Allogeneic Stem Cell Transplantation with T Cell-Depleted Grafts for Lymphoproliferative Malignancies

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ABSTRACT

In non-Hodgkin lymphoma allogeneic stem cell transplantation (SCT) can be curative, but with standard dose conditioning patients may have substantial morbidity and mortality from graft-versus-host disease (GVHD); for aggressive malignancies, reduced intensity conditioning may result in higher recurrence. Patients with advanced follicular lymphoma (n = 12), transformed B cell malignancy (n = 11), and non-CD30+ T cell lymphomas (n = 17) responsive to chemotherapy who had an HLA-identical sibling were offered T cell depleted (CAMPATH-1 G or H antibodies) SCT. Conditioning was with ablative doses of chemotherapy or radiotherapy. Before SCT, patients with follicular lymphoma had a median of 3 treatment courses, and those with transformed B cell and those diagnosed with T cell non-Hodgkin lymphoma had 2 (range, 1-3). At SCT the median age was 46 years (range, 21-59 years) and the number of CD34+ cells infused was 2.85 × 10^6/kg. All patients showed engraftment but 7 patients (17.5%) developed GVHD. In total 12 subjects expired of transplant-related causes (n = 6) or from disease recurrence. One-year transplant-related mortality was 15%. There was no difference in survival across diagnostic groups. At a median of 1051 days, 70% survived and 68% are without disease. By reducing the incidence and severity of GVHD, patients can tolerate myeloablative doses of chemotherapy satisfactorily. This has resulted in low treatment-related mortality and adequate protection from disease recurrence.

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KEY WORDS

Graft-versus-host disease • Stem cell transplantation • T cell depletion • Lymphoma

INTRODUCTION

Recent advances in the understanding of the biology of lymphoproliferative disorders have provided physicians with a more comprehensive therapeutic armamentarium and, at least for diffuse large B cell lymphoma, have led to improvement in survival [1]. In low-grade non-Hodgkin lymphomas (NHLs) modern strategies have also resulted in improvement in responses; however, a similar extension in survival still appears elusive [2]. Moreover, a proportion of patients has follicular lymphomas that tend to progress to histologically more aggressive forms, with particularly poor outcome. Depending on whether postmortem studies are included, the incidence of this histologic transformation varies from 30%-40% to as high as 70%, with reported median overall survivals of about 1 year [3-7]. Similarly, the management of T cell malignancies remains largely unsatisfactory, particularly for patients with lymphoblastic lymphoma and who present with extensive extranodal involvement or bone marrow infiltration and for those with peripheral T cell lymphomas. Although initially responsive, these malignancies tend to have a recurring course [8].

Compared with standard chemotherapy, myeloablative conditioning and stem cell support have been associated with prolonged disease-free survival in selected individuals with indolent malignancies and peripheral T cell lymphomas [9]. However, high disease recurrence rates after transplantation and secondary hematologic complications precluded many patients from having significant advantages in survival. In this regard, the therapeutic benefits of allogeneic grafting
range from the antiproliferative actions of the dose-intensive myeloablative conditioning to the putative “graft-versus-tumor” effect, often observed among patients who develop graft-versus-host disease (GVHD) [10,11]. This latter observation has been the basis of new strategies that induce powerful immunosuppression to favor engraftment, avoiding the side effects of myeloablative doses of chemotherapy or radiation that are particularly troublesome for older patients. However, GVHD may be protective against disease recurrence, it has been associated with high morbidity and substantial mortality, especially from opportunistic infections [12]. This has been particularly problematic for those undergoing reduced intensity conditioning combinations and receiving unfraccionated cytokine mobilized peripheral blood progenitor cell transplants [13,14].

T cell depletion of allogeneic stem cell grafts remains the most effective strategy in the prevention of GVHD, although some loss of the graft-versus-tumor effect has been suggested. We previously reported that, despite intense myeloablation, patients who received grafts that had been incubated with CAMPATH “in the bag” had low rates of GVHD, with low disease recurrence rates that transpired in good overall survival. We also showed that these beneficial effects were particularly maintained in older patients, even up to the age of 60 years [15,16]. We have now reviewed the outcome of a group of patients with NHLs and show that myeloablative conditioning followed by infusion of T cell-depleted grafts remains associated with favorable long-term outcome.

**METHODS**

This study included consecutive adults with NHL who received grafts between January 1990 and July 2005 from their HLA-identical siblings. The histologic groups treated included advanced stage grade I and II follicular lymphomas, transformed lymphoma, and non-CD30+ T cell malignancies. These groups are considered to have a poor prognosis with standard chemotherapy and their autologous stem cell transplants frequently fail. For this population, entry criteria included adequate performance status (0, 1, or 2), nonreactivity for human immunodeficiency virus testing, and malignancy that was still sensitive to salvage chemotherapy.

Individuals with indolent lymphomas were only considered for this program after a second response to alkylating agents, alone or in combination with vincristine and prednisone [17], particularly if the malignancy had progressed within 12 months of therapy. Transformation of follicular lymphoma was defined on biopsy material of suitable quality as change in histology to diffuse large cell lymphoma. Individuals with transformed NHL were typically treated first with a combination containing cyclophosphamide, daunorubicin, vincristine, and prednisone [18]. Patients with lymphoblastic lymphoma received as induction weekly doses of vincristine (2 mg/m²), asparaginase (10 000 U mg⁻¹), and daunorubicin (25 mg/m²) and daily doses of prednisone (40 mg/m²) for 5 weeks. Those achieving remission received as consolidation 3 weekly chemotherapy courses. Before transplantation these patients received spinal prophylaxis with cytarabine (20 mg) methotrexate (12 mg/m²), and dexamethasone (1 mg) [19]. Patients unresponsive to or progressive on these combinations were rescued with platinum or high-dose cytarabine based programs (dexamethasone, high-dose cytarabine, and cisplatin) [20]. Patients who on restaging were found to have responsive disease, defined as >50% reduction in tumor load, and had an HLA-identical sibling were offered allogeneic stem cell transplantation (SCT).

**Preparation for Transplantation**

The routine management of our patients in preparation for transplantation, transfusion strategy, and antibiotic policies have been previously described [15,16,21]. During the study period 2 myeloablative conditioning protocols were used. One was radiotherapy based and the other consisted of cytotoxic agents only. The selection of the conditioning was derived from the availability of radiotherapy space in a busy tertiary hospital oncology program. The radiation-based conditioning regimen was fractionated total body irradiation delivered in 6 twice-daily fractions of 2 Gy (total, 1200 cGy) and 4 fractions of total lymphoid irradiation of 1.5 Gy followed by cyclophosphamide 60 mg/kg (with mesna cover) on days −2 and −1 [14,16]. When radiotherapy was not available, individuals received conditioning with oral busulfan 1 mg/kg × 12, melphalan 70 mg/m² on 2 consecutive days (total dose, 140 mg/m²), followed by cyclophosphamide 60 mg/kg on 2 consecutive days. Post-transplantation patients received valacyclovir 1 g, 8 hourly, for 3 months. After leukocyte recovery cytomegalovirus (CMV) reactivation was monitored by weekly pp65 determination. Reactivation of CMV was treated with ganciclovir 5 mg/kg twice daily for 14 days followed by ganciclovir 3 mg/kg daily or oral valganciclovir for 3 months.

**Collection of Stem Cells for Transplantation**

The details of our stem cell harvest protocols have been published previously [15]. Briefly, bone marrow (BM) for transplantation was collected under general anesthesia by multiple needle aspirates. Mononuclear cells were subsequently concentrated with an IBM 2997 (Lakeside, Ill) or Cobe Spectra (Gambro, Lakewood, CO) apheresis units. Since October 1996, the
source of stem cells was cytokine (filgrastim, a granulocyte colony-stimulating factor [G-CSF], subcutaneous injections at 5-10 μg/kg daily for 5 days) mobilized peripheral blood progenitor cells (PBPCs) from HLA-identical siblings. Large-volume apheresis was started approximately 4 hours after the last dose of G-CSF. During each procedure, approximately 30 L of blood was processed. In the PBPC grafts, CD34+ progenitors were enumerated by flow cytometry according to guidelines of the International Society for Hematotherapy and Graft Engineering [22] using phycoerythrin-labeled CD34 antibody and fluorescein isothiocyanate-labeled CD45 antibody and appropriate isotypic controls. Based on a patient’s ideal body weight, the target cell dose was >5 × 10^6 mononuclear cells/kg or 2 × 10^6 CD34+ cells/kg. In the event that the target cell dose was not achieved, apheresis was repeated the following day. To confirm engraftment and to determine the origin of hematopoiesis, sex chromosome differences between donor and recipient were determined at 3 months after transplantation by standard cytogenetic analysis of BM cells.

**Treatment with Monoclonal Antibody**

CAMPATH-1G and CAMPATH-1H are directed against CD52, a surface antigen that is present in lymphocytes and monocytes [23]. CAMPATH-1H was prepared from the culture supernatant of Chinese hamster ovary cell transfectants and subjected to a final purification by size exclusion chromatography on a Superdex 200 (Therapeutic Antibody Centre, Oxford, UK) [24]. Stem cell-rich products were then fractionated using CAMPATH-1G and CAMPATH-1H (humanized) and 1-2 mg of antibody per 10^8 mononuclear cells was added in the bag, allowed to react at 20°C for 30 minutes, and infused intravenously without any filters. According to the mononuclear cell number in the transplant cell concentrate, the target dose of antibody was 7.5–45 mg.

In patients undergoing BM transplantation (BMT), no further immunosuppression was provided after BMT. However, as in patients receiving PBPC grafts, a higher incidence of GVHD was observed; 7 patients received prophylactic prednisone at 30 mg daily for 90 days. In the remaining 19 patients, intravenous cyclosporin was commenced on day –1 and, upon recovery of the gastrointestinal tract from the effects of the conditioning, it was continued as an oral formulation until day 90, while maintaining at all times therapeutic blood levels (120-275 ng/mL) [15].

**Graft-versus-Host Disease**

GVHD was defined according to the Seattle criteria [25]. Acute GVHD, grades II-IV, was treated with systemic prednisone (2-10 mg/kg daily) with or without cyclosporin (10 mg/kg daily or according to blood levels). Once this phenomenon was controlled, immunosuppression was tapered off according to clinical response.

**Statistical Analysis**

Chi-square statistic or Fisher exact tests were used to establish differences in the distribution of discontinuous variables and Student t test to compare continuous variables. All reported P values are 2-sided. Overall survival estimates were calculated from date of transplantation to date of death or last follow-up and calculated by the Kaplan-Meier method; comparisons were made using the log-rank test. Disease-free survival was computed from time of transplantation to death or disease recurrence. Univariate and multivariate analyses of variables predicting survival were performed using the log-rank test and the Cox model of proportional hazards, respectively. Multifactorial non-linear regression was used to analyze any relation between survival and the following covariates: type of lymphoma, patient gender, patient age, antibody dose, stem cell dose, and presentation International Prognostic Index (IPI) scores. All data analyses were performed using Statistica (StatSoft Inc, Tulsa Okla).

**RESULTS**

Between 1990 and 2005, 40 consecutive patients gave consent according to the guidelines of the University of Cape Town and Groote Schuur Hospital to undergo transplantation with hematopoietic stem cells from HLA-identical sibling donors. Demographic details, source of stem cells, diagnoses of the malignancy, distribution of disease groups, and outcome are presented in Tables 1 and 2.

In 10 patients the source of stem cells was the BM, whereas 30 received filgrastim (G-CSF) mobilized peripheral blood grafts. Prophylaxis of GVHD was the rat anti-CD52 antibody CAMPATH-1G in the first 12 patients, and the rest received PBPCs that had been treated with CAMPATH-1H, a humanized antibody. The median presentation corrected IPI score has been in use from 1990 (before the follicular lymphoma IPI [26] score became available) and for the entire cohort the score was 2 (range, 1-4). As presented in Table 1, high IPI score was significantly associated with treatment failure. Specific values for each histologic group are presented in Table 2. There was no significant difference in age at transplantation between patients undergoing BMT (median, 42.5; range, 29-55) or PBPC transplantation (median, 46; range, 17-59; P = .6) or between patients receiving the 2 antibody types for T cell depletion. Fourteen (35%) patients received chemotherapy-based conditioning, whereas another 26 patients were conditioned with myeloablative radiotherapy. At transplantation their respective
median ages were 42 years (range, 17-59 years) and 46.5 years (range, 17-62 years; \( P = .2 \)). Median follow-up was 1051 days (range, 16-5598 days), with 62% and 71% surviving. There was no difference in survival between the 2 conditioning groups (\( P = .15 \)).

**Engraftment and Treatment-related Mortality**

Graft characteristics are listed in Table 1 (also see Table 2). Although the median granulocyte-macrophage colony-forming units \( \times 10^4/\text{kg} \) was lower in the BM group (14.3 versus 27.9; \( P = .4 \)) than in the PBPC group, this difference was not significant. Results of CD34 \(^+ \) count were available in 26 collections. The median value was 2.85 \( \times 10^6/\text{kg} \) (range, 1.31-6.2). Except for 1 patient who died of a fungal infection on day 15, all patients recovered their blood parameters after graft infusion. Median time to a granulocyte count \( \geq 0.5 \times 10^9/\text{L} \) and platelet count \( \geq 50 \times 10^9/\text{L} \) was 13 days (range, 9-35 days) and was not significantly different between the BMT and PBSC groups.

Seventeen patients received a stem cell graft from an opposite-gender donor. A karyotypic analysis of their marrow cells showed full donor chimerism in each case. Seven (18%) patients developed GVHD (grade I). Reactivation of CMV was seen in 7 (18%) patients; 5 by a positive pp65 test and 2 after colonoscopy and intestinal biopsy showing CMV colitis. All patients responded to ganciclovir.

Twelve patients died, 6 of disease recurrence, 1 of refractory hepatic GVHD, and 5 of infections (Candida albicans, Pneumocystis carinii, pneumococcal meningitis, multilobar pneumonia), 4 after steroid treatment for clinically relevant GVHD. One patient died of liver failure from progressive hepatic GVHD despite therapy with high-dose steroids, tacrolimus, and azathioprine. One patient developed disease recurrence and is currently receiving donor lymphocyte infusions. Median time to death of the 12 patients was 265 days (range, 16-3863 days) and only 3 died 1000 days after transplantation. Overall, after transplantation, 70% survived at a median of 1719 days (range, 111-5039 days; Figure 1).

Of the various factors analyzed, age-corrected IPI (\( \leq 2 \) versus >2, \( P = .03 \)) and occurrence of GVHD (\( P = .001 \)) were significant adverse factors for survival. Proportional hazards (Cox) regression analysis confirmed that only absence of GVHD significantly predicted a favorable outcome (\( P < .001 \); Figure 2).
plantation. Their median age-adjusted IPI score on first admission was 2 (range, 1-3).

All patients with lymphoblastic lymphoma had extensive disease at presentation, including bulky (n = 4) and extranodal (n = 4) malignancies or infiltration of BM (n = 3) by lymphoma; all these findings are associated with poor prognosis with standard therapies. These patients underwent transplantation in complete remission (n = 3) and the median performance status was 1 (range, 1-2). Individuals with peripheral T cell malignancies received grafts in first complete remission (n = 5) or in subsequent responses after various salvage therapies. After graft infusion 2 died, 1 of fungal sepsis and the other of unresponsive hepatic GVHD.

After transplantation, relapse was seen in 8% of follicular, 18% of transformed, 11% of peripheral T cell, and 37% of lymphoblastic histology. As seen in Figure 3, Kaplan-Meier analysis showed no significant difference in survival in any of the 4 diagnostic groups. Moreover, log-rank analysis failed to confirm that presentation IPI influenced survival after transplantation (IPI 0 + 1 + 2 versus >2; P = .17; data not

Figure 1. Disease-free survival (DFS) and overall survival (OS) for all patients with non-Hodgkin lymphoma (NHL) who received allogeneic grafts depleted of lymphocytes by CAMPATH-1G or 1H.

Figure 2. Survival after allogeneic stem cell transplantation for NHL according to occurrence of graft-versus-host disease (GVHD). The difference is statistically significant with log-rank test.
shown). At the time of this analysis, median follow-up was 1051 days (range, 15-5039 days) and 27 patients (68%) survived without disease.

Source of Stem Cell Grafts, T Cell Depletion, and GVHD

CAMPATH-1G was employed in 10 patients who received BM and in 2 who had PBPC grafts, and the remainder received PBPC products treated with CAMPATH-1H (Table 2). For ex vivo treatment of grafts, the median dose of CAMPATH-1H employed was 13.75 mg (range, 10-40 mg), which was higher in the BMT group (20 mg; range, 10-30 mg) than in the PBPC group (median, 10 mg; range, 7.5-30 mg; P = .05). In total 7 patients developed acute or chronic GVHD, but none developed the hyperacute forms of this complication. None of the patients whose stem cells were treated with CAMPATH-1G received post-transplantation immunosuppression. From this group, 1 of 10 patients who received BM transplants developed grade II acute GVHD but this did not progress to the chronic form. Because all 3 patients who received PBPC grafts purged with CAMPATH-1H and had no further immunosuppression developed aggressive but corticosteroid-responsive GVHD (grade II), post-transplantation prednisone 30 mg/day or cyclosporin for 90-120 days was prescribed for the last 7 and 20 individuals, respectively. After this protocol amendment, only 2 subjects (P = .06) and 1 subject (P = .001), respectively, developed this complication. The corresponding survivals among patients receiving grafts that had been treated with CAMPATH-1G or 1H were 64% and 72% (P = .2), but increased to 84% in those who received cyclosporin.

After engraftment, acute GVHD grade ≥II was detected in 7 patients (grade II in 6; grade IV in 1), and 3 developed the chronic form (1 extensive chronic GVHD); all progressed from the acute presentation. Three patients died of infection while receiving treatment with corticosteroids and cyclosporin for symptomatic GVHD. Another who had no evidence of GVHD also died of infection while still on treatment with immunosuppressive therapy. Two individuals with clinical features of GVHD had disease recurrence and died of lymphoma despite salvage therapy. For the entire study group, the 2-year survival was 77%.

As part of another study, immune reconstitution analysis was done in 11 patients [27]. It showed rapid recovery of the CD8+ and CD56+ lymphocytes but significant delay in recovery of the CD3+CD45RA+ and CD4+CD45RA+ (naive) population, with normalization of all parameters by 18 months after transplantation (data not shown).

Although overall no significant difference in survival between the 2 antibody-treated groups was elicited, in univariate analysis the survival was significantly associated with a lower (than median) dose of CAMPATH-1, lower presentation IPI score (IPI = 0 + 1), absence of clinically relevant GVHD, and post-transplantation treatment with cyclosporin (surviving 84%; P = .05). Cox logistic regression analysis confirmed that only occurrence of GVHD remained significantly associated with worse outcome (Figure 2; P < .001). Median follow-up exceeded 3 years in 20 patients, and at median of 2610 days (range, 1120-4401 days) 3 individuals died of recurrence of lym-

Figure 3. Overall survival after allogeneic stem cell transplantation for NHL according to histologic type of lymphoma. T-NHL indicates transformed NHL.
phoma (n = 2) and infection (associated with chronic GVHD).

Toxicity

All patients developed grade IV hematologic toxicity and required transfusion support with red cells and platelets. Pyrexia requiring intravenous antibiotics was seen in 89% of patients and 1 died of unresponsive C. albicans sepsis. Radiotherapy-based conditioning was well tolerated and only 15% of patients (2 in BMT group and 4 in PBPC group) developed gastrointestinal toxicity of grade >2 according to the World Health Organization. In the chemotherapy-conditioning cohort, 4 patients developed grade >2 mucositis. One patient developed fatal GVHD of the liver.

DISCUSSION

Indolent NHLs are associated with favorable responses to various forms of chemotherapy and biological cell modifiers, but with conventional chemotherapy these diseases tend to recur and remain incurable. Further, despite modern salvage therapy, patients with follicular morphology who develop histologic transformation or have refractory disease have poor outcome and generally die of their malignancy within 1 year [3,4,28]. In an attempt to improve responses, investigators have applied myeloablative conditioning followed by autologous SCT and have shown that these lymphomas are generally sensitive to such intensified chemotherapy [9,10,28,29]. However, in patients with indolent NHL treated with SCT, a persistent tendency for disease recurrence has been observed [30,31]. In addition, a proportion of patients developed myelodysplastic syndromes and acute leukemia, probably secondary to extensive exposure to cytotoxic chemotherapy, and therefore no convincing improvement in survival has been demonstrated with this modality. Similarly, patients with T cell lineage (non-CD30+) lymphoma may initially be responsive to therapy but have high recurrence rate, and with conventional cytotoxic therapy their diseases have mainly remained incurable [8]. In this regard, lymphoblastic lymphoma is also highly responsive to chemotherapy; however, those who on presentation have extranodal disease, high disease bulk, or BM infiltration have less good outcome [8].

Allogeneic SCT has curative potential in patients with hematologic malignancies, particularly if patients have remained responsive to chemotherapy [10,28,29]. However, patients with lymphoproliferative disorders are older and may have already undergone autologous SCT, thus explaining the higher morbidity and mortality of the high-dose conditioning and particularly from GVHD. In another study, the incidence of GVHD (grade II-IV) in such patients was 55%, leading to 100-day mortality of 34%, although the overall survival was 45% [29,30]. Only at 6 years did the survival curves of autologously and allogeneically transplanted patients cross, with continuing relapses observed in the autologous group [30]. For this reason, less toxic conditioning schedules have been described that are mainly immunosuppressive and resulting in good engraftment rates with low toxicity-related mortality [14,32]. However, such combinations have been less successful in preventing malignant recurrence in patients with refractory or transformed lymphomas [33].

The role of myeloablative conditioning and transplantation in lymphoma has been better clarified by Bierman et al [29] who compared the outcome of patients receiving autologous, unfractionated allogeneic, T cell-depleted, and syngeneic stem cell grafts after myeloablative conditioning. There was no difference in relapse across the 3 forms of allogeneic SCT, suggesting that the graft-versus-lymphoma effect was not very different among the 3 sources of stem cells. This implied that absence of malignant cells from the graft in the allogeneic source had greater importance than the immunologic effect of transplantation. This has also been our experience with T cell depletion with CAMPATH-1H antibodies.

Lymphocyte purging of the graft remains the most effective strategy for the prevention of GVHD [34]. Although concerns have been raised regarding loss of the graft-versus-tumor effect, we recently found that in patient receiving grafts treated ex vivo with CAMPATH-1H and after transplantation with cyclosporin for 90 days, the disease relapse and treatment-related mortality rates were low, which resulted in good overall survival. Moreover, there was no difference in outcome between young and older patients, suggesting that this modality could be used up to the age of 60 years [16]. An important cause of mortality was infection, which even after hematopoietic recovery, led to recurrent admissions. It was the main cause of death in patients developing GVHD. Although in a previous study we reported delayed immune reconstitution, in the present study it did not lead to increased reactivation of CMV [27]. Overall, 8 individuals developed disease recurrence, at a median of 6.5 months. The 40-month event-free and overall survival rates were estimated at 54% and 59%, respectively (Figure 1). In the present study, patients with recurrent but still chemotherapy-sensitive follicular disease did particularly well (Figure 3) and only 1 patient relapsed. A similar experience was reported by Mandigers et al [35]. Particularly encouraging was the outcome of patients with transformed lymphoma because with standard approaches survival seldom exceeds 18 months. Although peripheral T cell lymphomas remain mostly incurable with standard chemotherapy
and even with high-dose therapy outcomes remain poor [36], in the present series their long-term disease-free survival remained at 78%. One strength of studies with conventional conditioning is the demonstration of very few late relapses, a feature that has yet to be confirmed in the majority of patients receiving reduced intensity conditioning schedules.

It may be argued that our patient cohort had a more favorable prognosis because none had undergone a previous SCT; however, all had advanced disease as evidenced by multiple courses of chemotherapy before transplantation or had aggressive histology. In our series, the median survival for the entire group has not been reached, and at a median follow-up of 1501 days 70% are alive (1 responding to donor lymphocyte infusion) and 68% are in response. This encouraging outcome in this group of lymphomas is suggestive that, when the procedure-related mortality is low, the strategy of earlier transplantation, before disease becomes refractory to salvage therapy, is appropriate and should be strongly considered.

In conclusion, this study reinforces our previous observations that allogeneic SCT with standard conditioning leads to adequate clearance of the disease and is well tolerated in the absence of GVHD. In our experience the prevention of clinically relevant GVHD has resulted in a significantly better outcome (Figures 1 and 3) and a better overall survival [15,16]. As previously described in another study in patients receiving autologous, syngeneic, and allogeneic T cell-depleted transplants for NHL, this latter strategy was also associated with a low recurrence rate in the long term [29]. However, only a randomized trial of adequate statistical power comparing well-defined groups of patients receiving reduced intensity conditioning or myeloablative approaches (with unfractionated or T cell-depleted grafts) can clearly show the role of each approach. Until such studies are completed, although patients with follicular lymphoma may be treated with either modality, those with transformed lymphoma and with T cell disease should be considered candidates for myeloablative conditioning.

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