VOLUME 24 · NUMBER 19 · JULY 1 2006

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Rituximab-CHOP Versus CHOP Alone or With Maintenance Rituximab in Older Patients With Diffuse Large B-Cell Lymphoma

Thomas M. Habermann, Edie A. Weller, Vicki A. Morrison, Randy D. Gascoyne, Peter A. Cassileth, Jeffrey B. Cohn, Shaker R. Dakhil, Bruce Woda, Richard I. Fisher, Bruce A. Peterson, and Sandra J. Horning

From the Mayo Clinic, Rochester; Veterans' Administration Medical Center, University of Minnesota, Minneapolis, MN; Dana-Farber Cancer Institute Statistical Center, Boston; University of Massachusetts Medical School, Worcester, MA; University of Miami, Miami, FL; Albert Einstein Cancer Center, Philadelphia, PA; Wichita Community Clinical Oncology Program, Wichita, KS; University of Rochester, Rochester, NY; Stanford University, Stanford, CA; and British Columbia Cancer Agency, Vancouver, British Columbia, Canada.

Submitted November 25, 2005; accepted April 14, 2006.

Supported in part by Public Health Service Grants No. CA13650, CA23318, CA66636, CA21115, CA16450, CA35431, CA11083, and CA32291 and by the National Cancer Institute, the National Institutes of Health, and the Department of Health and Human Services.

The contents of this article are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Address reprint requests to Thomas M. Habermann, MD, Division of Hematology, Mayo Clinic, 200 First St SW, Rochester, MN 55905; e-mail: habermann.thomas@mayo.edu.

0732-183X/06/2419-3121/$20.00

DOI: 10.1200/JCO.2005.05.1003

ABSTRACT

Purpose

To address early and late treatment failures in older patients with diffuse large B-cell lymphoma (DLBCL), we designed a two-stage randomized trial of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) versus rituximab plus CHOP (R-CHOP), with a second random assignment to maintenance rituximab (MR) or observation in responding patients.

Patients and Methods

Untreated DLBCL patients who were 60 years or older were randomly assigned to R-CHOP (n = 318) or CHOP (n = 314); 415 responders were randomly assigned to MR (n = 207) or observation (n = 208). The primary end point was failure-free survival (FFS). All *P* values were two sided.

Results

Three-year FFS rate was 53% for R-CHOP patients and 46% for CHOP patients ($P = .04$) at a median follow-up time of 3.5 years. Two-year FFS rate from second random assignment was 76% for MR compared with 61% for observation ($P = .009$). No significant differences in survival were seen according to induction or maintenance therapy. FFS was prolonged with MR after CHOP ($P = .0004$) but not after R-CHOP ($P = .81$) with 2-year FFS rates from second random assignment of 77%, 79%, 74%, and 45% for R-CHOP, R-CHOP + MR, CHOP + MR, and CHOP, respectively. In a secondary analysis excluding MR patients, R-CHOP alone reduced the risks of treatment failure ($P = .003$) and death ($P = .05$) compared with CHOP alone.

Conclusion

Rituximab administered as induction or maintenance with CHOP chemotherapy significantly prolonged FFS in older DLBCL patients. After R-CHOP, no benefit was provided by MR. These results, which are consistent with an additive effect of rituximab, suggest that future studies could focus on maintenance strategies with novel agents as well as new induction therapies.

J Clin Oncol 24:3121-3127.

INTRODUCTION

More than 60% of patients with diffuse large B-cell lymphoma (DLBCL) are older than 60 years at diagnosis.[1] Age was established as an adverse prognostic factor and is one of five factors included in the International Prognostic Index (IPI).[2] Cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy has been considered the standard treatment based on serial clinical investigations in which second- and third-generation chemotherapy regimens failed to demonstrate an advantage.[3,4] Whereas younger patients may benefit from dose-intensified strategies that include stem-cell transplantation, alternative approaches are required for many older patients.[5,6]

DLBCL routinely expresses the pan–B-cell antigen, CD20. Rituximab is a chimeric anti-CD20 human immunoglobulin G1 monoclonal antibody approved for treatment of recurrent follicular lymphoma.[7] In 1994, when development of this study began, encouraging data were reported for the use of rituximab with CHOP (R-CHOP) in indolent lymphoma.[8] The Eastern Cooperative Oncology Group (ECOG) 4494/Cancer and Leukemia Group B (CALGB) 9793 trial was designed to address the two major areas of treatment failure in DLBCL identified by the IPI, namely failure of induction therapy and failure to maintain response.[2] From February 1998 through July 2001, the ECOG and the CALGB, with participation from the Southwest Oncology Group, conducted the largest trial in this disease in the United States since 1986; the trial was a prospective

phase III study comparing failure-free survival (FFS) in older DLBCL patients randomly assigned to either R-CHOP or CHOP, followed by a second random assignment in responders to either maintenance rituximab (MR) or observation.

PATIENTS AND METHODS

Patients

Eligible patients were 60 years or older with a diagnosis of untreated DLBCL. Central pathology review was completed on 92% of patients; patients were classified according to WHO criteria.[9,10] CD20 expression was determined at the referring institution, and further immunostaining was performed on central review when lineage assignment was ambiguous. Eligible patients had an ECOG performance status of 0 to 3, stage I to IV disease, and at least one objective, measurable disease parameter. Exclusion criteria included transformed follicular lymphoma, CNS involvement, history of HIV infection, inadequate organ function, concomitant malignancy, and an ejection fraction less than 45%. This study was conducted in accordance with the ethical guidelines mandated by the Declaration of Helsinki. All patients signed informed consent documents approved by the institutional review board at each participating site.

Random Assignment and Treatment

A two-stage random assignment design was used. The induction random assignment was stratified by IPI risk factor (zero or one *v* ≥ two risk factors). CHOP was administered in the standard dosage (cyclophosphamide 750 mg/m^2 on day 1, doxorubicin 50 mg/m^2 on day 1, vincristine 1.4 mg/m^2 to a maximum of 2 mg on day 1, and prednisone 100 mg/m^2 on days 1 through 5) every 21 days. On the basis of a modification of the original design of Czuczman et al,[8] rituximab was administered at a dose of 375 mg/m^2 7 and 3 days before cycle 1 and 2 days before cycles 3, 5, and, if administered, 7. Patients in complete remission (CR) after four cycles received six total cycles. Patients in partial remission (PR) after four cycles were assessed again after six cycles; patients with a continued response completed eight cycles, whereas patients with no interval change underwent second random assignment. CR/PR patients underwent second random assignment 3 weeks after completing chemotherapy to start MR or observation and were stratified by IPI risk factor (zero or one *v* ≥ two risk factors), response (CR *v* PR), and induction therapy (CHOP *v* R-CHOP). MR was administered for four courses at 6-month intervals, with each course consisting of 375 mg/m^2 weekly times four. No radiotherapy was administered.

Use of granulocyte colony-stimulating factor (G-CSF) was recommended according to guidelines.[11] CHOP was delayed 1 week for a neutrophil count less than 1,500/μL and a platelet count less than 100,000/μL and then administered at full dose with G-CSF support. In the event of sepsis or neutropenic fever, G-CSF was used to support optimal dose-intensity in subsequent cycles. Cyclophosphamide and doxorubicin doses were decreased for repeated grade 3 or 4 neutropenia or infection. Intrathecal methotrexate was recommended for patients with epidural, testicular, sinus, or marrow DLBCL.

Response Criteria and Follow-Up

CR required complete regression of all palpable and radiologic (computed tomography) disease with repeat bone marrow biopsy, if initially involved, and confirmation at 4 or more weeks. PR was defined as a decrease of at least 50% in the sum of the products of the dimensions of measurable lesions for 4 or more weeks. Progressive disease was defined as an increase in size of more than 25% in the sum of the products of the pretreatment lesions or the appearance of new lesions. Relapse was defined as new disease in CR patients or as progressive disease in PR patients. Patients were observed every 3 months for 2 years, every 6 months during year 3, and annually thereafter.

Statistical Analysis

FFS was defined as the time from random assignment to relapse, nonprotocol treatment, or death. Survival was measured from random assignment to death from any cause. This study was designed to detect a 33% reduction in the induction FFS hazard ratios (82% power) and to detect a 40% reduction in the maintenance FFS hazard rates (80% power) using a two-sided log-rank test ($P = .05$ significance level). Comparisons were conducted according to the intent-to-treat principle among eligible patients. The Kaplan-Meier method and Cox proportional hazards regression model were used to estimate failure rates, hazard ratios (HRs), and 95% CIs.[12,13] Fisher's exact and the Wilcoxon rank sum tests were used to compare proportions and medians, respectively.

The induction analysis compared FFS after first random assignment for R-CHOP versus CHOP, regardless of response or second random assignment, whereas the maintenance analysis compared FFS after second random assignment for MR versus observation in responders only, regardless of induction. The Data Monitoring Committee released the study results early when the maintenance comparison crossed the prespecified O'Brien-Fleming boundary.[14] The current data represent 95% and 75% of the planned induction and maintenance information, respectively.

A significant difference in the effect of maintenance therapy was observed by induction therapy ($P = .05$ for the interaction term in Cox proportional hazards regression model) because MR improved the outcome after CHOP but not after R-CHOP. To compare induction treatments without the confounding effect of maintenance therapy, analyses cannot simply exclude the CHOP + MR (n = 80) and R-CHOP + MR (n = 94) patients because this leads to a biased estimate of FFS and overall survival (OS) as a result of over-representation by patients who did not undergo the second random assignment (52%, 194 of 372 patients) compared with the proportion of all assessable patients who did not undergo the second random assignment (36%, 194 of 546 patients). An unbiased estimate is achieved by applying an approach (weighted Cox regression) that approximately doubled the information for patients randomly assigned to observation.[15,16] As previously described for weighted Cox regression, the robust variance estimator provides a proper estimate of the variance of the relative risk estimate in this setting and can be implemented using the S-Plus function *coxph* (Statistical Sciences, Seattle, WA).[17] The concept of the weighted analysis, to remove the bias that can result from analyzing only a subset of the patients in two-stage randomized designs, is consistent with previously proposed methods for the missing data problem.[18-22] The results from the weighted Cox regression are denoted in this article as the analyses removing the effect of MR. Because this technique assumes that the MR and observation populations are comparable, we verified that the patient characteristics were similar in the two groups before conducting the analysis. There is a remote possibility that the two groups are different by a factor that we did not evaluate; this is unlikely because of the random assignment at the second step.

RESULTS

From February 1998 through July 2001, 632 patients were randomly assigned to induction, and 415 were randomly assigned to maintenance. There were 267 R-CHOP and 279 CHOP patients after exclusion for central pathology review (n = 76; most commonly because of follicular or marginal zone subtypes) and other reasons (n = 10). There were 174 MR and 178 observation patients after exclusion for pathology (n = 54 of the initial 76 exclusions) and other reasons (n = 9). The baseline patient characteristics were balanced for age, prognostic factors, and disease stage (Table 1). Nearly half of the patients in both groups had stage IV disease, and fewer than 15% had low-risk IPI disease.

There were no significant differences in adverse events between the induction arms ($P > .18$). The most common grade 3 and 4 toxicities after R-CHOP or CHOP therapy were neutropenia (78% and 78% of patients, respectively), anemia (17% and 16%, respectively), thrombocytopenia (14% and 10%, respectively), infection (17% and 16%, respectively), and cardiac toxicity (9% and 9%, respectively). The 27 lethal toxicities (5%) after R-CHOP or CHOP induction included infection (eight and seven patients, respectively),

Table 1. Characteristics of Patients

Characteristic		% of Patients R-CHOP (n = 267)		% of Patients CHOP (n = 279)
Age, years				
Median	69		70	
Range	60-92		60-90	
60-64		24		25
65-69		28		26
70-79		39		42
≥ 80		9		7
Male sex		52		48
ECOG performance status				
0		39		42
1		46		44
2		11		10
3		4		4
Disease stage				
I		6		7
II		19		20
III		26		24
IV		49		49
Elevated LDH		40		42
No. of extranodal sites				
0		37		36
1		33		34
≥ 2		30		30
International Prognostic Index				
1		12		14
2		26		26
3		33		37
≥ 4-5		28		24
Age-adjusted prognostic index				
0		12		14
1		35		36
2		44		41
3		9		9

Abbreviations: R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase.

cardiac toxicity (five and five patients, respectively), and pulmonary toxicity (one and one patient, respectively). Grade 3 or 4 granulocytopenia was more common in MR patients (n = 23, 12%) compared with observation patients (n = 8, 4%; $P = .008$). Overall, grade 3 or 4 nonhematologic toxicity of all types was reported in 36 patients (18%) randomly assigned to MR and 32 patients (17%) randomly assigned to observation ($P = .69$).

Forty-six percent of patients received six chemotherapy cycles, 33% received seven or more cycles, 20% received five or fewer cycles, and 1% had data missing. The number of rituximab infusions was four with six chemotherapy cycles and five with more than six cycles. The response rates before the second random assignment were similar for R-CHOP (77% CR/PR, 13% stable disease, 1% progressive disease, and 9% not assessable) and CHOP (76% CR/PR, 15% stable disease, 3% progressive disease, and 6% not assessable; $P = .92$). Because of the requirement for confirmation of responses at 4 weeks or later and the timing of the second random assignment within that period, CR rates (35% overall) are underestimated.

Figures 1A through 1D illustrate outcomes at a median follow-up time of 3.5 years. The estimated 3-year FFS rate was 53% for R-CHOP and 46% for CHOP induction (HR = 0.78; 95% CI, 0.61 to 0.99; $P = .04$; Fig 1A). Survival differences were not statistically significant (HR = 0.83; 95% CI, 0.63 to 1.09; $P = .18$; Fig 1B). MR therapy significantly prolonged FFS (HR = 0.63; 95% CI, 0.44 to 0.90; $P = .009$; Fig 1C). This benefit for maintenance therapy did not translate to longer survival (HR = 0.96; 95% CI, 0.63 to 1.47; $P = .85$; Fig 1D).

A significant difference in the effect of maintenance therapy was observed according to the type of induction therapy (HR = 2.10; 95% CI, 1.01 to 4.36; $P = .05$; Figs 2A to 2D). MR significantly prolonged FFS after CHOP (HR = 0.45; 95% CI, 0.29 to 0.71; $P = .0004$; Fig 2A) but not after R-CHOP (HR = 0.93; 95% CI, 0.53 to 1.66; $P = .81$; Fig 2B). The estimated 2-year FFS rates after second random assignment were 77%, 79%, 74%, and 45% after R-CHOP, R-CHOP + MR, CHOP + MR, and CHOP, respectively. These data indicate that rituximab as part of induction therapy or as maintenance in responding patients results in a significant prolongation of FFS ($P < .001$). There were no statistically significant survival differences with MR after CHOP ($P = .27$) or R-CHOP ($P = .48$; Figs 2C and 2D).

Because of the observed difference in effect of MR according to the type of induction, we performed a secondary analysis to further elucidate the effects of induction therapy without MR (Figs 3A and 3B). In this analysis, R-CHOP alone significantly decreased the risk of treatment failure compared with CHOP alone (HR = 0.64; 95% CI, 0.47 to 0.85; $P = .003$), with an estimated 3-year FFS rate of 52% for R-CHOP and 39% for CHOP. Survival was also longer after R-CHOP induction alone (HR = 0.72; 95% CI, 0.52 to 1.00; $P = .05$), with an estimated 3-year OS rate of 67% for R-CHOP and 58% for CHOP. FFS benefit for R-CHOP was observed for both low/low-intermediate–risk and high-intermediate/high–risk IPI patients ($P < .03$).

DISCUSSION

This US Intergroup study resulted in important observations that complement the results of other studies using different schedules and total doses of rituximab and chemotherapy. These results challenge current concepts of synergy between rituximab and chemotherapy and demonstrate the potential role of sequential or maintenance chemotherapy in DLBCL. During the conduct of the Intergroup study, reports were published in support of our hypotheses and results.[23,24] A landmark prospective randomized trial in older patients, primarily with DLBCL, demonstrated superior FFS and OS with R-CHOP (administered as rituximab on day 1 of each of eight CHOP cycles) compared with CHOP.[25,26]

Despite the use of fewer chemotherapy cycles and fewer rituximab treatments in the Intergroup trial, the FFS and OS results in the two studies are similar. Table 2 shows that the 3-year FFS results for R-CHOP alone (52%) versus CHOP alone (35%) for the Intergroup study are comparable to the 3-year Groupe d'Etude des Lymphomes de l'Adulte (GELA) R-CHOP (53%) and CHOP (35%) results.[27] The comparative HRs for FFS were 0.64 for the Intergroup study and 0.58 for the GELA study. Likewise, the 3-year survival rates are similar at 67% for R-CHOP versus 58% for CHOP (HR = 0.72) in the Intergroup study and 62% for R-CHOP versus 51% for CHOP (HR = 0.72) in the GELA study. In comparing patient characteristics

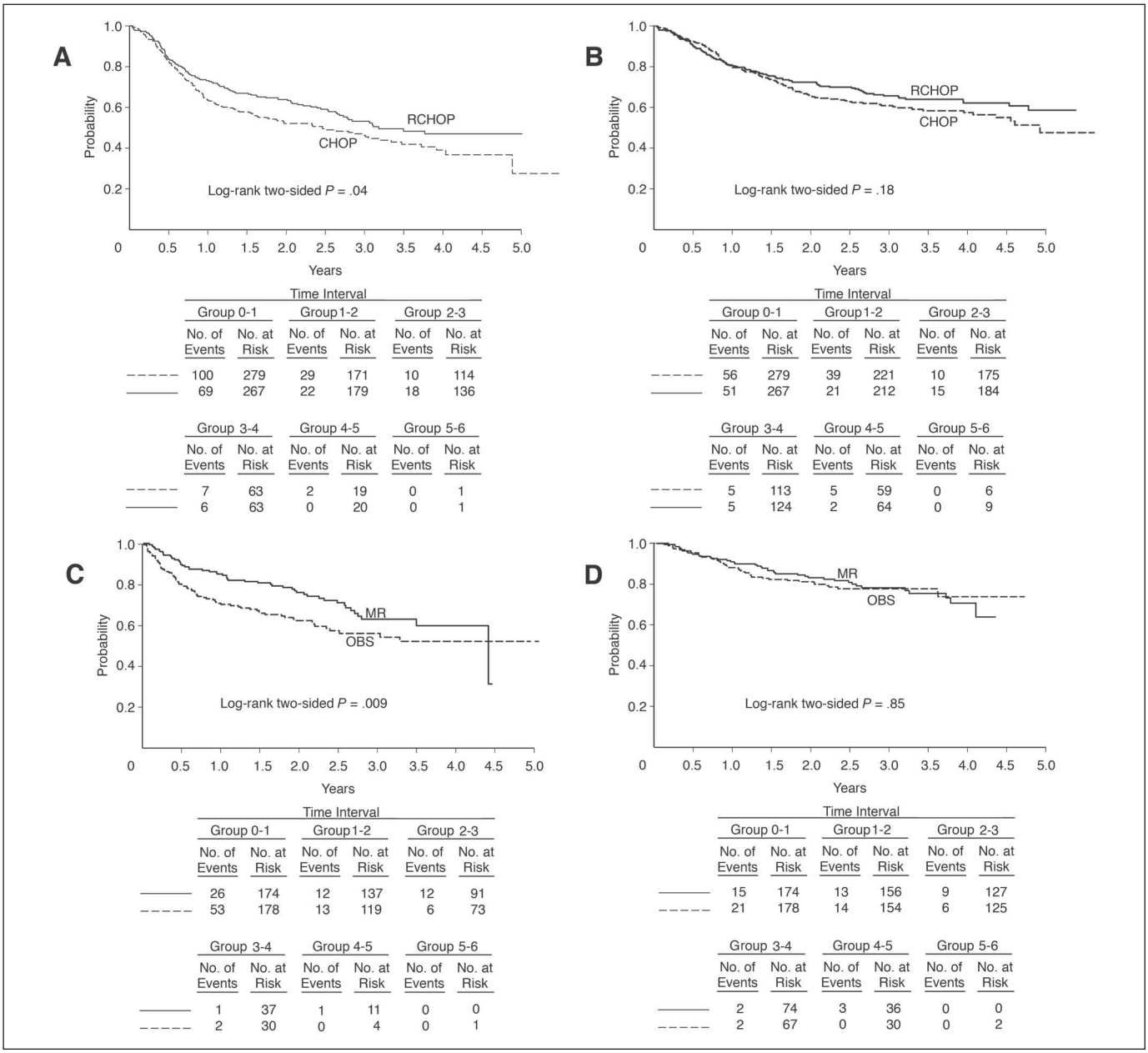

Fig 1. Failure-free survival (FFS) and overall survival (OS) according to induction treatment with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or rituximab with CHOP (RCHOP) and according to maintenance rituximab (MR) therapy or observation (OBS). (A) FFS according to induction. (B) OS according to induction. (C) FFS according to maintenance. (D) OS according to maintenance.

for the two studies, the median age is similar (69 years), but the Intergroup study patients were somewhat less favorable according to the IPI with 23% (R-CHOP) and 27% (CHOP) being high risk compared with 12% (R-CHOP) and 15% (CHOP) being high risk in the GELA study.[25] Although differences in the number of chemotherapy cycles may ultimately emerge as important based on GELA data demonstrating an increased risk of subsequent cardiomyopathy with a cumulative doxorubicin dose of more than 300 mg/m^2 (> six CHOP cycles), grade 3 to 4 cardiac toxicities were not different in our studies.[28] Of interest, no difference in the efficacy of six cycles versus eight cycles of R-CHOP in older DLBCL patients was reported in an interim analysis of a large randomized trial.[29]

The prolongation of FFS with MR after CHOP ($P = .0004$) is an important observation from the Intergroup study. Consistent with these results, the use of sequential consolidation with alternative therapy after doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone was superior to CHOP in poor-risk aggressive lymphoma patients,[30] and sequential consolidation with high-dose therapy and transplantation, in some trials, was superior to the standard treatment arm.[31,32] The necessity that a consolidation or maintenance strategy in DLBCL be novel or dose intense is indicated by our study results, which showed that continuing use of rituximab after R-CHOP failed to demonstrate benefit (Fig 2B).

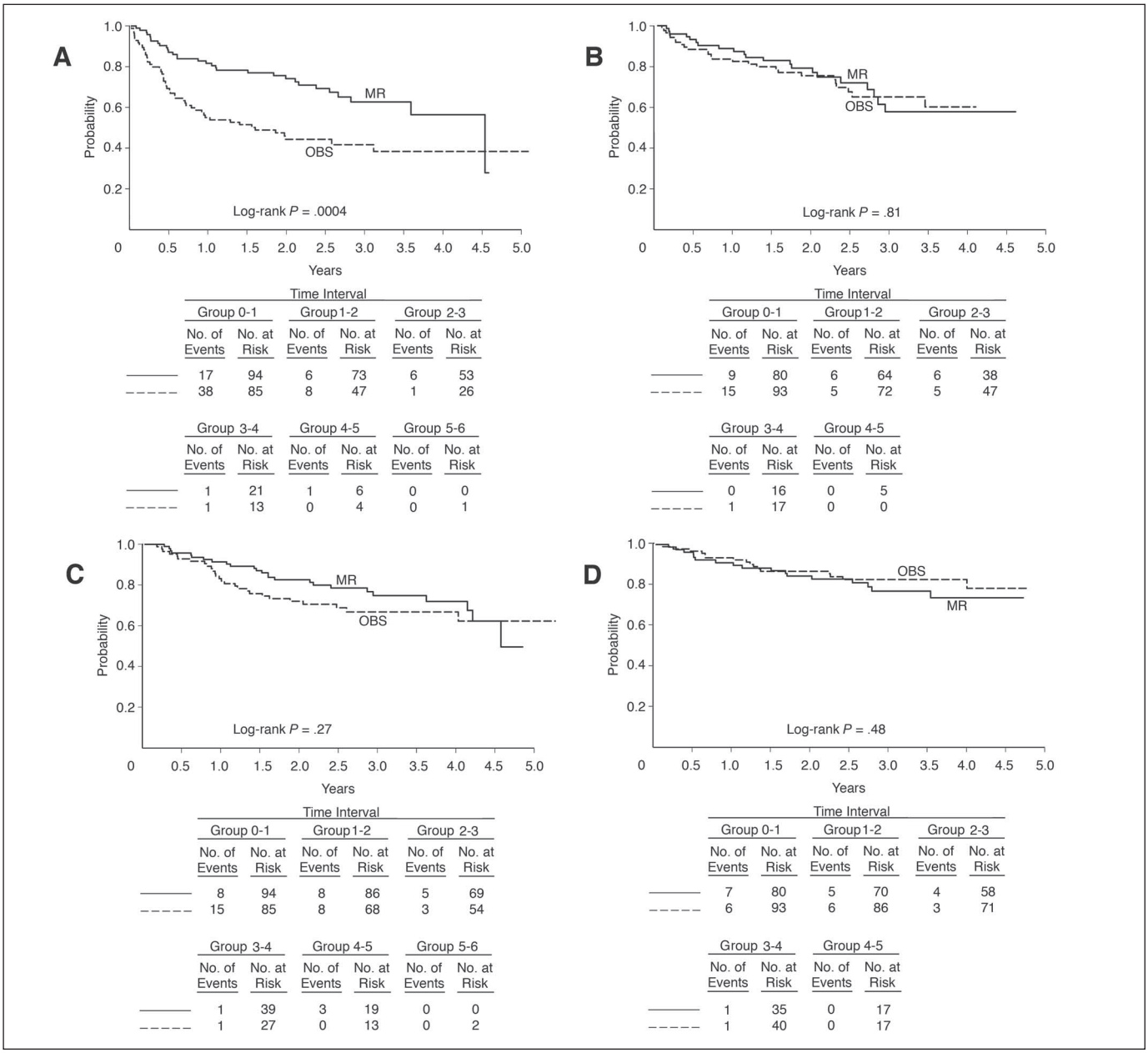

Fig 2. Failure-free survival (FFS) and overall survival (OS) according to maintenance rituximab (MR) therapy or observation (OBS) by induction treatment. MR significantly prolonged FFS after (A) cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) but not after (B) rituximab with CHOP (R-CHOP). No significant differences were observed in OS after (C) CHOP (hazard ratio [HR] = 0.73; 95% CI, 0.43 to 1.27; $P = .27$) or (D) R-CHOP (HR = 1.28; 95% CI, 0.65 to 2.53; $P = .48$).

The Intergroup study results with MR are also potentially important from the standpoint of designing new treatments for DLBCL. The estimated 2-year FFS rates (77%, 79%, 74%, and 45% after R-CHOP, R-CHOP + MR, CHOP + MR, and CHOP, respectively) are more consistent with an additive effect rather than a synergistic interaction. Thus, it is appropriate to study new initiatives in sequential as well as in combination strategies in DLBCL. The data from our study do not support the use of rituximab alone as maintenance strategy after rituximab-based induction therapy. Of note, the observations from this study in DLBCL may not pertain to other trial designs or lymphoma subtypes.

On the basis of the interaction (differences in effect of maintenance therapy according to induction therapy) observed in the Intergroup study, additional analyses were needed to elucidate the effects of R-CHOP alone compared with CHOP alone. Although outcomes were similar for patients who received rituximab either as induction or maintenance, MR was administered only to responding patients. At this time, our interpretation of the study results for clinical application is as follows. We recommend R-CHOP as the standard treatment for older DLBCL patients because induction treatment includes rituximab for all patients, whereas maintenance limits rituximab use to CHOP responders. Day 1 administration of each cycle is simple and convenient but also incurs more drug costs than the schedule used in the Intergroup study. Ultimately, the mature toxicity data as well as the efficacy associated with the number of chemotherapy cycles and the number of rituximab infusions must be considered. In a recent

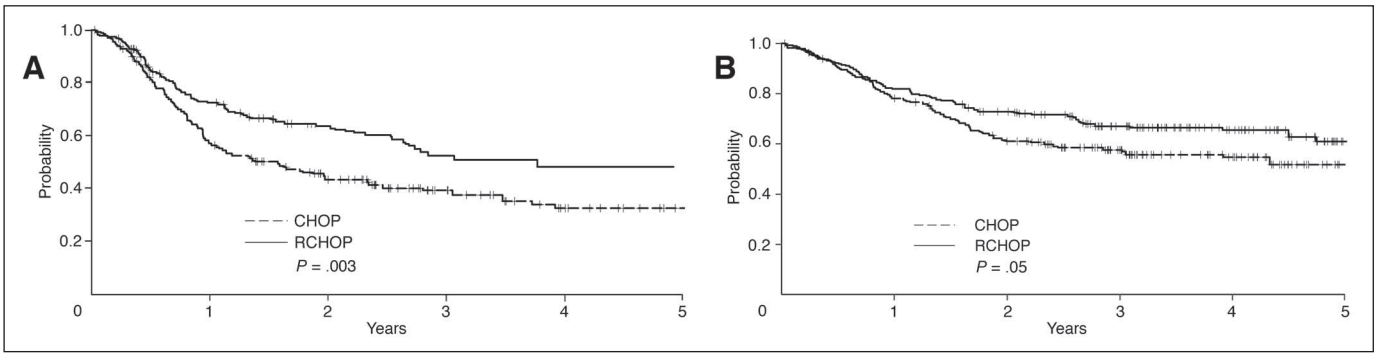

Fig 3. Failure-free survival (FFS) and overall survival (OS) after cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or rituximab with CHOP (RCHOP), excluding maintenance rituximab (MR) patients. (A) FFS according to induction without MR; RCHOP decreased the risk of treatment failure compared with CHOP (hazard ratio [HR] = 0.64; 95% CI, 0.47 to 0.85; $P = .003$). (B) OS according to induction without MR; RCHOP improved survival compared with CHOP (HR = 0.72; 95% CI, 0.52 to 1.00; $P = .05$).

update of the GELA study with median follow-up time of 5 years, 17 R-CHOP deaths were recorded in patients in continued remission (nine attributed to known, probable, or possible cardiac cause) compared with five CHOP deaths (none cardiac).[28] Further follow-up of all studies is necessary.

Table 2. Comparison of R-CHOP Alone Versus CHOP Alone

Outcome	3-Year Rate (%)		*P*	HR	95% CI
	R-CHOP	CHOP			
FFS*	52	39	.003	0.64	0.47 to 0.85
OS*	67	57	.05	0.72	0.52 to 1.0

Abbreviations: R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; HR, hazard ratio; FFS, failure-free survival; OS, overall survival.
*Maintenance rituximab excluded; see text.

After 30 years of CHOP as the treatment of choice for DLBCL, the addition of rituximab to CHOP defines the new standard of care. Continued efforts to prospectively identify biologic subsets of DLBCL and develop appropriate treatments are needed. The CALGB has initiated a study of R-CHOP versus the rituximab plus dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin regimen in conjunction with gene expression profiling. Two international phase III studies comparing 21-day cycle R-CHOP-21 with 14-day cycle R-CHOP-14, building on the superiority of dose-dense therapy without rituximab in older patients, are in progress.[33] Results from the US Intergroup study of R-CHOP with or without consolidative high-dose therapy and autologous transplantation in young high-risk patients are awaited. These studies will shed light on the optimal choice of chemotherapy for induction, the role of consolidation therapy, and important insights into the relationship between treatment and biologic subsets of DLBCL. In summary, the Intergroup study results inform future clinical trial design in that novel initiatives may be beneficial as combination or sequential strategies.

REFERENCES

1. Groves FD, Linet MS, Travis LB, et al: Cancer surveillance series: Non-Hodgkin's lymphoma incidence by histologic subtype in the United States from 1978 through 1995. J Natl Cancer Inst 92: 1240-1251, 2000

2. The International Non-Hodgkin's Lymphoma Prognostic Factors Project: A predictive model for aggressive non-Hodgkin's lymphoma. N Engl J Med 329:987-994, 1993

3. Gordon LI, Harrington D, Andersen J, et al: Comparison of a second-generation combination chemotherapeutic regimen (m-BACOD) with a standard regimen (CHOP) for advanced diffuse non-Hodgkin's lymphoma. N Engl J Med 327:1342-1349, 1992

4. Fisher RI, Gaynor ER, Dahlberg S, et al: Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. N Engl J Med 328:1002-1006, 1993

5. Haioun C, Lepage E, Gisselbrecht C, et al: Survival benefit of high-dose therapy in poor-risk aggressive non- Hodgkin's lymphoma: Final analysis of the prospective LNH87-2 protocol—A Groupe d'Etude des Lymphomes de l'Adulte study. J Clin Oncol 18:3025-3030, 2000

6. Milpied N, Deconinck E, Gaillard F, et al: Initial treatment of aggressive lymphoma with high-dose chemotherapy and autologous stem-cell support. N Engl J Med 350:1287-1295, 2004

7. McLaughlin P, Grillo-López 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 16:2825-2833, 1998

8. Czuczman MS, Grillo-Lopez AJ, White CA, et al: Treatment of patients with low-grade B-cell lymphoma with the combination of chimeric anti-CD20 monoclonal antibody and CHOP chemotherapy. J Clin Oncol 17:268-276, 1999

9. The Non-Hodgkin's Lymphoma Pathologic Classification Project: National Cancer Institute sponsored study of classifications of non-Hodgkin's lymphomas: Summary and description of a working formulation for clinical usage. Cancer 49:2112-2135, 1982

10. Gatter KC, Warnke RA: Diffuse large B-cell lymphoma, in Jaffe E, Harris NL, Stein H, et al (eds): World Health Organization Classification of Tumours: Pathology and Genetics of Haematopoietic and Lymphoid Tissues. Lyon, France, IARC Press, 2001, pp 171-174

11. American Society of Clinical Oncology: Update of recommendations for the use of hematopoietic colony-stimulating factors: Evidence-based clinical practice guidelines. J Clin Oncol 14:1957-1960, 1996

12. Kaplan E, Meier P: Nonparametric estimation from incomplete observations. J Am Stat Assoc 53:457-481, 1958

13. Cox DR: Regression models and life-tables. J R Stat Soc B 34:187-202, 1972

14. O'Brien PC, Fleming TR: A multiple testing procedure for clinical trials. Biometrics 35:549-556, 1979

15. Wahed AS, Tsiatis AA: Optimal estimator for the survival distribution and related quantities for treatment policies in two-stage randomization designs in clinical trials. Biometrics 60:124-133, 2004

16. Lunceford JK, Davidian M, Tsiatis AA: Estimation of survival distributions of treatment policies in two-stage randomization designs in clinical trials. Biometrics 58:48-57, 2002

17. Therneau TM, Grambsch PM: Statistics for Biology and Health: Extending the Cox Model. New York, NY, Springer-Verlag, 2000, pp 161-163

18. Horvitz DG, Thompson DJ: A generalization of sampling without replacement from a finite universe. J Am Stat Assoc 47:663-685, 1952

19. Prentice RL: A case-cohort design for epidemiologic cohort studies and disease prevention trials. Biometrika 73:1-11, 1986

20. Lin DY, Ying Z: Cox regression with incomplete covariate measurements. J Am Stat Assoc 88:1341-1349, 1993

21. Pugh M, Robins J, Lipsitz S, et al: Inference in the Cox proportional hazards model with missing covariate data. Cambridge, MA, Harvard School of Public Health, Department of Biostatistics, 1993

22. Wang CY, Chen HY: Augmented inverse probability weighted estimator for Cox missing covariate regression. Biometrics 57:414-419, 2001

23. Coiffier B, Haioun C, Ketterer N, et al: Rituximab (anti-CD20 monoclonal antibody) for the treatment of patients with relapsing or refractory aggressive lymphoma: A multicenter phase II study. Blood 92:1927-1932, 1998

24. Vose JM, Link BK, Grossbard ML, et al: Phase II study of rituximab in combination with chop chemotherapy in patients with previously untreated, aggressive non-Hodgkin's lymphoma. J Clin Oncol 19:389-397, 2001

25. Coiffier B, Lepage E, Briere J, et al: CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med 346:235-242, 2002

26. Feugier P, Van Hoof A, Sebban C, et al: Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: A study by the Groupe d'Etude des Lymphomes de l'Adulte. J Clin Oncol 23:4117-4126, 2005

27. Coiffier B, Herbrecht R, Tilly H, et al: GELA study comparing CHOP and R-CHOP in elderly patients with DLBCL: 3-year median follow-up with an analysis according to co-morbidity factors. Proc Am Soc Clin Oncol 22:596, 2003 (abstr 2395)

28. Hequet O, Le QH, Moullet I, et al: Subclinical late cardiomyopathy after doxorubicin therapy for lymphoma in adults. J Clin Oncol 22:1864-1871, 2004

29. Pfreundschuh M, Kloess M, Schmits R, et al: Six, not eight cycles of bi-weekly CHOP with rituximab (R-CHOP-14) is the preferred treatment for elderly patients with diffuse large B-cell lymphoma: Results of the RICOVER-60 trial of the German High-Grade Non-Hodgkin Lymphoma Study Group. Blood 106:9a, 2005 (abstr 13)

30. Tilly H, Lepage E, Coiffier B, et al: Intensive conventional chemotherapy (ACVBP regimen) compared with standard CHOP for poor-prognosis aggressive non-Hodgkin lymphoma. Blood 102:4284-4289, 2003

31. Fisher RI: Autologous stem-cell transplantation as a component of initial treatment for poor-risk patients with aggressive non-Hodgkin's lymphoma: Resolved issues versus remaining opportunity. J Clin Oncol 20:4411-4412, 2002

32. Lister TA: Who should receive myeloablative therapy for lymphoma? N Engl J Med 350:1277-1278, 2004

33. Pfreundschuh M, Trumper L, Kloess M, et al: Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of elderly patients with aggressive lymphomas: Results of the NHL-B2 trial of the DSHNHL. Blood 104:634-641, 2004

Authors' Disclosures of Potential Conflicts of Interest

Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Authors	Employment	Leadership	Consultant	Stock	Honoraria	Research Funds	Testimony	Other
Thomas M. Habermann					Genentech (A)			
Vicki A. Morrison					Amgen Inc (A); Pfizer Inc (A); Berlex (A)			
Richard I. Fisher			Genentech (A)		Genentech (A)	Genentech (C)		
Sandra J. Horning			Genetech (A); Biogen Idec (A)		Roche (A)	Biogen Idec (B); Genentech (B)		

Dollar Amount Codes (A) < $10,000 (B) $10,000-99,999 (C) ≥ $100,000 (N/R) Not Required

Author Contributions

Conception and design: Thomas M. Habermann, Edie A. Weller, Vicki A. Morrison, Peter A. Casselith, Jeffrey B. Cohn, Sandra J. Horning
Administrative support: Thomas M. Habermann, Edie A. Weller
Provision of study materials or patients: Thomas M. Habermann, Vicki A. Morrison, Peter A. Casselith, Shaker R. Dakhil, Richard I. Fisher, Bruce A. Peterson, Sandra J. Horning
Collection and assembly of data: Thomas M. Habermann, Edie A. Weller, Vicki A. Morrison, Randy D. Gascoyne, Bruce Woda, Sandra J. Horning
Data analysis and interpretation: Thomas M. Habermann, Edie A. Weller, Randy D. Gascoyne, Peter A. Casselith, Richard I. Fisher, Bruce A. Peterson, Sandra J. Horning
Manuscript writing: Thomas M. Habermann, Edie A. Weller, Vicki A. Morrison, Randy D. Gascoyne, Peter A. Casselith, Richard I. Fisher, Sandra J. Horning
Final approval of manuscript: Thomas M. Habermann, Edie A. Weller, Vicki A. Morrison, Randy D. Gascoyne, Peter A. Casselith, Jeffrey B. Cohn, Shaker R. Dakhil, Bruce Woda, Richard I. Fisher, Bruce A. Peterson, Sandra J. Horning