Indolent lymphomas account for approximately 30-35% of all non-Hodgkin’s lymphoma diagnoses. The bulk of indolent lymphomas are comprised of the follicular lymphomas which are further subdivided based on the number of centroblasts per high power field with grade 1, 2, and 3a behaving as indolent disease. These indolent lymphomas exhibit a waxing and waning course and multiple options for management exist, including both autologous and allogeneic transplantation. However, because of the multitude of therapeutic choices and the potential toxicities of allogeneic transplantation, this approach is usually reserved for patients who have relapsed/refractory disease or for younger patients. Despite significant options, no therapeutic intervention has clearly demonstrated a prolonged progression-free survival (PFS) plateau suggestive of cure except for allogeneic transplantation.

The evidence of a graft-versus-lymphoma effect with potential cure following allogeneic transplantation is clouded by multiple histologies and varied conditioning intensities represented in analyses (1-6). Additionally, limited data from prospective trials hinders obtaining solid evidence for safety and efficacy of this approach (7-10). Consequently, detailed review of published literature is required and should ideally be limited to more recent publications to allow for improved supportive care techniques and better donor matching. Several questions are relevant to the role of transplantation in management of follicular lymphomas. Specifically, issues as to the type of transplant (autologous versus allogeneic); timing of transplant (first relapse or later relapses); intensity of the conditioning regimen for allogeneic transplant; and consideration of maintenance therapy following autologous transplantation are all relevant. This review will focus primarily on issues of allogeneic transplantation.

The first issue relates to primarily type of transplantation. Available literature and prospective trials have demonstrated an improvement in PFS but no benefit in overall survival (OS) following autologous transplantation (11-14). This improvement appears to be limited to patients who proceed forward with autologous transplantation after salvage chemotherapy for the first relapse. For patients beyond first relapse, it is unclear if there should be a preference for allogeneic transplantation. Data from the IBMTR published in 2003 demonstrated similar OS for 904 patient’s receiving either allogeneic sibling graft (N = 176), purged autologous grafts (N= 131), and unpurged autologous grafts (N = 597) (6). However, as expected, patient characteristics varied significantly between the allogeneic and autologous cohorts. Patients receiving allogeneic transplantation were younger and less likely to have chemotherapy sensitive disease. Additionally, all allogeneic transplants were performed with myeloablative conditioning (MAC) regimens. An analysis from the UK also demonstrated similar OS and disease-free survival (DFS) in 44 patient’s receiving carmustine, etoposide, cytarabine, and melphalan (BEAM) and an allogeneic transplant compared to 82 patients receiving BEAM and autologous transplant (15). Again patients in the allogeneic group were younger and more heavily pretreated. In an attempt to prospectively answer...
the question, the Blood and Marrow Transplant Clinical Trials Network designed a biologic assignment study in which patients with an HLA identical sibling were assigned to receive a reduced intensity (RIC) allogeneic transplant whereas those without a matched sibling donor would receive autologous transplantation (7). Due to poor accrual, this trial closed early preventing comparison of these two groups. However, at a median follow-up of 3 years, 100% of patients (N = 8) were alive with a progression free survival (PFS) of 86% (95% CI: 63 – 100%). This contrasts to the autologous arm (and = 22) which had an OS of 73% (95% CI: 56 - 100%) and a PFS of 63% (95% CI: 44 – 89%). In summary, we do not yet know the answer of the optimal type of transplant for patients with follicular lymphoma. However, for those patients not referred early after initial relapse, data suggests that allogeneic transplantation for suitable candidates may be a more reasonable option despite higher treatment related mortality.

Timing of transplant is also relevant to transplant outcomes. As noted previously, autologous transplantation should be reserved for those patients who are in first—or perhaps second—relapse with chemotherapy sensitive disease. However, this may also be true for patients being considered for allogeneic transplantation. Multiple analyses have documented, regardless of conditioning intensity, that patients with chemotherapy resistant disease have inferior survival (1-5,10,16-20). A French retrospective analysis published in 2007 reported transplant outcomes on 73 patients with indolent lymphoma receiving allograft following a reduced intensity conditioning regimen (19). Of these 73 patients, 19 had chemotherapy resistant disease. The OS, event-free survival (EFS), and transplant related mortality (TRM) were 32%, 32%, and 63% respectively. This compared unfavorably to the OS for patients in CR or PR which were 66% and 64%; EFS in the CR and PR cohorts were 66% in 52%, respectively. Corradini and colleagues found a similar impact of chemotherapy refractory disease in a cohort of 170 patients with relapsed/ refractory lymphoma receiving RIC allogeneic transplant from sibling donors (4). This analysis included all histologies and only 63 patients were categorized as indolent lymphoma. In multivariate analysis, the presence of chemotherapy refractory disease resulted in a 3.6 fold greater risk of death. Although not statistically significant, there was a trend toward high-risk of relapse at 3 years for patients with only a partial remission or chemotherapy refractory disease at the time of transplant [CR: 28% (15 – 50%) vs PR: 38% (27 – 52%) vs Refractory: 50% (37 – 67); p = 0.057]. These other analyses demonstrate that chemotherapy sensitivity, as expected, has an impact on outcomes following transplantation suggesting that disease control is necessary in addition to the purported graft versus lymphoma effect.

The debate of conditioning intensity and its impact on transplant outcomes for indolent lymphoma, as well as other hematologic malignancies, continues. Several retrospective analyses have compared outcomes following MAC and RIC allogeneic transplantation for lymphoma patients (3,5,18,21). Two of these analyses included all histologies and found similar survival regardless of conditioning intensity (3,5). A CIBMTR analysis of 208 patients with follicular lymphoma receiving sibling allogeneic transplant with either MAC (N = 120) or RIC (N = 88) reported a 3 year OS of 71% (63-79%) MAC and 62% (51-72%) following RIC [p = 0.15]; PFS was also similar at 67% (58-75%) and 55% (44-65%) respectively [p = 0.07] (18). Multivariate analysis did demonstrate an increased risk of progression [HR 2.6, p = 0.04] following RIC. Similarly, the EBMT reported on 131 patients receiving MAC (N = 44) or RIC (N = 87) matched unrelated donor transplant for follicular lymphoma and demonstrated no statistical difference in OS or PFS at 3 years [OS: MAC 47% vs RIC 53%; PFS: MAC 43% vs RIC 49%]21. In all of these analyses patient characteristics were different with the MAC cohorts being younger, having a shorter time from diagnosis to transplant, and being less likely to have received a prior autologous transplant. In the absence of a randomized controlled trial comparing conditioning intensities, we will be unable to answer this question. However based on the literature available, it is reasonable to proceed with reduced intensity conditioning for all patients receiving allogeneic transplantation for indolent lymphoma provided evidence of chemotherapy sensitivity.

Prospective data on the outcomes of RIC allogeneic transplant for follicular lymphoma remain limited but outcomes are encouraging (7-10). Currently the longest follow-up is from a single center clinical trial from M.D. Anderson. At a median follow-up of 5 years, the estimated 8-year OS and PFS for 47 patients receiving either related (N = 45) or unrelated (N = 2) are 85% (71 – 93%) and 83% (69 – 91%) respectively. In this trial, all patients received high
doses of rituximab peri-transplant. The incidence of grade II - IV acute GVHD was 11% (5-24%) and the cumulative incidence of chronic GVHD was 60% (47 - 76%) (9). The GELTAMO group recently published long-term outcomes on 37 patients with follicular lymphoma who underwent allogeneic transplant in two separate prospective multicenter trials using fludarabine and melphalan-based RIC10. At a median follow-up of 52 months, the 4 year OS was 57% (48-65) with a DFS at 4 years of 55% (46-63). The non-relapse mortality at day 100 was 24% (13-42) and increased to 37% (25 – 57) by 4 years post transplant. The CALGB published the results of their phase II multicenter trial using fludarabine and cyclophosphamide reduced intensity conditioning followed by allogeneic sibling donor transplant for patients with indolent lymphomas (N = 44) (8). For the 16 patients with follicular lymphoma, at a median follow-up of 4.6 years, the 3 year OS was 81% (51-93) with the EFS of 75% (46-90). For the entire cohort, TRM was only 2.4% at 6 months and increasing to 9% by 3 years post transplant. Based on these excellent post active clinical trial results, it can be expected that patients receiving reduced intensity allogeneic transplant will have an overall survival ranging from 57% to 85% by 4 years post transplant. The BMT CTN is currently enrolling follicular lymphoma patients with either matched sibling or matched unrelated donors on a clinical trial receiving the M.D. Anderson conditioning regimen of fludarabine, cyclophosphamide, and high-dose rituximab to assess their excellent outcomes in a multicenter setting.

Based on the available data, reduced intensity allogeneic transplantation regardless of donor source is a feasible option for patients with relapsed/refractory follicular lymphoma. Outcomes are improved in patients who have chemotherapy sensitive disease, and, therefore, patients should be referred for discussion of his treatment approach earlier in the course of disease.

References


