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Long-Term Survival after Autologous Bone Marrow Transplantation for Follicular Lymphoma in First Remission

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ABSTRACT

The role of autologous stem cell transplantation (ASCT) in the treatment of follicular lymphoma is still being defined in the era of antibody therapy. Here we report the long-term 12-year clinical outcomes of patients treated with autologous bone marrow transplantation (ABMT) for follicular non-Hodgkin's lymphoma (NHL) in first remission. Between 1988 and 1993, advanced-stage follicular NHL patients in need of initial therapy were enrolled in 2 consecutive prospective treatment trials of either standard-dose CHOP induction (83 patients) or high-dose CHOP plus granulocyte-colony stimulating factor (G-CSF) (20 patients). Patients who achieved an adequate remission with induction therapy underwent conditioning with cyclophosphamide and total body irradiation (TBI) followed by ABMT in first remission using bone marrow (BM) purged in vitro with anti-B cell monoclonal antibodies and rabbit complement (96 patients). At 12-year follow-up, 61% of the patients are alive and 43% remain in continuing complete remission. The only predictors of decreased progression-free survival proved to be histologic BM involvement at time of harvest (hazard ratio [HR] 2.27, 95% confidence interval [CI] 1.3-3.9, $P < .004$) and PCR detectable disease in the BM product after purging (HR 4.18, 95% CI 1.99-8.8, $P = .0002$). No significant predictors of overall survival were identified. These results at 12-year follow-up suggest that a subset of follicular lymphoma patients can experience prolonged survival with ABMT in first remission.

KEY WORDS

Autologous • Bone marrow transplantation • Follicular lymphoma • First remission
Purging • PCR

INTRODUCTION

The role of high-dose chemoradiotherapy and autologous stem-cell transplantation (ASCT) in the treatment of follicular lymphoma (FL) remains controversial, particularly with the advent of antibody-based therapies. Multiple phase II studies in FL have suggested that ASCT can result in prolonged remissions, albeit at the cost of significant toxicity, primarily secondary myelodysplastic syndromes/acute myelogenous leukemia (MDS/AML) and now increasingly solid tumors [1-14].

Since the initiation of these Phase II studies, multiple randomized trials have now been reported that address the role of ASCT in follicular non-Hodgkin's lymphoma (NHL). For relapsed patients, the European CUP trial found that 2-year progression-free survival (PFS) was improved from 26% with standard chemotherapy to 55%-58% in the combined purged and unpurged ASCT arms, and that 4-year overall survival (OS) improved from 46% to 71%-77% [15]. For patients transplanted in first remission, both the German Low-Grade Lymphoma Study Group (GLSG) and the GOELAMS group have reported

significantly improved PFS with ASCT, albeit in the GLSG case offset by increased second malignancies [11,16]. The GELA failed to see any PFS benefit in an intent-to-treat analysis that included patients who did not respond to induction, and therefore did not receive ASCT, and with a comparison arm that received 18 months of continuous therapy [17]. These studies have therefore suggested a benefit of ASCT for relapsed patients with FL, and have been inconclusive with respect to patients in first remission, raising the possibility that PFS may be improved, if secondary toxicities could be minimized. In this study we report the very long-term clinical outcomes of a population of FL patients treated with autologous bone marrow transplantation (ABMT) for consolidation of first remission, with 43% of the patients remaining in continuous complete remission (CCR) with few late relapses at a median follow-up of 12 years.

PATIENTS AND METHODS

Selection of Patients and Treatment Protocol

Patient eligibility and selection were identical for each of these 2 sequential prospective studies. Patients were eligible for high-dose therapy and ABMT in first remission following CHOP induction if they met the following criteria: physiologic age 55 years or less; previously untreated follicular low-grade B cell NHL as defined by the Working Formulation (WF), including: follicular small cleaved cell (WF-B), and follicular mixed small cleaved and large cell (WF-C); and CD20 (B1) antigen expression on their lymphoma cells as previously described [18]. All pathology was reviewed at Brigham and Women's Hospital. Patients had to have advanced stage disease, including IIIB, IIIE, II with masses >10 cm, or stage IV disease. Patients with stage IV disease with minimal adenopathy (<1 cm) and <5% bone marrow (BM) involvement were excluded. Additional criteria for entry included the absence of comorbid disease of the heart, kidney, lung, and liver, and a Karnofsky score >80%. All protocols were approved by the Dana-Farber Cancer Institute (DFCI) institutional review board, and informed consent was obtained from all patients prior to therapy.

All patients were registered prior to initiation of CHOP; a subset of patients received their CHOP induction with their referring physicians. Eighty-three patients were treated with 6-8 cycles of SD-CHOP (cyclophosphamide 750 mg/m^2 i.v. on day 1; doxorubicin 50 mg/m^2 i.v. on day 1; vincristine 1.4 mg/m^2 (maximum 2 mg) i.v. on day 1; and prednisone 100 mg/day orally on days 1-5). Twenty patients received 4 cycles of HD-CHOP every 3 weeks [19]. This regimen consisted of cyclophosphamide 1.5 g/m^2/day i.v. on days 1 and 2; doxorubicin 50 mg/m^2 i.v. on day 1; vincristine 1.4 mg/m^2 (maximum 2 mg) i.v. on day 1; and prednisone 100 mg/day orally on days 1-5. Mesna was given by i.v. bolus as uroprotectant. Granulocyte-colony stimulating factor (G-CSF) 5 μg/kg/day s.c. was given on days 4-18 of each cycle. No dose modifications were permitted on either protocol. All patients received prophylactic acyclovir and trimethoprim-sulfamethoxazole during each cycle.

At the completion of SD-CHOP or HD-CHOP, patients in CR (<1 cm lymph nodes and no BM involvement) or minimal disease state (<2 cm lymph nodes and <20% BM involvement, defined as the percent involvement of the intertrabecular space on iliac crest biopsy) went on to BM harvest within 4 weeks of completing chemotherapy. After SD-CHOP, 10 patients (13%) with 1-3 masses >2 cm received involved field radiotherapy. After completion of HD-CHOP, 2 patients (11%) with 1 mass >2 cm received involved field radiotherapy.

In patients not receiving involved field radiotherapy, admission for ABMT was within 4 weeks of BM harvest. Conditioning therapy for ABMT consisted of cyclophosphamide 60 mg/kg infused on each of 2 consecutive days before radiotherapy. Total body irradiation (TBI) was administered in fractionated doses (200 cGy) twice daily on 3 consecutive days (total of 1200 cGy) in all patients. Patients who were treated with SD-CHOP induction did not receive any hematopoietic growth factors following ABMT. All patients who received HD-CHOP induction received hematopoietic growth factors following ABMT. A significant prolongation of neutrophil and platelet engraftment was observed in patients who had received HD-CHOP with G-CSF, as previously reported [20]. Supportive care was provided as previously described [21].

Collection, Processing, and Infusion of Marrow

BM was obtained, treated in vitro with anti-B1 (CD20), -B5, and -J5 (anti-CD10) monoclonal antibodies (mAb) and rabbit complement, and cryopreserved as previously described [21]. Nested PCR amplification at the major breakpoint region (MBR) and minor cluster region (mcr) of the bcl-2/IgH rearrangement of t(14;18) were performed as previously described; only those samples in which a rearrangement could be detected in initial diagnostic material were considered evaluable [22]. No patients were excluded from the protocol after BM harvest. Within 18 h of the completion of TBI the cryopreserved marrow cells were reinfused as previously described [21]. No subjects treated on these protocols received peripheral blood stem cells (PBSC).

Follow-up

All patients had routine physical examinations and laboratory studies, including complete blood counts,

every 3 months for the first year, then every 6 months for the second year, then annually following transplantation. Patients underwent BM aspiration and core biopsy for persistently low peripheral blood counts without an obvious explanation. For those patients alive but not continuing to obtain follow-up care at DFCI, follow-up phone calls to their physicians were made annually.

Classification of MDS

As in our previous reports of MDS in this patient population [4], MDS was strictly defined using the French-American-British (FAB) classification system and required BM dysplasia in at least 2 lineages with peripheral cytopenia(s). Although cytogenetic abnormalities were evaluated, their presence was not diagnostic. Patients with persistent cytopenias after bone marrow transplantation (BMT) without significant marrow dysplasia, or with alternative explanations for their cytopenias, were not considered to have MDS.

Statistical Methods

OS is defined as the time from the day of marrow infusion (day 0) to death from any cause. PFS is defined as the time from the day of marrow infusion to the first reported outcome event. Outcome events include progression of disease or death from any cause. PFS and OS curves were obtained using the Kaplan-Meier method, with 95% confidence intervals (CI) calculated using Greenwood's formula, and compared by the log rank test [23,24]. The effects of the potential prognostic factors for PFS and OS were assessed using Cox multivariable regression models.

The cumulative incidence of second malignancies or relapse in the presence of competing risks (death without second malignancies or death in remission, respectively) were calculated using competing risk analysis [25].

RESULTS

Patient Characteristics

Between April 1988 and June 1993, 103 patients with previously untreated, advanced stage FL were registered on 2 consecutive protocols of induction chemotherapy followed by ABMT. The characteristics of these patients have been previously described [18,20] and are summarized in Table 1. Follicular Lymphoma International Prognostic Index (FLIPI) scores have been retrospectively assigned for the majority of patients prior to therapy, with 58% having intermediate FLIPI scores. All patients were under 60 years of age, and because of the retrospective nature of the data collection, 21% of patients had missing data that if known may have upstaged their FLIPI risk group. There were no statistically significant differences between the patients who received SD-CHOP or HD-CHOP [20].

Table 1. *Patient Characteristics*

Total Registered	**103**
Induction	
Standard-dose CHOP	**83**
High-dose CHOP	**20**
Reached minimal disease, underwent	
ABMT	**96 (93%)**
CR	**35%**
Age (range)	**42 (19-57)**
Stage	
II	**4 (4%)**
III	**17 (18%)**
IV	**75 (78%)**
LDH	
High	**11 (11%)**
Normal	**64 (67%)**
Missing	**21 (22%)**
Nodal sites	
1-4	**24 (25%)**
5-8	**70 (73%)**
Missing	**2 (2%)**
FLIPI	
Low (0-1)	**24 (25%)**
Intermediate (2)	**56 (58%)**
High (3-5)	**16 (17%)**
Missing values*	**20 (21%)**

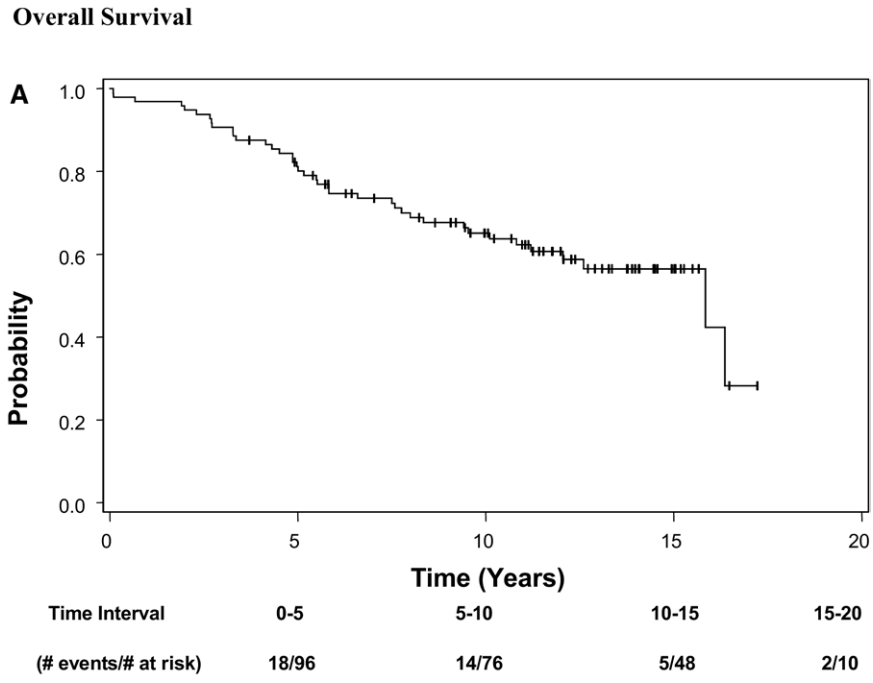
FLIPI indicates Follicular Lymphoma International Prognostic Index; LDH, lactate dehydrogenase; CR, complete remission; ABMT, autologous bone marrow transplantation.

*Twenty-one percent of patients had missing values assumed to be low risk in the classification above, which may therefore represent an underestimate of actual FLIPI score.

Following SD-CHOP 77 of 83 patients (93%) achieved a minimal disease state and went on to ABMT. Three patients did not attain a protocol eligible partial remission (PR), 2 patients were diagnosed with second tumors (melanoma and seminoma), and 1 patient declined further therapy. Following 4 cycles of HD-CHOP, 19 of 20 patients were in a minimal disease state, whereas 1 patient progressed with a high grade lymphoma within 1 month of induction therapy. The CR rates to SD-CHOP and HD-CHOP were 36% and 31%, respectively.

Clinical Outcomes

At a median follow-up of 12 years, 61% (95% CI 49.5-70.1) of patients are alive (Figure 1A), and 43% (95% CI 32.3-52.7) of patients remain in CCR (Figure 1B). The overall mortality is 41%, with a median PFS of 7.3 years (95% CI 4.3-NA), and median OS of 15.8 years (95% CI 12.1-NA). Forty-six percent (N = 44) of patients have relapsed with FL, with 25% (N = 24) dying of disease, 5% (N = 5) dying of other causes, and 16% (N = 15) alive following relapse (Table 2). The median time to relapse in patients who have relapsed was 2.3 years; only 6 relapses have occurred at more than 6 years posttransplant. The cu-



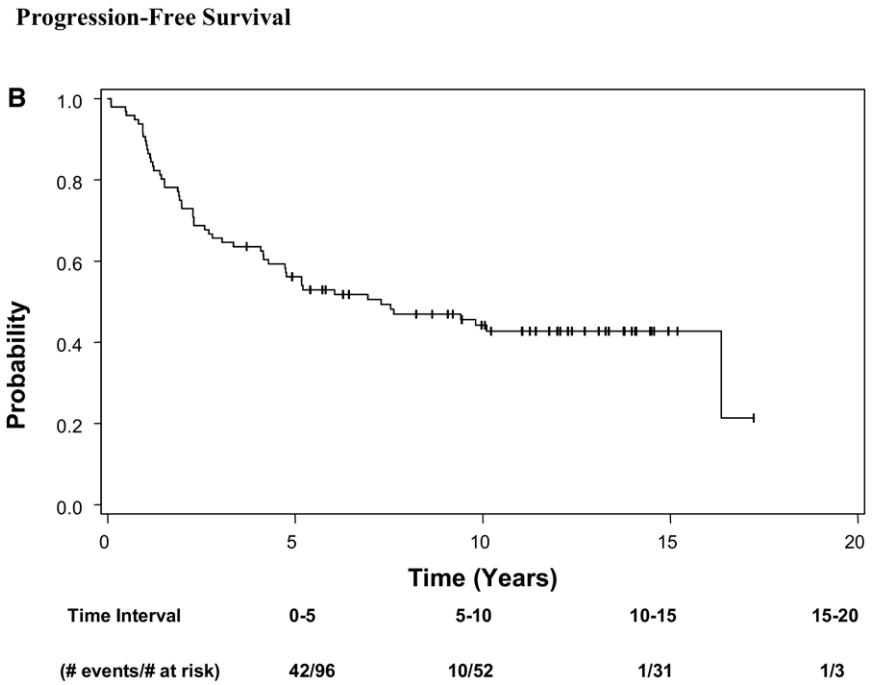


Figure 1. A, OS: at a median follow-up of 12 years, 61% (95% CI 49.5-70.1) of patients are alive. B, Progression-free survival: at a median follow-up of 12 years, 43% (95% CI 32.3-52.7%) of patients remain in ongoing complete remission.

mulative incidence of relapse, with death in remission a competing risk, is 37% at 5 years, and 47% at 10 and 15 years (Figure 2). The median survival following relapse is 6.1 years (95% CI 4.1-9.0). Ten patients have died in remission, 5 from MDS/AML, 2 early in hospital because of diffuse alveolar hemorrhage (DAH), 1 because of suicide, and 2 of unknown causes. The late deaths on the OS curve in Figure 1A are deaths in remission, primarily resulting from MDS.

Twenty-eight percent of patients (N = 27) have developed a second malignancy, at a median of 8.3 years following ABMT. These malignancies include: 10 cases of MDS/AML, 2 non-MDS hematologic malignancies, 9 solid tumors, and 10 nonmelanoma skin cancers (Table 2). The cumulative incidence of second malignancy, with death without second malignancy a competing risk, is 16% at 10 years and is estimated to be 38% at 15 years (Figure 3). 9.4% (N = 9) of

Table 2. *Clinical Outcomes*

Total subjects undergoing ABMT	**96**
Continuous complete remission	**42 (median F/U 12 years)**
Relapse (alive)	**44 (15)**
Deaths in remission	**10 (10%)**
DAH	**2**
MDS/AML	**5**
Other	**3 (1 suicide, 2 unknown)**
Secondary malignancies (N = 27 patients)	
MDS/AML	**10**
Non-MDS heme	**2**
Solid	**9**
Breast (3); prostate (1); rectal (1); melanoma (1); renal cell (1); bladder (1); anal in situ (1)	
Nonmelanoma skin	**10**

ABMT indicates autologous bone marrow transplantation; MDS, myelodysplastic syndromes; AML, acute myelogenous leukemia; DAH, diffuse alveolar hemorrhage.

patients have died of secondary malignancy (8 MDS/AML, 1 metastatic breast cancer).

Predictors of PFS and OS

Patient characteristics were investigated for their ability to predict PFS or OS in univariate log-rank analysis. No effect of age at ABMT, stage at diagnosis, sex, hemoglobin, lactate dehydrogenase (LDH), number of nodal sites, induction therapy (SD-CHOP versus HD-CHOP) or involved field radiation therapy was observed. No effect of FLIPI score was observed on PFS or OS (data not shown), including when the subgroup of patients with missing data is analyzed separately. Achieving a CR after induction chemotherapy was of borderline significance in predicting PFS ($P = .05$, log-rank test) but was not significant for OS.

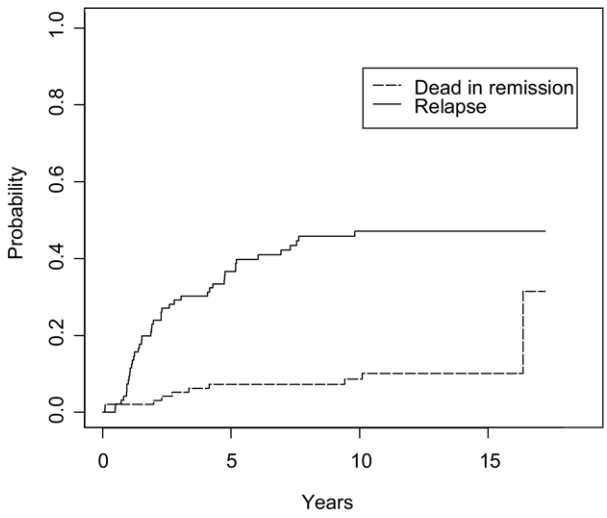


Figure 2. Cumulative incidence of relapse. The cumulative incidence of relapse, with death in remission taken as a competing risk, was 37% at 5 years and 47% at 10 and 15 years.

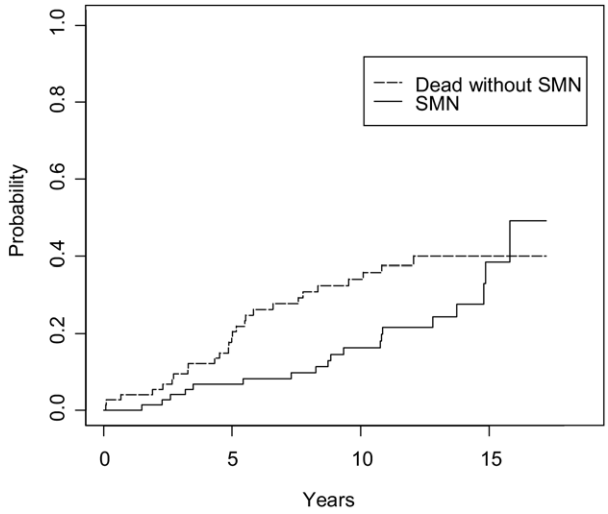
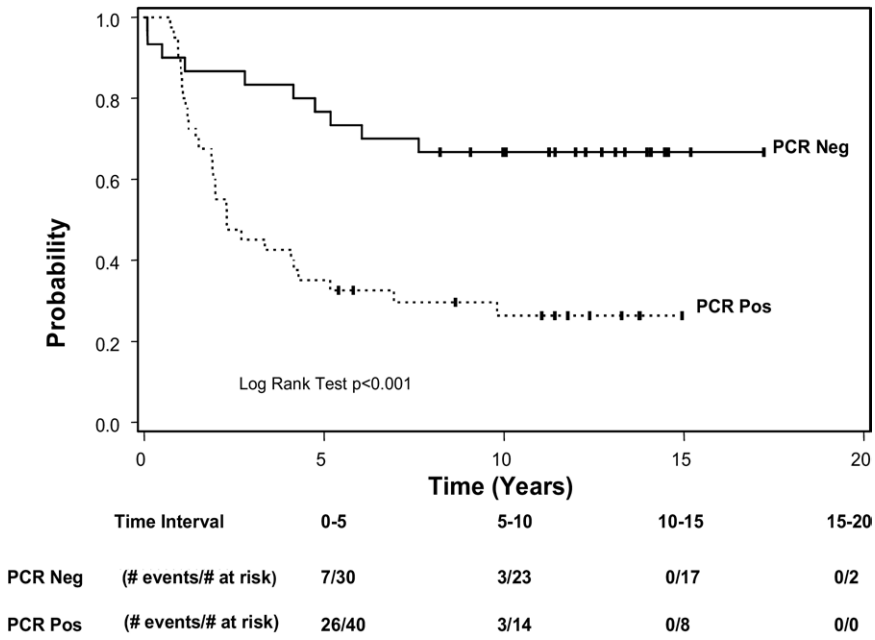


Figure 3. Cumulative incidence of second malignancy. The cumulative incidence of second malignancy, with death without second malignancy taken as a competing risk, was 16% at 10 years and 38% at 15 years.

Residual BM disease prior to harvest was found to be a significant predictor of PFS in univariate analysis, with subjects with no detectable tumor cells having a 12 year PFS of 50% (95% CI 34.8-63.5), whereas those with <5% BM involvement had PFS of 38.9% (95% CI 23.3-54.2) and those with 5%-20% BM involvement, 12.5% (95% CI 0.7-42) ($P = .005$ log-rank test; data not shown). No effect was observed on OS, however (data not shown, $P = .21$ log-rank test). When analyzed in a 2-group model (BM involved or uninvolved), the results for PFS and OS are similar (data not shown).

The effect of BM purging was also analyzed in 70 patients with known detectable bcl-2/IgH translocations prior to therapy, who had postpurging BM samples analyzed by PCR. Among the 30 patients whose BM infusion was PCR negative, 7 have relapsed. Among the 40 patients whose BM infusion was PCR positive, 25 have relapsed. The median time to relapse was 4.1 years in the PCR positive group, and has not been reached in the PCR negative group, 25% of whom have relapsed at 7.6 years ($P = .0005$, log-rank test). PCR status was a significant predictor of 12-year PFS, at 66.7% (95% CI 46.9-80.5) for the PCR negative group compared to 26.3% (95% CI 13.6-40.9) for the PCR positive group ($P = .001$ log rank test; Figure 4). No statistically significant effect was observed on OS, which was 76.7% (95% CI 57.2-88.1) for the PCR negative group and 50.7% (95% CI 33.8-65.3) for the PCR positive group ($P = .08$ log rank test).

We investigated the interaction between detectable disease in the BM and the likelihood of achieving



Time Interval		0-5	5-10	10-15	15-20
PCR Neg	(# events/# at risk)	7/30	3/23	0/17	0/2
PCR Pos	(# events/# at risk)	26/40	3/14	0/8	0/0

Figure 4. PCR detectable disease after purging predicts PFS. 12 year PFS was 66.7% (95% CI 46.9-80.5; n = 30) for those patients whose postpurging bone marrow was negative by PCR, compared to 26.3% (95% CI 13.6-40.9%; n = 40) for those with positive PCR (P = .001 log-rank test). No effect was observed on OS (76.7% for PCR negative and 50.7% for PCR positive, P = .08 log-rank test).

PCR negativity after purging. Of evaluable patients without histologically detectable BM disease, 21 of 35 were PCR positive (60%). Of those with <5% BM involvement, 14 of 29 were PCR positive (48%). Only 6 patients with 5%-20% BM involvement were evaluable and 5 of 6 were PCR positive (83%; P = .99 Exact Kruskal-Wallis test).

A multivariate Cox proportional hazards regression analysis was performed to evaluate the impact of pretransplant factors on PFS and OS. Variables that were investigated include age, sex, stage, LDH, hemoglobin, FLIPI, number of nodal sites, type of induction therapy, CR or PR after induction, presence or absence of residual BM disease, and PCR status after purging. The only significant predictors of PFS were presence of residual BM disease (HR 2.27 [95% CI 1.3-3.9], $P < .004$), and detectable disease by PCR (HR 4.18 [95% CI 1.99-8.8], $P = .0002$) (Table 3). Those patients without PCR data were included in the multivariate model, and had an intermediate hazard ratio (HR 2.39 [95% CI 1.06-5.4], $P < .04$). No variables were significant predictors of OS in multivariate Cox proportional hazards regression analysis.

DISCUSSION

Since the initiation of the studies reported here, new data have accumulated on the role of ASCT in the treatment of follicular NHL, including data from randomized trials that have failed to demonstrate OS benefit. The significant incidence of long-term treatment-related toxicity, particularly MDS/AML, has also become clear in numerous reports [1-14]. The role of ASCT in the treatment of FL has therefore remained controversial. The very long-term follow-up of this study does suggest that a significant subset of FL patients treated with ASCT for consolidation of first remission can experience prolonged disease-free survival (DFS). Given the low frequency of late relapses, these data do raise the question of cure with this modality.

Table 3. *Predictors of PFS and OS*

	PFS: Hazard Ratio	P	OS: Hazard Ratio	P
Residual bone marrow disease	**2.27 (1.3-3.9)**	**<.004**	**1.67 (0.87-3.2)**	**.12**
PCR detectable disease	**4.18 (1.99-8.8)**	**.0002**	**2.08 (0.9-4.6)**	**.069**

PFS indicates progression-free survival; OS, overall survival.

This Cox proportional hazards model includes all 96 patients, with three categories for postpurging PCR status: positive, negative, and missing. The missing category includes 19 patients whose postpurging PCR was not done, and 7 patients in whom a pretreatment translocation was not detected by PCR.

However, given the negative randomized trials, rate of second malignancies and availability of novel standard therapies that include rituximab, ASCT cannot be considered an appropriate standard therapy for FL in first remission. If ASCT is to be used routinely in patients with follicular lymphoma, patient selection will be critical. Since this study was designed, the FLIPI has been proposed to better standardize patient risk and predict prognosis [26]. Although the patients enrolled on this study were clinically perceived to be high risk, most are intermediate risk using the FLIPI score, which is likely in part because of missing data and in part because of their young age. Direct comparison to FLIPI results is difficult, but our observed OS of 61% at 12 years appears favorable for patients under 60 with intermediate FLIPI scores [26], the closest comparison group. Furthermore, ASCT as used in this study appears to overcome the adverse effects of intermediate to high FLIPI, a finding similar to that of the randomized trials of ASCT in FL in first remission [11,16,17]. These results also correlate well with 1 report that maintenance rituximab after induction may overcome the adverse prognosis of high FLIPI [27]. Taken together these data may suggest that consolidation or maintenance therapy in remission, including ASCT, may counteract the adverse impact of a higher risk FLIPI score. Ultimately, improved risk stratification is needed, and will likely be based on molecular features that are emerging from gene expression microarray studies [28].

In this study, the only disease- or ABMT-related factors that predicted 12-year PFS were BM involvement at harvest and PCR-detectable disease in the purged BM product. These factors remain predictive at this very long follow-up. Patients with unmistakable histologic BM involvement were at high risk of early relapse but were too few in number to assess the likelihood of achieving PCR negativity after purging. Patients with BM <5% involved histologically were evenly split with respect to PCR status, likely reflecting 2 groups of patients: some with true disease involvement who responded to purging, and others in whom the <5% lymphoid aggregates may not have represented actual disease. These possibilities may explain why both BM involvement and PCR status remain significant in the multivariate model. Those patients who were PCR positive had a very high relapse rate, possibly resulting from a direct effect of tumor contamination of the autograft, but alternatively PCR positivity may be a surrogate marker of aggressive treatment resistant disease. Conversely, 28% of patients with PCR positive BM products remain progression-free, with a suggestion of a plateau on the survival curve. This finding may represent residual DNA contamination without viable cells in the purged product, immunologic control of residual disease, or good fortune.

Assessing the true benefit of ASCT has been complicated by the high incidence of second malignancies after ASCT. Deaths in remission primarily from second malignancy may explain our inability to identify factors predictive of OS in this study. The rate of long-term secondary malignancies in this ABMT population treated in first remission is comparable to our previously reported rates in the ABMT population treated in second or greater remission [4,8], suggesting that earlier use of ASCT does not reduce the incidence of second malignancy. In the GOELAMS randomized trial [16] using a TBI-containing regimen, a higher event-free survival (EFS) for the ASCT arm was offset in OS by excess second malignancies. At the DFCI, second malignancies have declined since chemotherapy-based conditioning replaced the cyclophosphamide-TBI conditioning regimen used in these studies [4].

Ultimately the role of ASCT in the current treatment of follicular NHL remains to be defined, particularly given the advent of nonmyeloablative allogeneic stem cell transplantation [29-31], as well as the range of novel antibody-based therapies, radioimmunotherapy, and small molecule targeted inhibitors increasingly available for the treatment of this disease. Since the initiation of these studies, the addition of rituximab to chemotherapy has significantly improved PFS and OS in FL, with additional benefit likely from maintenance therapy [32-34]. Nonetheless, rituximab-containing therapies explored to date are not likely to be curative, and may therefore need to be considered in combination, perhaps with ASCT. The GITMO group recently reported a 30% improvement in 3-year EFS for upfront rituxan-containing high-dose therapy in comparison to R-CHOP, raising the possibility that ASCT outcomes may also be improved by these novel therapeutic approaches [35]. The similarity in ABMT outcomes reported here in DFCI patients treated in first remission, and our recently reported outcomes of patients treated in second remission at DFCI and St. Bartholomew's Hospital in London [36], suggest that FL patients treated with ASCT whether in first or slightly later remission may achieve similar benefits with similar risk of second malignancy. Given the findings of the randomized CUP trial suggesting benefit of ASCT in second remission, this time point may be the most appropriate for further investigation of the role of ASCT in FL, likely in combination with rituximab.

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