-CDA, and/or ATG	MA, 42 (4–58); RIC, 48 (19–66)	MA, 39 (23–106); RIC, 36 (12–56)	MA, 43% (30%–56%); RIC, 58% (46%–70%); $p = .47$	MA, 35% (22%–48%); RIC, 55% (41%–69%); $p = .12$	MA, 43% (31%–55%); RIC, 17% (9%–25%); $p = .05$	3-yr estimates: MA, 44% (31%–57%); RIC, 31% (18%–49); $p = .82$ (all histologies)	4-yr estimates: MA, 46% (34%–59%); RIC, 49% (37%–61%); $p = .34$ (all histologies)

^aTotal number of patients treated with each approach.

^bNumber of follicular lymphoma or indolent lymphoma patients among other non-Hodgkin's lymphoma subtypes treated with each approach.

Abbreviations: 2-CDA, 2-chloro-deoxyadenosine (also known as cladribine); aGVHD, incidence of grade 2–4 acute graft-versus-host disease; ATG, antithymocyte globulin; Bu, busulfan; cGVHD, incidence of extensive chronic graft-versus-host disease; CI, confidence interval; CIBMTR, Center for International Blood and Marrow Transplant Research; FHCRC, Fred Hutchinson Cancer Research Center; HR, hazard ratio; MA, myeloablative; NR, not reported; OS, overall survival; PFS, progression-free survival; PO, orally; RIC, reduced-intensity conditioning; TBI, total body irradiation; TRM, transplant-related/nonrelapse mortality.