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Long-Term Outcomes of Autologous Stem Cell Transplantation for Follicular Non-Hodgkin Lymphoma: Effect of Histological Grade and Follicular International Prognostic Index

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ABSTRACT

Although results of autologous stem cell transplantation (SCT) for recurrent follicular non-Hodgkin lymphoma (NHL) have been previously reported, the long-term results and evaluation of prognostic factors in a large patient population receiving this therapy are difficult to find in the literature. To address these issues, we evaluated 248 patients with recurrent follicular NHL treated with high-dose chemotherapy and autologous SCT between 7/87 and 6/03. According to the World Health Organization (WHO) classification system, 64 patients (26%) had follicular NHL grade 1 (FL 1), 98 (40%) had FL 2, and 86 (35%) had FL 3. At the time of transplantation, 88 of the patients (35%) had a Follicular Lymphoma International Prognostic Index (FLIPI) score of low risk, 87 (35%) had an intermediate-risk FLIPI score, 37 (15%) had a high-risk FLIPI score, and 36 (15%) had at least 1 missing value, preventing calculation of the FLIPI score. The 5-year overall survival (OS) for all patients was 63%, and the 5-year progression-free survival (PFS) was 44%. In a multivariate analysis, a histological grade of FL 3, a high-risk FLIPI score at the time of transplantation, and having received 3 or more previous chemotherapy regimens were significant factors for predicting a worse OS. In addition, the use of a transplantation regimen including a monoclonal antibody decreased the relative risk of progressive lymphoma. These data suggest that transplantation earlier in the course of the disease for patients with follicular lymphoma with use of a monoclonal antibody–based regimen may lead to improved outcomes.

KEY WORDS

Autologous stem cell transplantation • Follicular • Non-Hodgkin lymphoma

INTRODUCTION

Although patients with grades 1 and 2 follicular non-Hodgkin lymphoma (NHL) typically have an indolent clinical course, the disease is not believed to be curable with standard chemotherapy or monoclonal antibodies (mAb). Most patients can experience prolonged remissions with combination chemotherapy with or without immunotherapy [1-4]. However, once a patient relapses after initial therapy, the time that the patient stays in remission with each subsequent therapy typically decreases from the previous remission duration [5].

Numerous treatment options are available for recurrent follicular NHL are numerous, and the optimal therapy is unknown. The role of high-dose chemotherapy and autologous stem cell transplantation (SCT) for recurrent follicular NHL remains controversial. Although several phase II trials have reported outcomes of patients with recurrent follicular NHL receiving this therapy [6-9], only 1 phase III trial

comparing autologous SCT to conventional therapy—the CUP trial [10]—has been published. These trials support the position that high-dose chemotherapy in chemosensitive follicular lymphoma (FL) patients may improve the progression-free survival (PFS) compared with conventional chemotherapy in historical controls [6-9] or matched controls in the case of the CUP trial [10]. However, in some of these trials, advantages in overall survival (OS) are more difficult to discern compared with historical controls [7]. Determining the patient population most likely to benefit from this type of intense therapy may improve the outlook for patients with recurrent follicular NHL and spare others from toxicity if this therapy is less likely to be beneficial. In addition, few studies have addressed the long-term results of autologous SCT in a large group of FL patients. Therefore, we evaluated 248 patients with recurrent FL in a multivariate analysis of factors predicting for improved OS, PFS, and decreased progression rates after high-dose chemotherapy and autologous SCT.

PATIENTS AND METHODS

Patients

A total of 248 patients with recurrent follicular NHL who received high-dose chemotherapy and autologous stem cell transplantation at the University of Nebraska Medical Center were identified in the clinical database. All of the patients underwent transplantation between July 1987 and June 2003 and received a high-dose chemotherapy regimen that was in effect at the time of their transplantation. All patients received an unpurged autologous stem cell or bone marrow product according to standard techniques described previously. All patients signed a valid informed consent for their therapy, and all studies were approved by the Scientific Review Committee and the Institutional Review Board of the University of Nebraska Medical Center (UNMC) and the UNMC/Eppley Cancer Center.

Data Collection and Review

Hospital, clinic, and follow-up notes were reviewed for patient and transplant characteristics in the pretransplantation, transplantation, and posttransplantation time frames. All patients had a central pathology review at UNMC and were classified as follicular grade 1, 2, or 3 according to the World Health Organization (WHO) criteria [11]. Excisional biopsy specimens obtained at the patient's original diagnosis and at the most recent diagnosis at relapse were reviewed. The most recent biopsy specimen was used to classify the type of lymphoma according to the WHO classification system. The Follicular Lymphoma International Prognostic Index (FLIPI) score was calculated based on the patient's age, disease stage, serum lactate dehydrogenase (LDH) value, number of nodal sites, and hemoglobin level immediately before transplantation [12]. These tests were performed after salvage chemotherapy but before high-dose chemotherapy for pretransplantation preparation. The response to transplantation was assessed according to the original Cheson criteria [13]. These criteria were used prospectively from their inception in 1998 and were applied retrospectively to cases before that time. Chemosensitive disease was defined as at least a partial response to the last chemotherapy before transplantation. Each patient was placed into 1 of 3 categories of transplantation regimen: (1) chemotherapy only, (2) chemotherapy with total body irradiation (TBI), or (3) chemotherapy with monoclonal antibody (mAb) therapy including either unconjugated or radiolabeled anti-CD20 antibodies.

Statistical Analysis

OS was defined as the time from transplantation to death from any cause. PFS was defined as the time from transplantation to documented progression/relapse of lymphoma or death from any cause. Progression was defined as an increase in bidimensionally measurable disease $\geq$ 50%, new lymph nodes $\geq$ 1.5 cm, or new sites of disease.

The univariate probability of progression was estimated using cumulative incidence with nonprogression mortality as the competing risk. The probabilities of PFS and OS were estimated using the Kaplan-Meier method [14]. Multivariate analysis was performed using the Cox proportional hazards regression method [15]. Proportionality was tested using time-dependent covariates. Stepwise forward model building was used, and covariates with a P value $\leq$ .05 were entered into the model. Interactions among covariates were tested in the final model.

Variables evaluated included age, sex, ethnicity, histological grade (follicular NHL grade [FL] 1 and FL 2 vs FL 3), interval from diagnosis to transplantation ($\leq$ 12 months vs $>$ 12 months), stage before conditioning regimen (in complete remission, stage I/II, stage III/IV), bone marrow involvement at conditioning (yes or no), extranodal involvement at conditioning (yes or no), LDH level at conditioning (normal or elevated), disease state at conditioning (second complete remission [CR2], primary induction failure sensitive/untreated, relapse 1 sensitive/untreated, relapse 2 or more), FLIPI score at transplant (low, 0/1; intermediate, 2; high, $\geq$ 3), number of previous chemotherapies (1, 2, or $\geq$ 3) and type of conditioning regimen (chemotherapy only, chemotherapy + total body irradiation [TBI], or chemotherapy + monoclonal antibodies).

Table 1. *Patient characteristics*

Variable	n (%)/median (range)
n	248
Age, years	46 (20-67)
20-40	52 (21)
41-54	158 (64)
≥ 55	38 (15)
Sex	
Female	115 (46)
Male	133 (54)
Race/ethnicity	
White, non-Hispanic	240 (96)
White, Hispanic	2 (1)
Black, non-Hispanic	3 (1)
Asian	1 (1)
Other	2 (1)
Histology type	
FL 1	64 (26)
FL 2	98 (40)
FL 3	86 (35)
Interval from diagnosis to transplantation	
≤ 1 year	59 (24)
> 1 year	189 (76)
Stage before conditioning	
CR	49 (20)
Stage I or II	52 (21)
Stage III or IV	113 (46)
Unknown	34 (14)
Bone marrow involvement before conditioning	
No	152 (61)
Yes	81 (33)
Unknown	15 (6)
Extranodal involvement before conditioning	
No	135 (55)
Yes	90 (36)
Unknown	23 (9)
Lactate dehydrogenase level before conditioning	
Normal	178 (72)
Elevated	67 (27)
Unknown	3 (1)
Disease stage/sensitivity	
CR1	8 (3)
CR2 or more	32 (13)
Primary induction failure (sensitive/untreated)	84 (34)
Relapse 1 (sensitive/untreated)	69 (28)
Relapse 2 or more	32 (13)
Not evaluable	23 (9)
Number of previous chemotherapies	
One	58 (23)
Two	108 (44)
Three or more	82 (33)
Conditioning regimen	
Chemotherapy*	110 (44)
Chemotherapy† + TBI	99 (40)
Chemotherapy‡ + monoclonal antibodies	39 (16)
Median follow-up of survivors, months	72 (12-192)

MICE indicates mesna, ifosfamide, carboplatin, and etoposide; BEAM, carmustine, etoposide, cytarabine, and melphalan; BEAC, carmustine, etoposide, cytarabine, and cyclophosphamide; BECH, carmustine, etoposide, cyclophosphamide, and hydroxyurea; Cy/TBI, cyclophosphamide and TBI; Cy/Thio/TBI, cyclophosphamide thiotepa and TBI; Bexxar-BEAC, 131-iodine tositumomab, carmustine, etoposide, cytarabine, and cyclophosphamide; Bexxar-BEAM, 131-iodine tositumomab, carmustine, etoposide, cytarabine, and melphalan; Rituxan-BEAM, rituximab, carmustine, etoposide, cytarabine, and melphalan.

*Conditioning regimen includes MICE (n = 1), BEAM (n = 38), BEAC (n = 64), and BECH (n = 7).

†Conditioning regimen includes Cy/TBI (n = 98) and Cy/Thio/TBI (n = 1).

‡Conditioning regimen includes Bexxar-BEAC (n = 2), Bexxar-BEAM (n = 4), and Rituxan-BEAM (n = 33).

RESULTS

Patient Characteristics

Selected patient characteristics are detailed in Table 1. The median patient age was 46 years (range, 20 to 67 years). Sixty-four patients had FL1, 98 (40%) had FL 2, and 86 (35%) had FL 3. No patients with transformed FL were included in this analysis. Most of the patients (189 [76%]) underwent transplantation more than 12 months from their original diagnosis. Patients had received a median of 2 previous chemotherapy regimens, and 82% of the patients had chemotherapy-sensitive disease at the time of transplantation. Sixty-seven patients (27%) had an elevated LDH at the time of transplantation, and 81 (35%) had bone marrow (BM) involvement with NHL at the time of transplantation. Eighty-eight patients (35%) had a low-risk FLIPI score, 87 (35%) had an intermediate-risk FLIPI score, 37 (15%) had high-risk FLIPI score, and 36 (15%) had a missing value, preventing calculation of FLIPI score at the time of transplantation. The patients with a missing value were mostly from the earlier years of the study; however, their other characteristics and treatments received were identical to the patients who underwent transplantation during the same time period. A total of 110 patients received a high-dose chemotherapy-only regimen, 99 patients received a chemotherapy/TBI regimen, and 39 patients received a chemotherapy/mAb–based regimen. Of the 39 patients who received mAb in their conditioning regimen, and 4 (10%) had received mAb with previous initial or salvage therapy.

Outcomes

The median follow-up of surviving patients was 6.0 years (range, 1.0 to 15.0 years). Of the 117 patients who progressed (47%), 80 subsequently died, and 37 remained alive after progression. Thirty-three patients (13%) died without NHL progression. The 5-year PFS was 44%, and the 5-year OS was 63%. The distribution of 5-year PFS by histological grade was 47% FL 1, 49% FL 2, and 36% FL 3; that of 5-year OS was 61% FL, 70% FL 2, and 57% FL 3 (Table 2). Patients were alive up to 15 years after the transplantation. A multivariate analysis of factors predicting for

Table 2. *Univariate outcome probabilities, percent (95% CI)*

Outcome	1 year	3 years	5 years
Progression*	22 (17-27)	37 (31-43)	46 (39-52)
PFS†	72 (66-78)	54 (48-60)	44 (37-50)
OS†	90 (85-93)	73 (67-79)	63 (56-69)
Outcome by histological grade	**FL 1**	**FL 2**	**FL 3**
Progression*			
1 year	25 (16-34)	18 (11-26)	23 (15-33)
3 years	35 (24-47)	34 (25-44)	41 (31-52)
5 years	41 (28-53)	45 (34-55)	50 (39-61)
PFS†			
1 year	70 (57-80)	78 (69-85)	67 (56-76)
3 years	55 (41-66)	60 (50-69)	47 (36-57)
5 years	47 (34-59)	49 (38-59)	36 (25-47)
OS†			
1 year	94 (84-98)	93 (86-96)	84 (74-90)
3 years	75 (61-84)	78 (68-85)	68 (56-76)
5 years	61 (47-73)	70 (59-78)	57 (45-67)

*Cumulative incidence.
†Kaplan-Meier estimate.

a higher progression rate and inferior PFS and OS was performed.

Analysis of Prognostic Factors

The results of multivariate analysis for progression are given in Table 3. Variables increasing the risk for lymphoma progression include having a FL 3 histology ($P = .006$), a high-risk FLIPI score at transplantation ($P = .007$), having received 3 or more previous chemotherapy regimens before transplantation ($P = .002$), and not having received an mAb–based transplantation conditioning regimen ($P = .006$).

Table 4 gives the multivariate analysis results for PFS. Variables contributing to decreased PFS included FL 3 histology ($P = .004$), a high-risk FLIPI score ($P = .002$), and having received 3 or more previous chemotherapy regimens ($P < .001$). The same variables were significant for OS, as shown in Table 5. The patients with at least 1 value missing for the FLIPI calculation behaved similarly to the high-risk FLIPI patients. The probability of OS is shown by histological grade (Figure 1), FLIPI score (Figure 2), and number of chemotherapy regimens before transplantation

Table 3. *Multivariate analysis for progression*

Variable	n	Relative risk of progression (95% CI)	*P* value
Histological grade			.01*
FL 1	64	1.00	
FL 2	98	1.20 (0.73-1.98)	.48
FL 3	86	2.14 (1.24-3.68)	.006
FLIPI score			
Low (0 or 1)	88	1.00	
Intermediate (2)	87	1.17 (0.73-1.88)	.52
High (≥ 3)	37	2.13 (1.23-3.69)	.007
Missing	36	1.20 (1.10-3.61)	.02
Number of previous chemotherapies			.008†
One	58	1.00	
Two	108	1.62 (0.097-2.70)	.06
Three or more	82	2.35 (1.36-4.04)	.002
Conditioning regimen			.004†
Chemotherapy + TBI	99	1.00	
Chemotherapy alone	110	0.87 (0.57-1.31)	.50
Chemotherapy + monoclonal antibodies	39	0.35 (0.17-0.74)	.006

*Two degrees of freedom test.
†Four degrees of freedom test.

Table 4. *Multivariate analysis for PFS*

Variable	n	Relative risk of treatment failure (95% CI)	*P* value
Histological grade			.007*
FL 1	64	1.00	
FL 2	98	1.21 (0.79-1.88)	.38
FL 3	86	1.97 (1.24-3.12)	.004
FLIPI score			
Low (0 or 1)	88	1.00	
Intermediate (2)	87	1.13 (0.74-1.72)	.58
High (≥ 3)	37	2.13 (1.32-3.45)	.002
Missing	36	2.79 (1.70-4.60)	< .001
Number of previous chemotherapies			.02†
One	58	1.00	
Two	108	1.35 (0.87-2.10)	.19
Three or more	82	1.92 (1.21-3.02)	< .001

*Two degrees of freedom test.
†Four degrees of freedom test.

Table 5. *Multivariate analysis for OS*

Variable	n	Relative risk of progression (95% CI)	*P* value
Histological grade			.01*
FL 1	64	1.00	
FL 2	98	1.13 (0.69-1.84)	.63
FL 3	86	2.00 (1.18-3.39)	.01
FLIPI score			< .001
Low (0 or 1)	88	1.00	
Intermediate (2)	97	1.35 (0.80-2.28)	.26
High (≥ 3)	37	2.50 (1.43-4.37)	.001
Missing	36	3.96 (2.23-7.05)	< .001
Number of previous chemotherapies			< .002†
One	58	1.00	
Two	108	1.48 (0.84-2.60)	.17
Three or more	82	3.00 (1.70-5.28)	< .001

*Two degrees of freedom test.
†Four degrees of freedom test.

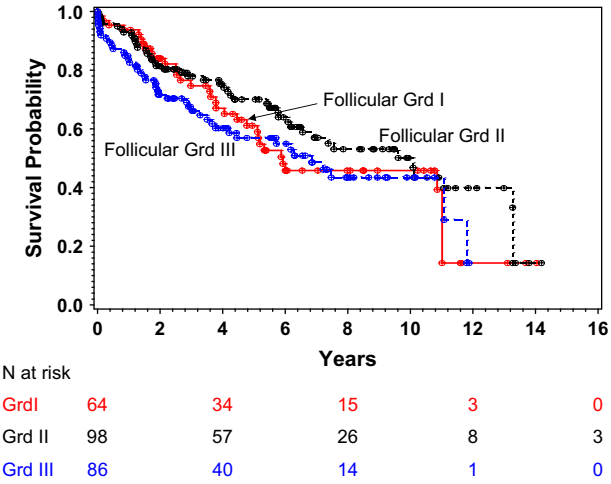

Figure 1. OS survival based on WHO histological grade.

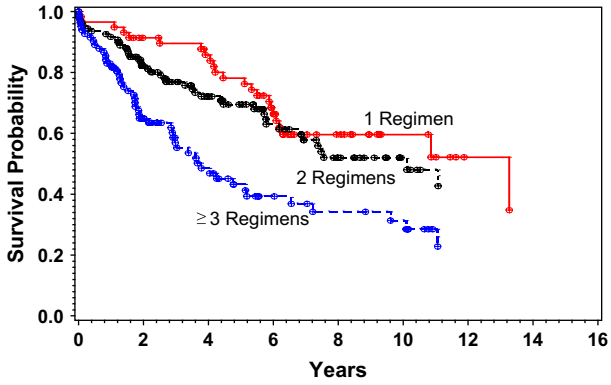

Figure 3. OS based on the number of previous chemotherapy regimens received before transplantation.

(Figure 3). Patients who failed only 1 previous chemotherapy regimen before proceeding to stem cell transplantation had a 5-year OS of 87% for FL 1, 72% for FL2, and 77% for FL3 (Figure 4).

In addition, a new risk factor model was constructed using this information in an attempt to identify recurrent follicular NHL patients with the best expected transplantation outcomes. A risk model was formulated using the risk factors of FL3 histology, a high-risk FLIPI score at transplantation, and 3 or more previous chemotherapy regimens. The 5-year probability of OS was 82% (95% confidence interval [CI] = 71%-90%) for patients with none of these risk factors (n = 78), 67% (95% CI = 57%-76%) for those with 1 risk factor (n = 106), 36% (95% CI = 22%-49%) for those with 2 risk factors (n = 57), and only 14% (95% CI = 1%-46%) for those with all 3 of these risk factors (n = 7) (Figure 5).

DISCUSSION

Although most patients with FL 1 and 2 NHL have a relatively indolent course of disease, the disease is not considered curable with standard chemotherapy [1-4]. Several studies have recently analyzed the changes in treatment approaches over time and have identified possible improvements in PFS and perhaps OS from adding an mAb to the therapy [16-19]. High-dose chemotherapy with autologous SCT is one option for patients with relapsed follicular NHL. Several studies of autologous SCT in this patient population have demonstrated improved disease-free survival (DFS) but no consistent improvement in OS compared with a historically controlled population [6-9]. The only randomized trial reported to date (the CUP trial) was conducted in Europe and randomized patients with relapsed follicular NHL to standard chemotherapy, unpurged autologous stem cell transplantation, or purged transplantation [10]. In this trial, 140 patients with relapsed, chemosensitive follicular NHL were randomized to 1 of the 3 arms. The OS at 4 years was 46% for the chemotherapy arm, 71% for the unpurged transplantation arm, and 77% for the purged transplantation arm. The 2-year PFS was 26% for the chemotherapy arm, 58% for the unpurged transplantation arm, and 55% for the purged transplantation arm. Significant reduction in the hazard rates for both PFS and OS were seen when comparing the

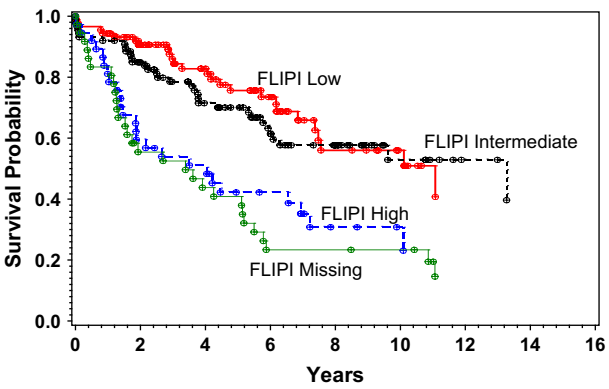

Figure 2. OS based on FLIPI score.

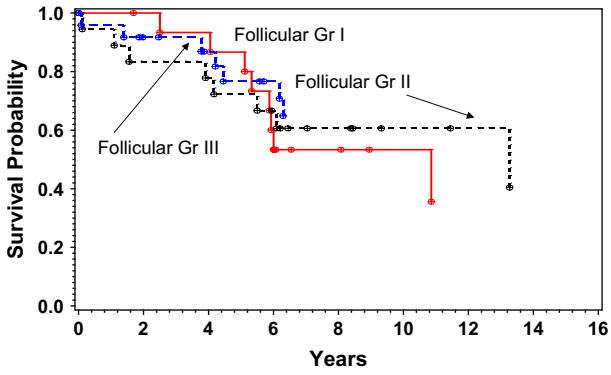

Figure 4. OS for patients failing only 1 previous chemotherapy regimen by follicular grade.

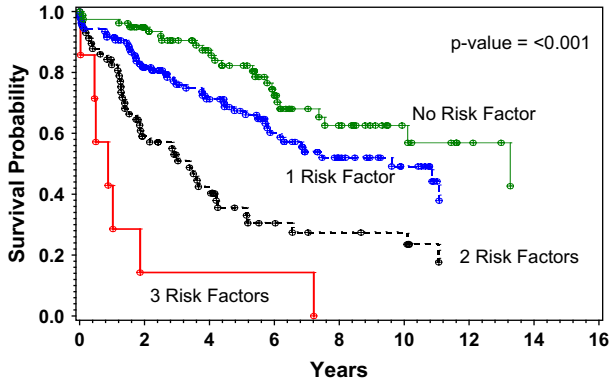

Figure 5. OS based on number of risk factors according to the prognostic model index.

chemotherapy arm with the 2 transplantation arms; however, there was no difference between the 2 transplantation arms. Although the accrual goal was not met in the CUP trial, the trial did demonstrate improved PFS and OS in the transplantation arms over standard chemotherapy.

The next issue to be addressed is which follicular NHL patient population would benefit the most from high-dose chemotherapy and autologous stem cell transplantation. Various studies have evaluated the prognostic indicators that predict for better outcome with autologous transplant for follicular NHL, including chemotherapy sensitivity, bulk of disease, number of previous chemotherapies received, and the FLIPI [6-9]. Because it is relatively new, the FLIPI has been less widely used in clinical trial evaluations of transplantation. Our study has demonstrated a worse outcome for patients with 3 or more previous chemotherapies, FL 3 disease, and a high FLIPI score at the time of transplantation. Patients with all 3 of these characteristics have a 5-year OS of only 14%, compared with an 82% 5-year survival in patients with none of these characteristics. This information should be of assistance when considering autologous SCT for patients before they have been heavily treated with chemotherapy or have progressed to a higher grade of follicular NHL. Therefore, standard autologous SCT should not be considered solely as a last option for follicular NHL patients who have failed all other options, but rather should be considered earlier in the course of disease, when the optimum benefit can be realized.

This information needs to be placed into context with the finding of clinical trials using other therapies, such as immunotherapy with rituximab [20], radiolabeled mAb [21,22], or other novel agents currently under study in clinical trials [23,24]. Because few of the patients in this retrospective analysis had received previous rituximab therapy, the use of an mAb in the transplantation regimen may have improved the results over what would be seen in patients who had received previous mAb therapy. However, a retrospective analysis of diffuse large B cell lymphoma did not demonstrate a difference in outcome of autologous transplantation in patients receiving CHOP chemotherapy versus those receiving CHOP-R (CHOP + rituximab) [25]. This question needs to be addressed in recently treated follicular NHL patients with a history of rituximab therapy.

Without the benefit of large randomized trials, we must consider the individual patient characteristics, such as histological grade of the follicular NHL, FLIPI score, type and number of previous therapies, and the patient's condition and individual preferences, when weighing the choice of therapy for patients with recurrent follicular NHL.

REFERENCES

1. McLaughlin P, Fuller LM, Velasquez WS, et al. Stage III follicular lymphoma: durable remissions with a combined chemotherapy-radiotherapy regimen. *J Clin Oncol*. 1987;5:867-874.
2. Flinn IW, Byrd JC, Morrison C, et al. Fludarabine and cyclophosphamide with filgrastim support in patients with previously untreated indolent lymphoid malignancies. *Blood*. 2000;96:71-75.
3. Czuczman MS, Weaver R, Alkuzeny B, et al. Prolonged clinical and molecular remission in patients with low-grade or follicular non-Hodgkin's lymphoma treated with rituximab and CHOP chemotherapy: 9-year follow-up. *J Clin Oncol*. 2004;22:4711-4716.
4. Marcus R, Imrie K, Belch A, et al. CVP chemotherapy plus rituximab compared with CVP as first-line treatment for advanced follicular lymphoma. *Blood*. 2005;105:1417-1423.
5. Johnson PW, Rohatiner AZ, Whelan JS, et al. Patterns of survival in patients with recurrent follicular lymphoma: a 20-year study from a single center. *J Clin Oncol*. 1995;13:140-147.
6. Bierman PJ, Vose JM, Anderson JR, et al. High-dose therapy with autologous hematopoietic rescue for follicular low-grade non-Hodgkin's lymphoma. *J Clin Oncol*. 1997;15:445-450.
7. Rohatiner AZ, Freedman A, Nadler L, et al. Myeloablative therapy with autologous bone marrow transplantation as consolidation therapy for follicular lymphoma. *Ann Oncol*. 1994;5(Suppl 2):143-146.
8. Freedman AS, Neuberg D, Mauch P, et al. Long-term follow-up of autologous bone marrow transplantation in patients with relapsed follicular lymphoma. *Blood*. 1999;94:3325-3333.
9. Bastion Y, Brice P, Haioun C, et al. Intensive therapy with peripheral blood progenitor cell transplantation in 60 patients with poor-prognosis follicular lymphoma. *Blood*. 1995;86:3257-3262.
10. Shouten HC, Qian W, Kvaloy S, et al. High-dose therapy improves progression-free survival and survival in relapsed follicular non-Hodgkin's lymphoma: results from the randomized European CUP trial. *J Clin Oncol*. 2003;21:3918-3927.
11. Harris NL, Jaffe ES, Diebold J, et al. World Health Organization (WHO) classification of neoplastic diseases of the hematopoietic and lymphoid tissues: report of the Clinical Advisory Committee meeting-Arlie House, Virginia. November 1997. *J Clin Oncol*. 1999;17:3835-3849.

12. Solal-Celigny P, Roy P, Colombat P, et al. Follicular lymphoma international prognostic index (FLIPI). *Blood*. 2004;104: 1258-1265.
13. Cheson BD, Horning SJ, Coiffier B, et al. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. *J Clin Oncol*. 1999;17:1244-1253.
14. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc*. 1958;53:457-481.
15. Cox DR. Regression models and life tables. *J R Stat Soc B*. 1972; 34:187-202.
16. Fisher RI, LeBlanc M, Press OW, et al. New treatment options have changed the survival of patients with follicular lymphoma. *J Clin Oncol*. 2005;23:8447-8452.
17. Swenson WT, Wooldridge JE, Lynch CF, et al. Improved survival of follicular lymphoma patients in the United States. *J Clin Oncol*. 2005;23:5019-5026.
18. Forstpointner R, Unterhalt M, Dreyling M, et al. Maintenance therapy with rituximab leads to significant prolongation of response duration after salvage therapy with a combination of rituximab, fludarabine, cyclophosphamide, and mitoxantrone (R-FCM) in patients with recurring refractory follicular and mantle cell lymphomas: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group (GLSG). *Blood*. 2006;108:4003-4008.
19. van Oers MHJ, Klasa Richard, Marcus RE, et al. Rituximab maintenance improves clinical outcome of relapsed/resistant follicular non-Hodgkin's lymphoma in patients both with and without rituximab during induction: results of a prospective randomized phase 3 intergroup trial. *Blood*. 2006;108: 3295-3301.
20. McLaughlin P, Grillo-Lopez AJ, Link BK, et al. Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. *J Clin Oncol*. 1998;16:2825-2833.
21. Horning SJ, Younes A, Jain V, et al. Efficacy and safety of tositumomab and I-131-tositumomab (Bexxar) after rituximab. *J Clin Oncol*. 2005;23:712-719.
22. Gordon LI, Witzig T, Molina A, et al. Yttrium 90–labeled ibritumomab tiuxetan radioimmunotherapy produces high response rates and durable remissions in patients with previously treated B-cell lymphoma. *Clin Lymphoma*. 2004;5:98-101.
23. Koc ON, Redfern C, Wiernik PH, et al. Active immunotherapy with FavId (Id/KLH) following rituximab induction: long-term follow-up of response rate improvement (RRI) and disease progression in follicular lymphoma [abstract]. *ASHA*. 2006;108: 691a.
24. Witzig TE, Vose JM, Kaplan HP, et al. Preliminary results from a phase II study of lenalidomide monotherapy in relapsed/refractory aggressive non-Hodgkin's lymphoma [abstract]. *Blood*. 2006;108:160a.
25. Vose JM, Bierman PJ, Lynch JC, et al. Autologous transplant event-free survival (EFS) following failure of CHOP-rituximab (CHOP-R) for diffuse large B-cell lymphoma (DLBCL) is the same as the EFS following failure of CHOP alone [abstract]. *Blood*. 2004;104:890a.