VOLUME 34 · NUMBER 33 · NOVEMBER 20, 2016

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Randomized Trial Comparing R-CHOP Versus High-Dose Sequential Chemotherapy in High-Risk Patients With Diffuse Large B-Cell Lymphomas

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Published online ahead of print at www.jco.org on October 3, 2016.

Supported in part by the Associazione Italiana Lotta alla Leucemia sezione di Bergamo, the Associazione Italiana per la Ricerca sul Cancro (Grants No. 9962 to A.R. and No. 10007 to S.P.), Ministero Istruzione, Università e Ricerca (Grant No. PRIN 2010), and unrestricted grants from Roche SpA and Amgen, Italy.

Presented in part at the 54th American Society of Hematology Annual Meeting, Atlanta, GA, December 8-11, 2012, and the 12th International Conference on Malignant Lymphoma, Lugano, Switzerland, June 19-22, 2013.

Authors' disclosures of potential conflicts of interest are found in the article online at www.jco.org. Author contributions are found at the end of this article.

Clinical trial information: NCT00355199.

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0732-183X/16/3433w-4015w/$20.00

DOI: 10.1200/JCO.2016.67.2980

ABSTRACT

Purpose

The benefit of high-dose chemotherapy with autologous stem-cell transplantation (ASCT) as first-line treatment in patients with diffuse large B-cell lymphomas is still a matter of debate. To address this point, we designed a randomized phase III trial to compare rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP)-14 (eight cycles) with rituximab plus high-dose sequential chemotherapy (R-HDS) with ASCT.

Patients and Methods

From June 2005 to June 2011, 246 high-risk patients with a high-intermediate (56%) or high (44%) International Prognostic Index score were randomly assigned to the R-CHOP or R-HDS arm, and 235 were analyzed by intent to treat. The primary efficacy end point of the study was 3-year event-free survival, and results were analyzed on an intent-to-treat basis.

Results

Clinical response (complete response, 78% *v* 76%; partial response, 5% *v* 9%) and failures (no response, 15% *v* 11%; and early treatment-related mortality, 2% *v* 3%) were similar after R-CHOP versus R-HDS, respectively. After a median follow-up of 5 years, the 3-year event-free survival was 62% versus 65% ($P = .83$). At 3 years, compared with the R-CHOP arm, the R-HDS arm had better disease-free survival (79% *v* 91%, respectively; $P = .034$), but this subsequently vanished because of late-occurring treatment-related deaths. No difference was detected in terms of progression-free survival (65% *v* 75%, respectively; $P = .12$), or overall survival (74% *v* 77%, respectively; $P = .64$). Significantly higher hematologic toxicity ($P < .001$) and more infectious complications ($P < .001$) were observed in the R-HDS arm.

Conclusion

In this study, front-line intensive R-HDS chemotherapy with ASCT did not improve the outcome of high-risk patients with diffuse large B-cell lymphomas.

J Clin Oncol 34:4015-4022. © 2016 by American Society of Clinical Oncology

INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is an aggressive, but potentially curable, malignancy accounting for approximately 30% to 35% of all newly diagnosed B-cell lymphomas.[1] The outcome of the disease is heterogeneous and can be predicted by validated prognostic scores.[2-4] In young patients with a good prognosis according to the International Prognostic Index (IPI), the long-term cure rate after rituximab-containing conventional chemotherapy programs now exceeds 80%.[5] Long-term results for patients belonging to high-risk and high-intermediate–risk groups have also been improved by similar chemoimmunotherapy programs, but still remain unsatisfactory.[6,7] In the prerituximab era, high-dose (HD) chemotherapy programs followed by autologous stem-cell transplantation (ASCT) have been proposed as a way to improve the outcome of high-risk patients with DLBCL[8-11];

however, conflicting results have been reported.[12-15] Three meta-analyses have been published, and none found clear evidence for the use of HD therapy.[16-18] The addition of the anti-CD20 antibody rituximab and HD cytarabine (HD-Ara-C) to the original HD sequential schedule[8] was reported as an innovative program for patients with mantle cell lymphoma and bone marrow involvement.[19] This rituximab-based HD sequential therapy (R-HDS) was further developed and proved feasible and active in a multicenter phase II study in untreated patients with DLBCL with a high age-adjusted IPI (aaIPI) score.[20] Similar results have been obtained in another phase II study with intensive immunochemotherapeutic protocols and ASCT.[21]

The study group Gruppo Italiano Terapie Innovative Linfomi launched a phase III trial to compare this R-HDS program with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in adult patients with DLBCL with high and high-intermediate risk according to IPI.

PATIENTS AND METHODS

Study Design and Procedures

This open-label, multicenter, randomized phase III trial was sponsored by the Ospedale Papa Giovanni XXIII of Bergamo. The study was conducted in accordance with the International Conference on Harmonization for Good Clinical Practice guidelines and the Declaration of Helsinki, and was approved by the local ethical committees. Written informed consent was obtained before enrollment. The trial is registered at www.clinicaltrials.gov as NCT00355199.

Patients

Inclusion criteria were age of 18 to 65 years, biopsy-confirmed CD20-positive DLBCL according to the 2008 WHO criteria,[22] advanced Ann Arbor stage (stage III to IV or II with bulk defined as $\geq$ 10 cm or B symptoms) without CNS involvement, and no previous treatment. All patients from 18 to 60 years of age were in an aaIPI high-intermediate or high-risk group (aaIPI: two and three risk factors, respectively), as were those 61 to 65 years of age (IPI: 3 and 4 to 5 risk factors, respectively). Exclusion criteria were concurrent severe heart, kidney, lung, or liver disease or a positive serology for hepatitis B, hepatitis C, or HIV. Eligible patients were stratified by aaIPI or IPI, using the biased coin algorithm to ensure that the balance of patients' characteristics were within the randomization strata. Randomization was centralized at Mario Negri Sud Research Foundation through a Web-based system. A retrospective central pathology review was performed to determine the cell of origin[23-25] by immunohistochemistry criteria.[26]

Treatment Plan

Patients enrolled in the control arm received R-CHOP (rituximab 375 mg/m^2 intravenously [IV], cyclophosphamide 750 mg/m^2 IV, doxorubicin 50 mg/m^2 IV, vincristine 1.4 mg/m^2 IV given on day 1 and 100 mg/d oral prednisone given on days 1 to 5), given every 14 days for eight cycles. The neutropenic phase was supported by granulocyte colony-stimulating factor (filgrastrim 5μg/kg subcutaneously given daily or pegfilgrastim subcutaneously given once on day 1 of each cycle). CNS prophylaxis with intrathecal chemotherapy (methotrexate, Ara-C, corticosteroids) was given to high-risk patients who, at diagnosis, had infiltration of the bone marrow, testes, Waldeyer ring, cranial air sinuses (including nasal), salivary glands, and epidural space. In the R-CHOP group, 33 patients (27%) received intrathecal prophylaxis. The experimental arm (R-HDS)[20] was based on three initial courses of doxorubicin-containing chemotherapy (first doxorubicin administration at 50 mg/m^2 IV, then the full dose of 75 mg/m^2 IV at 14 and 28 days; vincristine 1.4 mg/m^2 IV on days 1, 14, and 28; oral prednisone 40 mg/m^2 on days 1 to 28). Subsequently, patients received (1) HD cyclophosphamide 7 g/m^2 IV (day 1) and rituximab 375 mg/m^2 IV (days 3 and 11), followed by the harvest of peripheral blood progenitor cells (PBPCs); (2) HD-Ara-C 2 g/m^2 IV (twice a day for 6 days), followed on day 7 by the infusion of 1.5 to 2 $\times$ 10^6 autologous CD34+ cells/kg and rituximab 375 mg/m^2 IV (day 8 and day 16); a second PBPC harvest was scheduled after HD-Ara-C if inadequate harvesting was obtained after HD-cyclophosphamide or in the case of initial bone marrow involvement; (3) HD etoposide 2.4 g/m^2 IV (day 1), cisplatin 100 mg/m^2 IV (day 2); a small amount of PBPC (2 $\times$ 10^6 CD34+ cells/kg) were reinfused following etoposide/cisplatin. The final ASCT was conditioned with mitoxantrone (60 mg/m^2 IV) on day $-$5 and melphalan (180 mg/m^2 IV) on day $-$2 or carmustine, etoposide, cytarabine, and melphalan (carmustine 300 mg/m^2 IV on day $-$6, etoposide 200 mg/m^2 IV on days $-$5 to $-$2, Ara-C 200 mg/m^2 IV every 12 h $\times$ eight doses on days $-$5 to $-$2, melphalan 140 mg/m^2 IV on day $-$1), and supported by PBPC autograft on day 0. The target harvest for ASCT was 5 $\times$ 10^6 CD34+ cells/kg. Two additional rituximab doses were scheduled on days 14 and 24 after ASCT. In both arms, patients with initial bulky ($\geq$ 5 cm) or residual lesions received involved-field radiotherapy within 2 to 3 months after the chemotherapy program (Appendix Fig A1, online only). Patients received antiprophylaxis with sulfamethoxazole/trimethoprim and acyclovir prophylaxis for *Pneumocystis jiroveci* and herpes virus.

Evaluation of Response and Toxicity

After four cycles, patients assigned to R-CHOP underwent a first response evaluation (on the basis of a computed tomography scan and bone marrow biopsy, when indicated). Patients who achieved at least a partial response (PR) were given four additional courses; patients with less than a PR or refractory disease were shifted to salvage treatment. Clinical response was assessed by complete restaging according to Cheson criteria,[27,28] including total-body positron emission tomography (PET). Residual computed tomography and [^{18}F]fluorodeoxyglucose-PET–positive masses should be biopsied whenever possible. In the absence of a confirmed positive biopsy, isolated [^{18}F]fluorodeoxyglucose-PET positivity was not considered an event. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3).

Statistical Analysis

The primary end point of the study was event-free survival (EFS), measured from the time of study entry to any treatment failure, including death, disease progression, or treatment discontinuation for any reason (eg, toxicity and patient or medical decision). This composite end point was chosen for its value in evaluating highly toxic therapies.[28] The sample size of the study protocol was estimated to test a difference of 20% of the 3-year EFS rate between R-CHOP-14 and R-HDS. A sample of 224 patients randomly assigned to a treatment group (112 for each arm) over a period of 3 years, with 2 years of additional follow-up, was required for a power of 0.80 with a one-sided α level of .05. We assumed a dropout rate of 10%; we estimated that 240 patients would be needed to allocate 112 patients per arm.

According to Cheson guidelines,[28] the secondary end points were response rate, progression-free survival (PFS), disease-free survival (DFS), overall survival (OS),[29] and toxicity. Cox proportional hazards models were used to estimate the effects of the variables by univariable and multivariable setting. Proportional hazards assumption was verified for all models. Qualitative data were analyzed by the use of the χ^2 test and, if appropriate, by Fisher's exact test. Statistical analyses were performed by R software (version 3.1.2; R Foundation for Statistical Computing, Vienna, Austria; https://www.R-project.org/) and SAS (version 9.3; SAS Institute, Cary, NC) software. All *P* values are based on two-sided tests and considered significant when $<$ .05.

RESULTS

Characteristics of Patients and Procedures

From June 2005 to June 2011, 249 patients were assessed for eligibility (Fig 1). Of the 249 registered patients, three were excluded because of an unconfirmed diagnosis (follicular lymphoma, n = 1), hepatitis B serology (n = 1), and withdrawn consent before randomization (n = 1). Of the remaining 246 patients randomly assigned to R-CHOP (n = 126) and R-HDS (n = 120), the pathology review excluded seven patients who did not fulfil the histology criteria. One patient in the R-CHOP group (death before starting treatment) and five in the R-HDS group (death before starting treatment, n = 1; consent withdrawal, n = 4) did not receive the allocated treatment. The characteristics at enrollment of the 235 patients who formed the intention-to-treat-population are listed in Table 1. The two arms were well balanced with respect to all presenting features. Eight patients (3.4%) had a residual low-grade histology. The median age was 51 years (range, 19 to 66 years), with 26 patients (11%) $>$ 60 years of age. Adverse clinical features were as follows: Ann Arbor stage III to IV (92%), elevated lactate dehydrogenase level (85%), Eastern Cooperative Oncology Group Performance Status $>$ 1 (62%), $\geq$ 2 extranodal sites (44%), bone marrow infiltration (20%), bulky disease (69%), and B symptoms (59%). Accordingly, the risk score evaluation by IPI was high-intermediate in 57% of patients and high in 43%. No randomization imbalance was found according to the cell of origin evaluated retrospectively. The National Comprehensive Cancer Network–IPI[4] was also retrospectively calculated, and 63% of patients had a risk score $>$ 3.

Clinical Response

A complete response (CR) or unconfirmed complete response (CRu) was observed in 95 of 122 patients treated with R-CHOP (78%) versus 86 of 113 patients treated with R-HDS (76%; $P = .74$), whereas a PR was documented in six of 122 (5%) and 10 of 113 (9%) patients, respectively ($P = .23$). Accordingly, the overall response rate was 83% versus 85% ($P = .65$). Progressive disease was observed in 19 of 122 patients (15%) in the R-CHOP arm and 12 of 113 patients (10%) in the R-HDS arm ($P = .36$), with only one patient with stable disease in the R-HDS arm; these were considered primary refractory patients. One patient in the R-HDS group was not evaluable (Table 2). In the R-CHOP and R-HDS groups, the treatment was discontinued in six patients (5%) versus 22 patients (19%), respectively ($P < .001$), because of infections (one *v* six), other toxicities (hematologic, one *v* six; cardiovascular, one *v* three; other, one *v* two; medical, one *v* two), or patient decision (one *v* three). The final autograft was performed in 80 of 113 patients (71%) in the R-HDS group, with a median of 7.2×10^6/kg CD34+ cells (range, 3 to 30×10^6/kg). No graft failures were reported. Radiotherapy was performed in 37 of 122 patients (30%) in the R-CHOP group and 16 of 113 patients (14%) in the R-HDS group ($P = .003$).

Clinical Outcomes

In the R-CHOP group, 73 of the 95 patients who had achieved CR/CRu remained alive and in continuous CR (73 of 122 patients; 60%), seven died in CR, and 15 relapsed (12 patients died and three are alive after achievement of a second CR). In the R-HDS group, of the 86 patients who had achieved CR/CRu, 74 remained alive in continuous CR (74 of 113; 65%), six died in CR, and six experienced relapse (four later died, two are still alive). Of the six

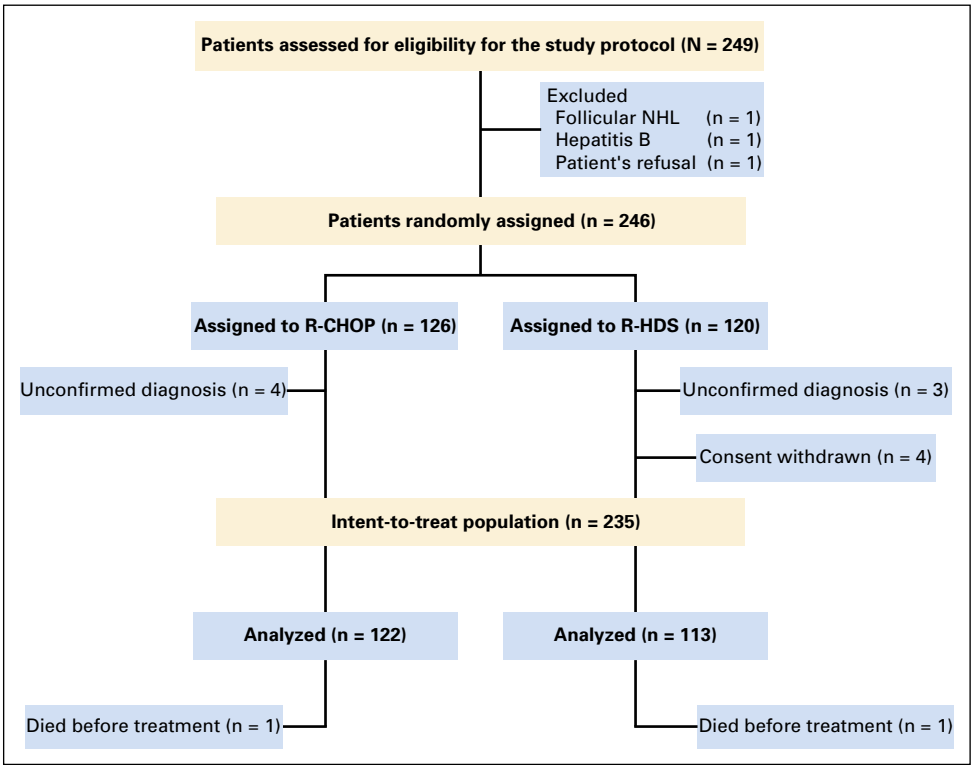

Fig 1. CONSORT diagram of the study. NHL, non-Hodgkin lymphoma; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; R-HDS, rituximab plus high-dose sequential chemotherapy.

Table 1. Demographic Characteristics by Study Arm

Characteristic	All Patients, No. (%) (N = 235)	R-CHOP, No. (%) (n = 122)	R-HDS, No. (%) (n = 113)	*P*
Age, years				
Median (range)	51 (19-66)	49 (19-66)	53 (19-65)	.44
≤ 60	209 (89)	108 (89)	101 (89)	.83
> 60	26 (11)	14 (11)	12 (11)	
Sex				
Male	136 (58)	71 (58)	65 (58)	.92
Female	99 (42)	51 (42)	48 (42)	
ECOG performance status				
0	37 (16)	21 (17)	16 (14)	.36
1	53 (23)	25 (20)	28 (25)	
2	117 (50)	65 (53)	52 (46)	
3	28 (12)	11 (9)	17 (15)	
Ann Arbor clinical stage				
II	19 (8)	9 (7)	10 (9)	.91
III	54 (23)	28 (23)	26 (23)	
IV	162 (69)	85 (70)	77 (68)	
Bulky disease*				
No	72 (31)	37 (30)	35 (31)	.88
Yes	162 (69)	85 (70)	77 (68)	
B symptoms*				
No	93 (40)	51 (42)	42 (37)	.54
Yes	138 (59)	70 (57)	68 (60)	
Bone marrow infiltration*				
No	177 (75)	93 (76)	84 (74)	.86
Yes	47 (20)	24 (20)	23 (20)	
No. of extranodal sites				
0-1	132 (56)	70 (57)	62 (55)	.70
≥ 2	103 (44)	52 (43)	51 (45)	
Elevated LDH (ratio to ULN)				
≤ 1	34 (14)	17 (14)	17 (15)	.93
> 1-≤ 3	165 (70)	87 (71)	78 (69)	
> 3	36 (15)	18 (15)	18 (16)	
IPI†				
High-intermediate risk	133 (57)	67 (55)	66 (58)	.59
High risk	102 (43)	55 (45)	47 (42)	
NCCN IPI				
≤ 3	87 (37)	45 (37)	42 (37)	.96
> 3	148 (63)	77 (63)	71 (63)	
Cell of origin				
Non-GCB	112 (48)	54 (44)	58 (51)	.68
GCB	64 (27)	35 (29)	29 (26)	
PML	27 (11)	14 (11)	13 (12)	
NE	32 (14)	19 (16)	13 (12)	

Abbreviations: ECOG, Eastern Cooperative Oncology Group; GCB, germinal center B-cell–like; IPI, International Prognostic Index; LDH, lactate dehydrogenase; NCCN, National Comprehensive Cancer Network; NE, not evaluable for lack of material; PML, primary mediastinal lymphoma; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; R-HDS, rituximab plus high-dose sequential chemotherapy; UNL, upper limit of normal range.

*One missing datum in the R-HDS arm for bulky disease; three missing data for B symptoms in the R-HDS arm and one in the R-CHOP arm; six and five missing data for bone marrow in the R-HDS arm and in the R-CHOP arm, respectively.

†High-intermediate: age-adjusted IPI = 2, IPI = 3; high risk: age-adjusted IPI = 3, IPI = 4-5.

Table 2. Response to Treatment and Causes of Death

Response to Treatment	R-CHOP, No. (%) (n = 122)	R-HDS, No. (%) (n = 113)
Complete/unconfirmed complete response	95 (78)	86 (76)
Partial response	6 (5)	10 (9)
Progressive/stable disease	19 (15)	13 (11)
Lost to follow-up	—	1 (0.8)
Overall response rate	101 (83)	96 (85)
Causes of death		
Total No. of deaths	35 (29)	30 (26)
Early death*	2 (1.6)	3 (2.6)
Disease related		
After progression	14 (11)	15 (13)
After relapse	12 (10)	4 (3.5)
Treatment related†		
Infections	2 (1.6)	1 (0.9)
Heart failure	1 (0.8)	2 (1.8)
Secondary malignancy	2 (1.6)	3 (2.7)
Other	2 (1.6)	2 (1.8)

Abbreviations: R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; R-HDS, rituximab plus high-dose sequential chemotherapy.

*Within 100 days from randomization.

†Death in remission (two patients in partial remission, 13 in complete remission).

patients who achieved a partial remission after R-CHOP, three remained alive, two experienced disease progression (one died and one is alive in second CR), and one was lost to follow-up. Of the 10 patients treated with R-HDS who were judged as partial remitters, three are alive without additional treatment, five experienced disease progression (three died and two are in CR following additional treatment), one died of a secondary cancer, and one died of treatment-related toxicity. A CNS progression/relapse occurred in seven of 122 patients (5.7%) in the R-CHOP arm and five of 113 (4.4%) in the R-HDS arm ($P = .65$). Of the 19 patients who had progressive disease after R-CHOP, 13 died and six are alive. All 12 patients with progressive disease after receiving R-HDS died. The patient with stable disease was lost to follow-up.

After a median follow-up of 5 years (range, 0.05 to 9.49), by an intent-to-treat analysis, the 3-year EFS was 62% (95% CI, 54% to 71%) for patients treated with R-CHOP versus 65% (95% CI, 56% to 74%) for patients treated with R-HDS ($P = .83$; hazard ratio, 0.99; 95% CI, 0.66 to 1.48; Fig 2A). The same lack of difference was observed when data were analyzed within the IPI subgroups (Figs 2B and 2C). Similarly, treatments did not significantly affect the 3-year PFS, which was 65% in the R-CHOP arm (95% CI, 57% to 74%) versus 75% (95% CI, 67% to 83%; P = .119) after R-HDS in the whole population (Fig 2D), as well as within IPI subgroups (Figs 2E and 2F). Interestingly, the 3-year DFS was better in the experimental arm, at 79% (95% CI, 71% to 87%) versus 91% (95% CI, 85% to 97%) in the R-CHOP and R-HDS arms, respectively ($P = .033$), even though this difference was lost after a longer follow-up (Fig 3A). No difference was found in terms of OS, at 74% (95% CI, 67% to 82%) in the R-CHOP arm versus 77% (95% CI, 70% to 86%) in the R-HDS arm ($P = .64$), no matter what the IPI risk subgroup was (Figs 3D, 3E, and 3F). Interestingly, the subgroup analysis describing the outcome of patients who did not discontinue the allocated treatment because of medical or patient decision or toxicity showed a significant benefit of the R-HDS program in terms of PFS and DFS, but not OS (Appendix Fig A2).

By univariable analysis, factors affecting age, performance status, and IPI subgroups showed a significant impact on EFS, PFS, and OS. Bulky disease was also significant on EFS (Appendix Table A1, online only). No evidence of differential benefit according to the cell of origin emerged from treatment intensification. By multivariable analysis, IPI remained the only factor significantly affecting the same outcomes (Appendix Table A2, online only).

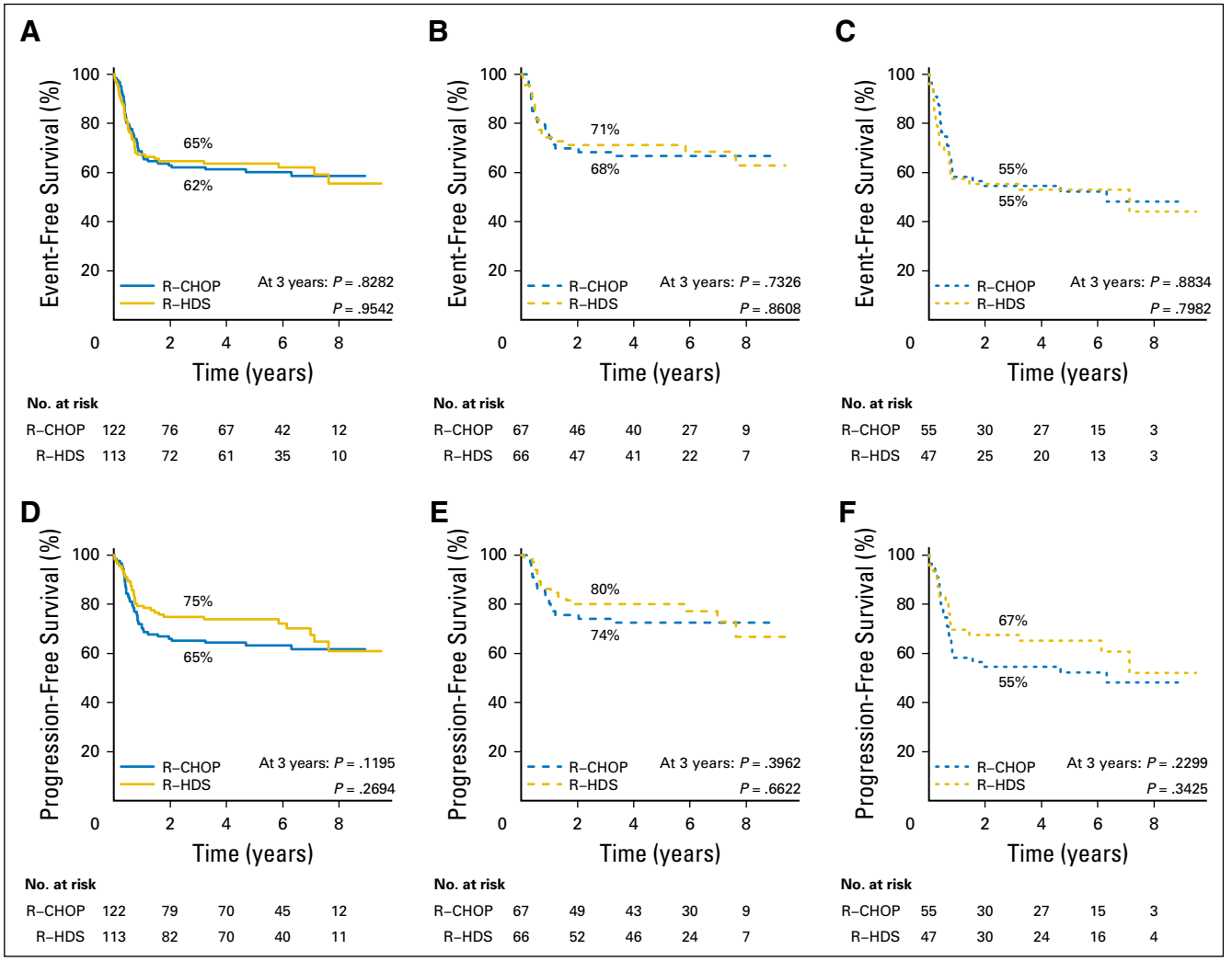

Fig 2. Event-free survival (EFS) and progression-free survival (PFS) curves according to treatment randomization. (A) EFS in all patients; (B) EFS in high-intermediate–risk patients; (C) EFS in high-risk patients; (D) PFS in all patients; (E) PFS in high-intermediate–risk patients; and (F) PFS in high-risk patients. EFS was measured from the time of study entry to any treatment failure, including disease progression, or discontinuation of treatment for any reason (eg, disease progression, toxicity, patient preference, initiation of new antilymphoma treatment, or death) or date of the last follow-up visit. PFS was defined as the time from study entry to disease progression or death as a result of any cause or date of the last follow-up visit. R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; R-HDS, rituximab plus high-dose sequential chemotherapy.

Toxicity

A lower rate of grade 3 to 4 hematologic toxicity was recorded in the R-CHOP arm compared with the R-HDS arm, with at least one episode of neutropenia in 34% versus 84% of patients ($P < .001$), anemia in 15% versus 71% of patients ($P < .001$), and thrombocytopenia in 5% versus 86% of patients ($P < .001$; Table 3). Patients receiving R-CHOP had fewer episodes of mucositis, diarrhea, nausea, and vomiting (11% *v* 29%; $P < .001$). A deeper neutropenia contributed to a higher frequency of severe infections in R-HDS patients (54% *v* 8%; $P < .001$). Sensory neurologic adverse effects were more frequent after R-CHOP (7% *v* 0%), possibly as a consequence of the higher cumulative dose of vincristine received during treatment. A lower number of adverse events occurred in the R-CHOP arm versus the R-HDS arm (14 *v* 45; $P < .001$), including those classified as serious (five *v* 24; $P < .001$).

Cause of Death

Thirty-five patients (29%) in the R-CHOP group and 30 (26%) in the R-HDS group died. Two patients in the R-CHOP group and three in R-HDS group died within 100 days of diagnosis (early death). In the R-CHOP and R-HDS groups, 26 and 19 patients died as a result of disease, whereas seven and eight responding patients , respectively, died as a result of treatment-related toxicities (Table 2).

DISCUSSION

This randomized phase III trial demonstrates that the clinical outcome of patients with high-risk DLBCL treated with R-CHOP or an intensive R-HDS program is comparable. Both treatments provided similar results in terms of overall response rate and long-term outcomes. Therefore, the primary objective of this study to

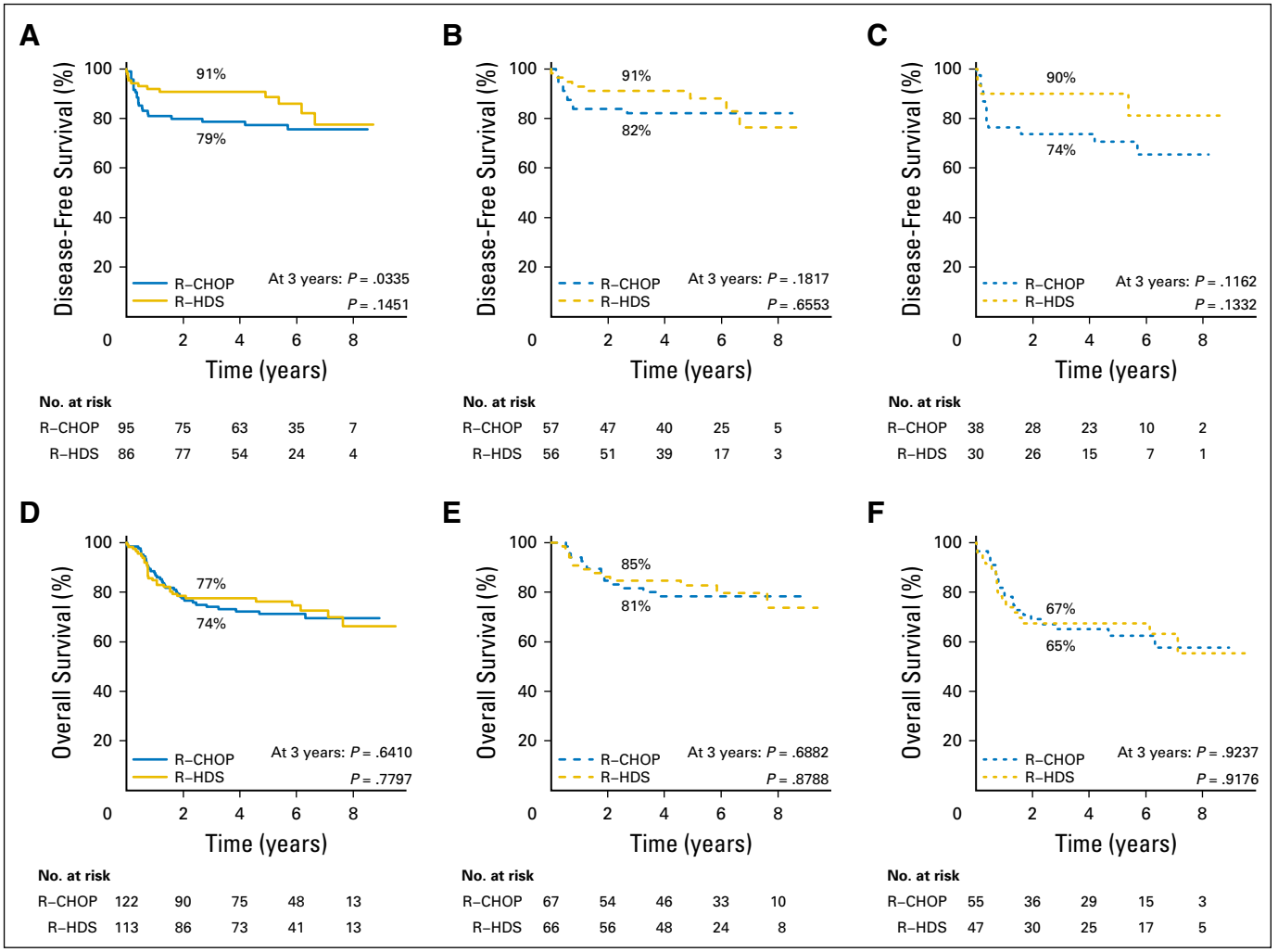

Fig 3. Disease-free survival (DFS) and overall survival (OS) curves according to treatment randomization. (A) DFS in all patients; (B) DFS in high-intermediate–risk patients; (C) DFS in high-risk patients; (D) OS in all patients; (E) OS in high-intermediate–risk patients; and (F) OS in high-risk patients. DFS was defined as the time from documentation of complete response to time to relapse or death as a result of lymphoma or acute toxicity of treatment or date of the last follow-up visit. OS was defined as the time from study entry to death as a result of any cause or date of the last follow-up visit. R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; R-HDS, rituximab plus high-dose sequential chemotherapy.

improve the EFS by the use of HD chemotherapy and ASCT was not achieved. Our study was conducted entirely in the rituximab era and was offered only to a homogeneous group of patients with DLBCL with unfavorable risk factors at diagnosis. Our results indicate that CHOP chemotherapy, optimally supplemented by eight doses of rituximab,[30] remains the standard of care also for this group of patients at higher risk for disease resistance or recurrence. In a multicenter setting, R-HDS therapy had a higher rate of acute hematologic and infectious toxicities and was more difficult to complete when considering the higher rate of treatment discontinuation. The appropriate long-term follow-up allowed observation of better DFS at 3 years after R-HDS, although the robustness of the remission achieved after this intensive treatment vanished subsequently with the occurrence of late events.

When this study was designed, R-CHOP-14 treatment for eight cycles was selected as the control arm on the basis of the preliminary data of the German study group, which suggested an advantage of the dose-dense rituximab-based chemoimmunotherapy in elderly patients with DLBCL,[31] and to avoid the possibility that a potential superior result of the intensive experimental arm could be attributable to a weaker conventional therapy. Nonetheless, the results of our study, which enrolled only high-risk (IPI 2 to 3) patients, are similar to those reported by using R-CHOP (× six cycles every 14 days plus two cycles of rituximab or × eight cycles every 21 days)[32] and comparable to those achieved when adopting an induction therapy also including etoposide.[33]

On the contrary, compared with standard R-CHOP, intensified immunochemotherapy with rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone significantly improved survival of low-risk patients,[34] and this benefit was mostly observed in patients with non–germinal center B-cell (GCB) DLBCL.[35] In our study, similar to the report on the phase II trial we previously published,[20] the GCB versus non-GCB cell of origin did not predict a different outcome and was at variance with what was reported by the LNH03-2B study; we did not observe a better outcome among GCB patients treated with high-dose

Table 3. Grade III or IV Toxicity During Treatment

Toxicity	R-CHOP, No.* (%) (n = 122)	R-HDS, No.* (%) (n = 113)	*P*
Neutropenia	42 (34)	95 (84)	< .001
Anemia	18 (15)	80 (71)	< .001
Thrombocytopenia	6 (5)	97 (86)	< .001
GI	13 (11)	33 (29)	< .003
Cardiac	9 (7)	5 (4)	.34
Neurologic	9 (7)	—	.0032
Hepatic and metabolic	7 (6)	8 (7)	.67
Infection	10 (8)	61 (54)	< .001

Abbreviations: R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; R-HDS, rituximab plus high-dose sequential chemotherapy.
*No. of patients with at least one reported episode of Common Terminology Criteria for Adverse Events (version 3) grade III or IV toxic events.

chemotherapy. However, in the French study,[34] patients with only one aaIPI adverse factor were enrolled, which could explain better tolerance and results from the experimental treatment. Overall, the clinical value of a stratification on the basis of an immunostaining algorithm remains controversial with conflicting results.[36,37] The lack of information about double- or triple-hit lymphomas remains a potential limitation of our study.[38,39] The SWOG (Southwest Oncology Group)-9704 trial, which included different subtypes of B-cell and T-cell lymphomas, found that early consolidation with ASCT improved the PFS of patients with high-intermediate risk or high risk who had a response to induction chemotherapy (2-year PFS, 69% *v* 55%) without any difference in OS between the two treatment arms.[40] It is worth noting that the superiority of ASCT was limited to 35% of patients with high-risk IPI in whom either the PFS or OS was better than that of patients who received conventional chemotherapy, whereas in the prevailing group of patients with high-intermediate risk, there was no difference in terms of PFS and OS between the two treatment arms. Preliminary results from another Italian study reported an advantage in terms of PFS but not OS in chemosensitive patients who proceeded to ASCT.[41]

In conclusion, this randomized trial indicates that both dose-dense R-CHOP for eight cycles and R-HDS followed by autograft are equally effective in high-risk patients with DLBCL. Whether the addition of new drugs, such as lenalidomide[42] and ibrutinib[43] or monoclonal antibodies such as obinotuzumab,[44] to R-CHOP therapy will be able to improve the outcome of high-risk patients with DLBCL is still under investigation.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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Randomized Trial Comparing R-CHOP Versus High-Dose Sequential Chemotherapy in High-Risk Patients With Diffuse Large B-Cell Lymphomas

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Appendix

Table A1. Univariable Analysis

Characteristic	EFS (n = 235; events = 93)		PFS (n = 235; events = 79)		DFS (n = 181; events = 34)		OS (n = 235; events = 65)	
	HR (95% CI)	*P**	HR (95% CI)	*P**	HR (95% CI)	*P**	HR (95% CI)	*P**
Treatment arm								
R-CHOP	1.00		1.00		1.00		1.00	
R-HDS	0.99 (0.66 to 1.48)	.9536	0.78 (0.50 to 1.22)	.2702	0.6 (0.29 to 1.21)	.1501	0.93 (0.57 to 1.52)	.7796
Age, years								
≤ 60	1.00		1.00		1.00		1.00	
> 60	1.86 (1.07 to 3.23)	.0284	1.93 (1.06 to 3.5)	.0306	2.39 (0.99 to 5.77)	.0535	1.95 (1.02 to 3.73)	.0437
Sex								
F	1.00		1.00		1.00		1.00	
M	1.15 (0.76 to 1.74)	.5123	1.02 (0.65 to 1.6)	.9198	0.8 (0.41 to 1.58)	.5232	0.88 (0.54 to 1.44)	.621
ECOG performance status								
0	1.00		1.00		1.00		1.00	
1	1.24 (0.55 to 2.80)	.6077	1.70 (0.65 to 4.44)	.2745	1.46 (0.37 to 5.86)	.59	2.28 (0.74 to 7.01)	.1485
2	2.41 (1.19 to 4.86)	.0143	3.28 (1.41 to 7.65)	.0059	3.1 (0.93 to 10.35)	.0662	3.61 (1.29 to 10.1)	.0143
3	1.6 (0.65 to 3.94)	.3059	1.93 (0.67 to 5.58)	.2222	1.46 (0.29 to 7.23)	.6442	2.76 (0.83 to 9.16)	.0978
Ann Arbor clinical stage								
II	1.00		1.00		1.00		1.00	
III	1.26 (0.51 to 3.15)	.6144	1.06 (0.38 to 2.91)	.9147	0.44 (0.1 to 1.97)	.2829	1.03 (0.33 to 3.18)	.9634
IV	1.42 (0.61 to 3.26)	.4146	1.46 (0.59 to 3.64)	.4149	1.16 (0.35 to 3.82)	.8084	1.53 (0.55 to 4.24)	.4142
Bulky disease								
No	1.00		1.00		1.00		1.00	
Yes	0.55 (0.36 to 0.83)	.0043	0.79 (0.5 to 1.26)	.3216	0.52 (0.27 to 1.03)	.0599	0.8 (0.48 to 1.35)	.4043
B symptoms*								
No	1.00		1.00		1.00		1.00	
Yes	1.15 (0.75 to 1.76)	.5142	1.17 (0.74 to 1.85)	.5129	1.31 (0.65 to 2.64)	.4546	1.25 (0.75 to 2.08)	.3953
BM infiltration								
No	1.00		1.00		1.00		1.00	
Yes	0.94 (0.56 to 1.58)	.8134	0.89 (0.51 to 1.57)	.6937	1.61 (0.79 to 3.31)	.1935	0.97 (0.53 to 1.79)	.9253
No. of extranodal sites								
0-1	1.00		1.00		1.00		1.00	
≥ 2	1.34 (0.89 to 2.02)	.1571	1.27 (0.82 to 1.98)	.2881	1.25 (0.64 to 2.45)	.516	1.35 (0.83 to 2.2)	.2239
Elevated LDH (ratio to ULN)								
≤ 1	1.00		1.00		1.00		1.00	
> 1 ≤ 3	0.83 (0.47 to 1.46)	.5217	0.88 (0.47 to 1.66)	.6897	0.61 (0.25 to 1.45)	.2616	0.95 (0.46 to 1.97)	.8910
> 3	1.24 (0.63 to 2.44)	.5318	1.69 (0.82 to 3.49)	.1528	1.57 (0.58 to 4.21)	.3736	2.17 (0.97 to 4.83)	.0584
IPI								
Intermediate-high	1.00		1.00		1.00		1.00	
High	1.78 (1.18 to 2.67)	.0058	2.08 (1.33 to 3.25)	.0013	1.63 (0.83 to 3.21)	.1536	2.17 (1.32 to 3.55)	.0022
NCCN IPI								
≤ 3	1.00		1.00		1.00		1.00	
> 3	1.81 (1.14 to 2.87)	.0112	1.82 (1.1 to 3.00)	.0190	1.67 (0.80 to 3.50)	.1712	1.58 (0.92 to 2.69)	.0960
Cell of origin								
GCB	1.00		1.00		1.00		1.00	
Non-GCB	0.90 (0.56 to 1.45)	.6638	0.75 (0.45 to 1.26)	.2848	0.72 (0.33 to 1.58)	.4100	0.77 (0.43 to 1.36)	.3692
PML	0.54 (0.24 to 1.24)	.1458	0.62 (0.27 to 1.43)	.2629	0.41 (0.09 to 1.86)	.2485	0.76 (0.32 to 1.80)	.5304
NE	1.01 (0.53 to 1.92)	.9715	1.02 (0.52 to 1.99)	.9621	1.13 (0.44 to 2.92)	.7996	0.94 (0.44 to 2.01)	.8699

Abbreviations: BM, bone marrow; DFS, disease-free survival; EFS, event-free survival; GCB, germinal center B-cell–like; HR, hazard ratio; IPI, International Prognostic Index; LDH, lactate dehydrogenase; NCCN, National Comprehensive Cancer Network; NE, not evaluable for lack of material; OS, overall survival; PFS, progression-free survival; PML, primary mediastinal lymphoma; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; R-HDS, rituximab plus high-dose sequential chemotherapy; ULN, upper limit of normal.

*Result of Wald test in a univariate Cox model.

Table A2. Multivariable Analysis

Characteristic	EFS (n = 235; events = 93) HR (95% CI)	*P*	PFS (n = 235; events = 79) HR (95% CI)	*P*	DFS (n = 181; events = 34) HR (95% CI)	*P*	OS (n = 235; events = 65) HR (95% CI)	*P*
Treatment arm								
R-CHOP	1.00		1.00		1.00		1.00	
R-HDS	1.05 (0.7 to 1.6)	.8011	0.84 (0.53 to 1.32)	.4464	0.58 (0.29 to 1.2)	.142	1 (0.61 to 1.64)	.9946
Sex								
F	1.00		1.00		1.00		1.00	
M	1.16 (0.76 to 1.76)	.4965	1.01 (0.64 to 1.59)	.974	0.84 (0.42 to 1.68)	.6153	0.9 (0.55 to 1.48)	.6785
Age								
≤ 60	1.00		1.00		1.00		1.00	
> 60	1.66 (0.92 to 2.98)	.0905	1.7 (0.91 to 3.18)	.0973	2.01 (0.8 to 5.05)	.1371	1.74 (0.88 to 3.43)	.1097
BM infiltration								
No	1.00		1.00		1.00		1.00	
Yes	0.84 (0.5 to 1.43)	.5232	0.81 (0.45 to 1.43)	.4599	1.47 (0.7 to 3.08)	.3037	0.87 (0.47 to 1.62)	.6646
B symptoms								
No	1.00		1.00		1.00		1.00	
Yes	1.09 (0.7 to 1.69)	.7004	1.09 (0.68 to 1.76)	.7093	1.3 (0.63 to 2.68)	.4824	1.2 (0.71 to 2.03)	.4899
IPI								
Intermediate-high	1.00		1.00		1.00		1.00	
High	1.7 (1.11 to 2.62)	.0149	1.95 (1.23 to 3.11)	.0049	1.48 (0.73 to 3)	.2818	1.99 (1.19 to 3.33)	.0084
Cell of origin								
GCB	1.00		1.00		1.00		1.00	
Non-GCB	0.82 (0.5 to 1.33)	.4175	0.7 (0.41 to 1.18)	.1839	0.71 (0.32 to 1.58)	.4029	0.7 (0.39 to 1.25)	.2304
PML	0.53 (0.23 to 1.22)	.1365	0.6 (0.26 to 1.39)	.2326	0.39 (0.09 to 1.8)	.2304	0.74 (0.31 to 1.76)	.4898
NE	0.97 (0.5 to 1.89)	.9327	0.99 (0.5 to 1.98)	.9809	1.03 (0.38 to 2.76)	.953	0.88 (0.41 to 1.92)	.7563

Abbreviations: BM, bone marrow; DFS, disease-free survival; EFS, event-free survival; GCB, germinal center B-cell–like; HR, hazard ratio; IPI, International Prognostic Index; NE, not evaluable for lack of material; OS, overall survival; PFS, progression-free survival; PML, primary mediastinal lymphoma; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; R-HDS, rituximab plus high-dose sequential chemotherapy.

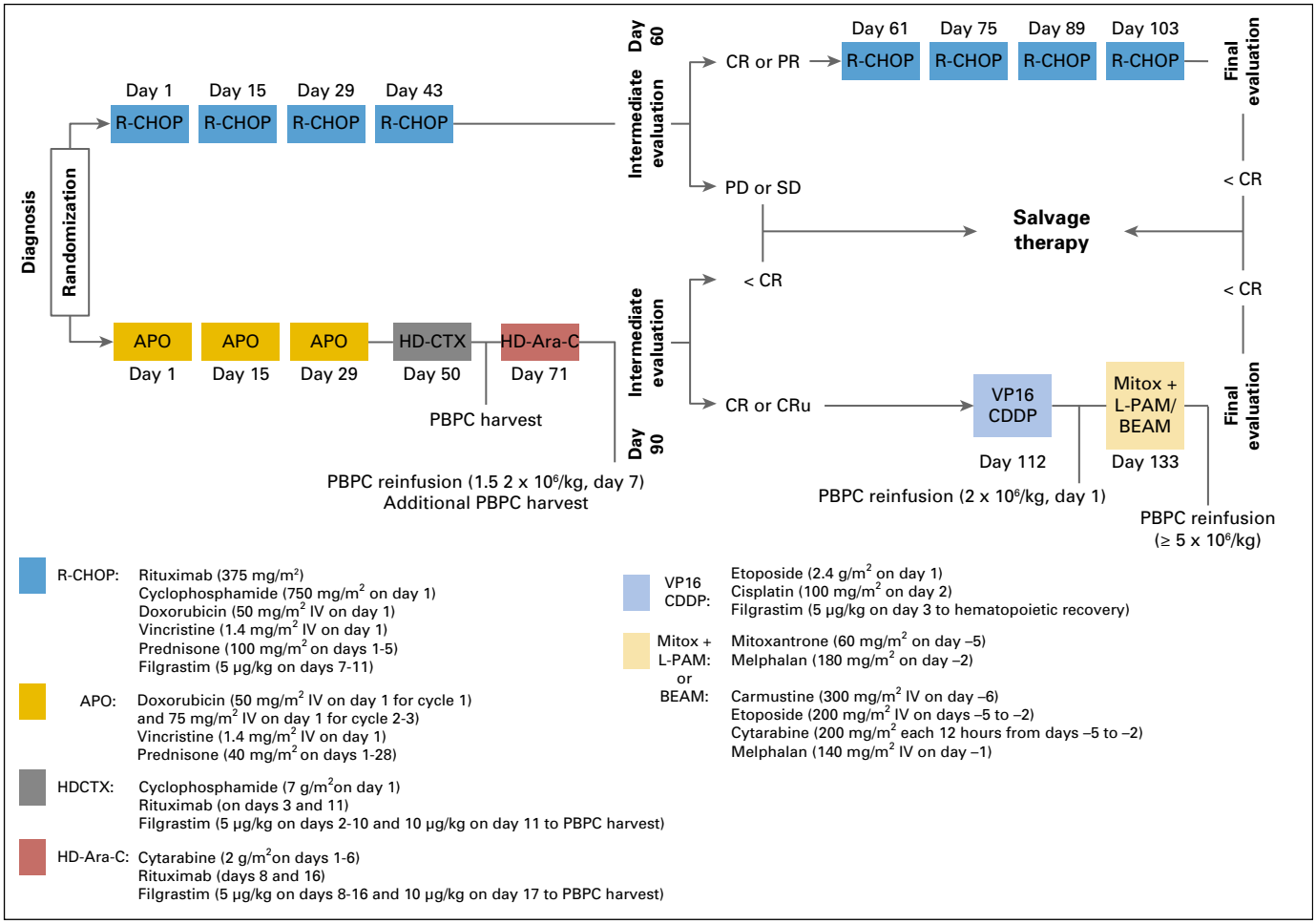

Fig A1. Study design. APO, doxorubicin 50 mg/m^2 IV followed by the full dose of 75 mg/m^2 IV at 14 and 28 days, vincristine 1.4 mg/m^2 IV on days 1, 14, and 28, and oral prednisone 40 mg/m^2 on days 1 to 28; BEAM, carmustine, etoposide, cytarabine, melphalan; CDDP, cisplatin; CR, complete response; CRu, complete response unconfirmed; HD-Ara-C, high-dose cytarabine; HD-CTX, high-dose cyclophosphamide; IV, intravenously; L-PAM, melphalan; mitox, mitoxantrone; PBPC, peripheral blood progenitor cells; PD, progressive disease; PR, partial response; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; SD, stable disease; VP16, etoposide.

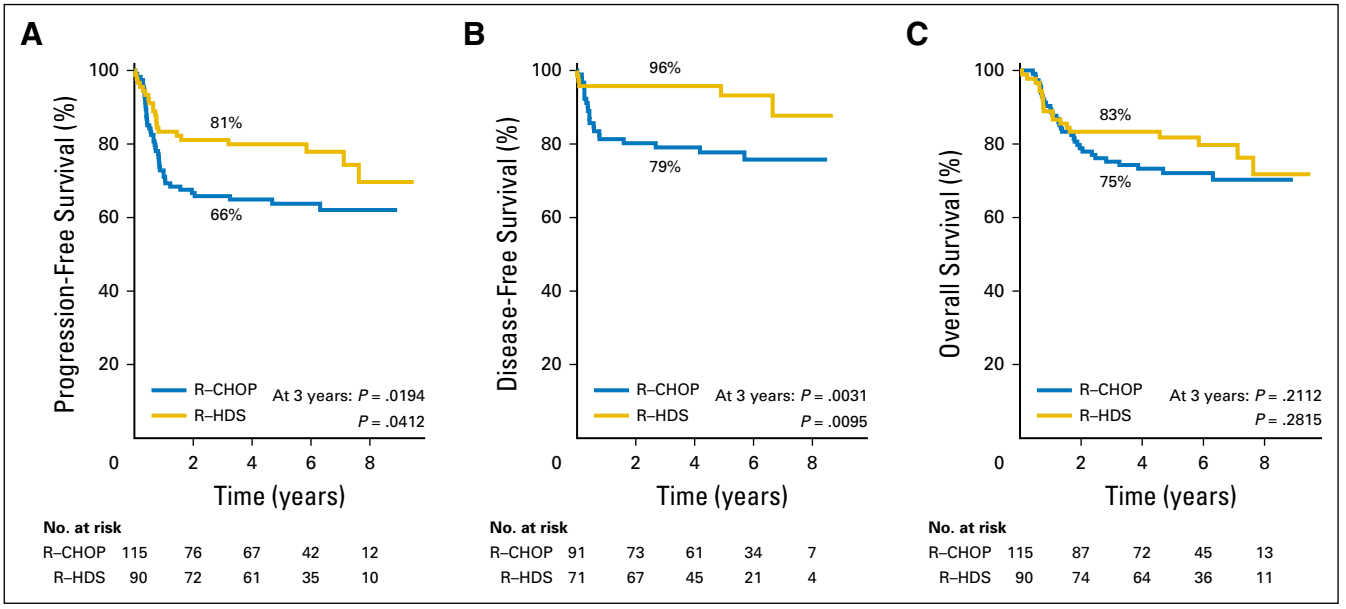

Fig A2. (A) Progression-free survival, (B) disease-free survival, and (C) overall survival of patients not discontinuing the allocated treatment because of toxicities (medical or patient's decision). R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; R-HDS, rituximab plus high-dose sequential chemotherapy.