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Pegylated liposomal doxorubicin replacing conventional doxorubicin in standard R-CHOP chemotherapy for elderly patients with diffuse large B-cell lymphoma: An open label single arm phase II trial

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Abstract

Objectives—This multicenter phase II trial evaluated the safety and efficacy of pegylated liposomal doxorubicin (PLD) in place of conventional doxorubicin in standard RCHOP therapy for elderly patients with diffuse large B-cell lymphoma.

Methods—Patients 60 years of age who had stage II to IV disease were included. Treatment consisted of rituximab 375 mg/m² intravenously (IV); cyclophosphamide 750 mg/m² IV; PLD 40 mg/m² (maximum, 90 mg) intravenously over 1 hour; and vincristine 2.0 mg IV all on day 1.

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This study was in part presented at the annual meeting of the American Society of Clinical Oncology in 2011 (abstract #83967).

Potential Conflicts of Interests

Other authors reported no conflicts of interests to disclose.

Additionally prednisone, 40 mg/m² was given orally on days 1 to 1–5 (DRCOP). Cycles were repeated every 3 weeks for 6 to 8 cycles.

Results—Eighty patients were enrolled and were evaluable for toxicity. The median age was 69 years. All except one had additional cardiac risk factors for anthracycline induced cardiac toxicity beyond advanced age. Based on the intent-to-treat analysis in 79 eligible patients, overall response rate was 86%, and complete response rate was 78%. Cardiac events of grade 3 were identified in 3 patients (4%); grade 1–2 events, mostly asymptomatic declines in ejection fraction, were noted in an additional 16 patients. There was one death attributed to cardiac failure. The estimated 5-year event-free and overall survival rates were 52% and 70%, respectively.

Conclusions—DRCOP represents an effective strategy for potentially mitigating cardiotoxicity in elderly patients with aggressive B-cell lymphoma. Future studies to incorporate baseline cardiac risk assessment as well as long-term follow-up, and biospecimen collection for correlative science should be undertaken.

Keywords

diffuse large B-cell lymphoma; elderly patients; anthracycline; pegylated liposomal doxorubicin; cardiac toxicity

INTRODUCTION

Anthracyclines are considered a crucial part of intent-to-cure regimens for patients with diffuse large B-cell lymphoma (DLBCL).¹ Unfortunately anthracyclines exhibit cumulative dose-related cardiotoxicity; while myocytes destruction is universally seen, the extent and expression of this injury is variable and dependent on the degree of prior myocytes compromise and the sensitivity of the heart.^{2,3} Older patients and those with pre-existing cardiac disease are known to have higher incidences of both overt heart failure and asymptomatic declines of cardiac parameters.^{2–4} Less cardiotoxic approach is critically needed⁵

Modern anti-cancer regimens have incorporated strategies to reduce the cardiotoxic burdens of anthracyclines, such as reducing the cumulative dose of cardiotoxic agents, the use of the cardioprotective agent dexrazoxane, and the incorporation of continuous-infusion administration schedules. Each presents a compromise either in increased non-cardiac adverse events, convenience, or concerns regarding reduced efficacy.

Pegylated liposomal doxorubicin (PLD) offers an additional strategy for limiting cardiotoxicity which allows localized penetration of the anthracycline molecule selectively through the impaired vasculature, thereby concentrating the delivery of the agent to the tumor. Additionally, the overall peak plasma concentration to which the heart is exposed is reduced with the use of PLD.⁶ To test the efficacy and the safety of PLD in patients with DLBCL, we conducted a multicenter phase II trial of DRCOP (rituximab, cyclophosphamide, PLD, vincristine, and prednisone).

MATERIALS AND METHODS

Patients

This study was approved by our institutional review board and registered at clinicaltrials.gov (NCT00101010). All patients provided written consent. The primary objectives of this study were to determine the overall rate of response and to determine the extent of grade 3 or 4 overall and cardiac-specific toxicity. The secondary objectives were to determine the event-free survival (EFS) and overall survival (OS).

Inclusion criteria were: age > 60 years; histologically confirmed untreated DLBCL; stage II or greater disease; measurable disease; Eastern Cooperative Oncology Group performance status 0 to 2; adequate bone marrow reserve evidenced by an absolute neutrophil count > 1,000/ μ L and a platelet count >100,000/ μ L; as well as adequate kidney and liver function (a serum creatinine concentration < 2 mg/dL and a serum bilirubin concentration < 2 mg/dL). Additionally, a left ventricular ejection fraction (LVEF) $\geq$ 50% by 2-dimensional echocardiography using the method of disks or multi-gated acquisition scan (MUGA) was required.⁷ Patients with known heart disease were eligible if their cardiac disease was stable and had been evaluated by a cardiologist to optimize all cardiovascular status. Exclusion criteria included primary central nervous system lymphoma, recent myocardial infarction (within 6 months of the inclusion evaluation), symptomatic heart failure, uncontrolled hypertension, uncontrolled ventricular arrhythmia, or unstable coronary ischemia.

Treatment

The cancer treatment regimen of DRCOP consisted of rituximab 375 mg/m² intravenously (IV), cyclophosphamide 750 mg/m² IV, PLD 40 mg/m² (maximum, 90 mg) IV over 1 hour, and vincristine 2.0 mg IV, all on cycle day 1. Additionally patients received prednisone, 40 mg/m² given orally on days 1 to 5 of each cycle. All patients received either filgrastim, 5 μ g/kg subcutaneously daily starting on day 2 and continuing until the neutrophil count had recovered from its nadir (> 3,000/ μ L) or pegfilgrastim (one 6-mg dose subcutaneously) on day 2. This regimen was administered approximately every 21 days. The treatment was planned for 6 to 8 cycles, at the discretion of the treating physician.

If the absolute neutrophil nadir was < 500/ μ L for > 10 days or if the platelet nadir was < 50,000/ μ L, doses of cyclophosphamide and PLD were decreased by 1 level for the next cycle. For neutropenic fever or bleeding of grade 1 or 2, doses in all subsequent cycles were reduced by 1 level. For grade 3 or 4 non-cardiac toxicity, subsequent doses were reduced by 1 level. Doses of PLD and cyclophosphamide for patients in whom dose reduction was undertaken were 35 mg/m² and 600 mg/m² respectively at dose reduction level 1, and 30 mg/m² and 450 mg/m² respectively at dose reduction level 2.

Toxicity and Response Evaluation

Toxicity was graded based on Common Terminology Criteria for Adverse Events, version 3 and assessed from the initiation time of the regimen until the end of chemotherapy. Repeat echocardiogram or MUGA imaging was planned after 4 cycles and at the end of treatment to assess the change in LVEF. Decreases in LVEF were graded as follows; Grade 2, LVEF

decrease to 40–49% or LVEF decrease from baseline by 10–19 percentage points; Grade 3, LVEF 20–39% or LVEF decrease from baseline by 20 percentage points; and Grade 4, LVEF decrease to <20%.

Response was evaluated either upon completion or termination of treatment and was coded as complete response (CR), CR unconfirmed (CRU), partial response, stable disease, or progressive disease, and was determined by International Working Group (IWG) criteria based on computed tomographic scans and bone marrow biopsy.⁸ Since most responding patients had had Positron Emission Tomographic (PET) scans performed for response evaluation, responses were also coded using revised IWG criteria.⁹

Statistical Consideration

The primary efficacy measure was the combined CR and CRU (CR/CRU) rate. A previous phase III report of RCHOP targeting a similar population had a CR/CRU rate of 75%.¹⁰ We planned to enroll 80 patients in this study. With this maximum accrual, the CR/CRU rate could be estimated with a 90% confidence interval of width 0.18, assuming at least a 75% of CR/CRU rate. To ensure that DRCOP was not providing less effective treatment than the standard RCHOP, the response rate was calculated after every 12 patients were enrolled; and if the upper bound of the 90% confidence interval of the CR/CRU rate was less than 75%, accrual would have been stopped.

Grade 3 or 4 cardiac toxicity was also monitored for early stopping rules and if lower bound of the 90% confidence interval of the rate of such toxicity exceeded 8%, then the study would have been closed. An event was defined as the first occurrence of any of the following: disease progression, initiation of unplanned new treatment, or death from any cause. Event-free survival (EFS) was calculated from the date of study registration to the date of the first event or last follow-up. When the LVEF was reported as a range, the rounded average is reported. Overall survival (OS) was calculated from the date of study registration to the date of death from any cause. EFS and OS were estimated using the Kaplan-Meier method.

RESULTS

Eighty patients were enrolled in this trial between August 2005 and May 2009 (Table 1). One patient received only 1 cycle of DRCOP treatment and was eventually found to have small lymphocytic lymphoma and was therefore removed from the study; this patient is included in the toxicity assessments but not the efficacy assessments. The median age was 69 (range, 61 to 92), and 16% of patients had an Eastern Cooperative Oncology Group performance status of 2.

The majority of patients (98%) had at least 1 of the following traditional cardiac risk factors for increased anthracycline-associated cardiotoxicity in addition to age >60: obesity (body mass index ≥ 30 ; $n = 32$), diabetes mellitus (history or presentation with fasting blood glucose > 126 mg/dL; $n = 27$), hypertension ($n = 73$), hyperlipidemia ($n = 45$), and/or history of tobacco use ($n=35$).¹¹ Other important comorbidities that increase the risk of developing heart failure included history of coronary artery disease (CAD, $n = 20$) and

history of hypothyroidism (n = 16) (Table 1). No patient had clinical or echocardiographic/MUGA evidence of left ventricular dysfunction at study entry.

Treatment Delivery and Toxicity

Of the 80 patients who received at least 1 cycle of treatment, 62 completed at least 6 cycles of therapy. All 80 patients were evaluated for toxicity. A total of 492 cycles of treatment were given. The median number of cycles given per patient was 6 (range, 1 to 8). Reasons for discontinuation of treatment in patients who received fewer than 6 cycles (n = 18) included infection, and weakness, as well as progressive disease. Only one patient stopped prematurely because of cardiac dysfunction after 4 cycles of treatment. Of the 17 patients who discontinued treatment because of toxicity, 3 continued treatment with standard RCHOP (hand and foot syndrome; colitis leading to treatment delay and off study; thrombotic event and off study by treating physician's decision) and 2 received radiation therapy as an alternative treatment.

The grade 3 or greater toxicities, including both cardiac and non-cardiac events observed during treatment, are summarized in Table 2. All patients received filgrastim or pegfilgrastim, and 39% of patients experienced grade 3 or 4 neutropenia. In addition, 13% experienced at least 1 event of grade 3 febrile neutropenia from which two patients died. Hand-foot syndrome was observed in 13% of patients. Grade 3 hand-foot syndrome was observed in 3 patients (4%) and was conservatively managed, but 1 patient eventually discontinued DRCOP and received standard RCHOP. DRCOP was otherwise well tolerated.

LVEF was assessed prior to therapy (n=79), after 4 cycles (n=65) and at the end of therapy (n=38). The LVEF findings are summarized in Figure 1. A total of 11 patients (14%) had documented decrease in LVEF (Grade 3, n=8 (10%); Grade 4, n=3 (4%)) at mid-treatment and/or end of treatment evaluations. Grade 3 decreases in LVEF were all asymptomatic. While one of Grade 4 LVEF decrease was based on an asymptomatic decrease in LVEF from 86% to 63%, two were associated with symptoms. The first patient was a 71-year-old woman with a history of hypertension. The LVEF on MUGA scan decreased from 58% at baseline to 38% after 4 cycles of DRCOP, at which point she was found to have decreased performance status as well. A 2-dimensional echocardiography showed a diffuse left ventricular wall hypokinesis with an LVEF of 23%. This patient had achieved CRU at that point and was removed from the study. The patient died 6 weeks later of progressive heart failure (grade 5). No autopsy was performed. The second patient was a 70 year-old woman with a history of CAD and prior stent placement who experienced multiple episodes of syncope, 10 days after cycle 6 of DRCOP and was found to have third-degree atrioventricular block, for which a pacemaker was implanted. LVEF on 2-dimensional echocardiography after the pacemaker implantation was 37%, while baseline was 58%. The extent to which her cardiac dysfunction was related to her treatment versus exacerbation of her coronary disease could not be determined. In addition to these two patients, one experienced a symptomatic Grade 4 cardiac toxicity; an 83-year old obese man (BMI=31) with known CAD (previous bypass grafting surgery), hyperlipidemia, hypertension, and a long history of paroxysmal atrial fibrillation developed dyspnea and palpitation on cycle 1 day 7 of treatment due to atrial fibrillation with rapid ventricular response while on a beta-

adrenergic blocking agent (Grade 3 toxicity). The patient regained sinus rhythm after initiation of amiodarone and was discharged in a stable condition.

Two patients (3%) developed therapy-related myelodysplasia/acute myelogenous leukemia, 24 and 35 months after initiation of treatment. One patient died from his hematologic complication 28 months after initiation of treatment. The second patient was alive and in stable condition at the last follow up (41 months after initiation of treatment).

Response and Survival

Response rates were calculated based on the intent-to-treat analysis in 79 eligible patients. Using IWG criteria defined primarily by CT scans, we observed CR in 56 patients (71%), CRU in 6 (8%), and PR in 6 (8%). The overall response rate was 86%, and the CR/CRU rate was 78%. PET scans were also performed in most responding patients and were used to help classify all patients with CRU or PR as having CR or PR. According to the revised IWG criteria,⁹ the CR rate was 75% and the overall response rate was 86%. (Table 3) The details of 11 patients who did not achieve response on this study are the following: disease progression while on study (n=2) or less than PR upon completion of study treatment (n=4) requiring salvage therapy; premature termination of therapy due to complication (colitis n=1, hand and foot syndrome n=1, deep vein thrombosis n=1) and all 3 continued therapy with conventional R-CHOP (2 CR and 1 progression); and general deconditioning after 1 cycle and the patients were considered not candidates for further systemic therapy (n=2). None of 11 patients here had evidences of cardiac dysfunction.

The median duration of follow-up in surviving patients was 46 months. We observed 34 events (Table 4). The most common event was disease progression (n = 20). One patient died of heart failure, possibly associated with the chemotherapy as described above (4 months after initiation of treatment). One patient died from secondary myelodysplasia, 28 months after initiation of treatment. The estimated 5-year EFS rate was 53% (Figure 2). The estimated 5-year OS rate was 70% (Figure 3).

DISCUSSION

This study of PLD demonstrated similar activity to that of standard R-CHOP in elderly patients with untreated DLBCL (Table 5) for a group of patients who were deemed to be at increased risk for cardiotoxicity because of age and other cardiac risk factors. The incidence of cardiac events of any grade in elderly patients receiving RCHOP was 47%, and of grade 3 or 4 was 8% in the LNH98-5 study.¹⁰ In the RICOVER-60 study for elderly patients with aggressive B-cell lymphomas, grade 3 or 4 cardiac events that included arrhythmia as well as cardiac dysfunction were observed in 4% and 2% respectively.¹² More recent result from LNH03-6B study¹³ showed even lower incidence of cardiac toxicity, with grade 3/4 toxicity rate of 3% (Table 5). Although the inclusion criteria in these studies are similar to our study, cardiac risk factors have not been reported in detail for the LNH98-5, LNH03-6B or RICOVER-60 studies.

Several studies substituting PLD for conventional doxorubicin in the CHOP regimen have been reported. Across the 5 studies involving 123 patients with aggressive lymphoma (with

bleomycin administered in one study, and AIDS related lymphoma in one study), the CR rate was 59%.^{14–18} In a smaller study also using rituximab for patients with DLBCL (n = 30), the CR rate was 59% and the overall response rate was 76%.¹⁹ The doses of PLD ranged from 25 mg/m² to 40 mg/m², and there was no significant difference in toxicity profile by doses except a greater incidence of hand-foot syndrome at higher doses. In the phase II study of D (40 mg/m²) RCOP in AIDS-related lymphoma (n=40), the treatment was generally well tolerated and the CR rate was 48%.²⁰ Our study is the largest to date of this kind assessing the role of PLD in elderly patients, with a detailed description of the cardiac findings.

Non-pegylated liposomal doxorubicin is another lipid form of doxorubicin, which has different plasma pharmacokinetics and tissue distribution. This agent has also been studied in a setting of CHOP or RCHOP for aggressive lymphomas. Across four studies involving 162 patients, CR rate was 64%, and the treatment was generally well tolerated.^{18, 21, 22} This drug does not display appreciable hand and foot syndrome and thus may be associated with a better tolerability.

One limitation of this study is the lack of randomization. As such, we cannot directly compare the efficacy and toxicity of DRCOP to the RCHOP regimen in this population. Additionally, Hequet et al. have reported that late cardiac abnormalities can occur in patients receiving doxorubicin, with subclinical cardiomyopathy observed in 39 of 141 patients (28%). However, the median follow-up of 46 months for this study is appropriate for short to middle term toxicity observation.²³

In summary, DRCOP offers similar oncologic efficacy with an acceptable level of cardiotoxicity and can be considered in older patients who may have additional cardiac risk factors.

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REFERENCES

1. Wilson WH. Treatment strategies for aggressive lymphomas: what works? *Hematology Am Soc Hematol Educ Program*. 2013; 2013:584–590. PMID: 24319235. [PubMed: 24319235]
2. Ewer MS, Ewer SM. Troponin I provides insight into cardiotoxicity and the anthracycline-trastuzumab interaction. *J Clin Oncol*. 2010 Sep 1; 28(25):3901–3904. PMID: 20679626. [PubMed: 20679626]
3. Lotrionte M, Biondi-Zoccai G, Abbate A, et al. Review and meta-analysis of incidence and clinical predictors of anthracycline cardiotoxicity. *Am J Cardiol*. 2013 Dec 15; 112(12):1980–1984. PMID: 24075281. [PubMed: 24075281]

4. Sarkozy C, Coiffier B. Diffuse large B-cell lymphoma in the elderly: a review of potential difficulties. *Clin Cancer Res.* 2013 Apr 1; 19(7):1660–1669. PMID: 23339126. [PubMed: 23339126]
5. Suter TM, Ewer MS. Cancer drugs and the heart: importance and management. *Eur Heart J.* 2013 Apr; 34(15):1102–1111. PMID: 22789916. [PubMed: 22789916]
6. Yildirim Y, Gultekin E, Avci ME, Inal MM, Yunus S, Tinar S. Cardiac safety profile of pegylated liposomal doxorubicin reaching or exceeding lifetime cumulative doses of 550 mg/m² in patients with recurrent ovarian and peritoneal cancer. *Int J Gynecol Cancer.* 2008 Mar-Apr; 18(2):223–227. PMID: 17511800. [PubMed: 17511800]
7. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr.* 2005 Dec; 18(12):1440–1463. PMID: 16376782. [PubMed: 16376782]
8. 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 Apr; 17(4):1244. PMID: 10561185. [PubMed: 10561185]
9. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. *J Clin Oncol.* 2007 Feb 10; 25(5):579–586. PMID: 17242396. [PubMed: 17242396]
10. 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.* 2002 Jan 24; 346(4):235–242. PMID: 11807147. [PubMed: 11807147]
11. Von Hoff DD, Layard MW, Basa P, et al. Risk factors for doxorubicin-induced congestive heart failure. *Ann Intern Med.* 1979 Nov; 91(5):710–717. PMID: 496103. [PubMed: 496103]
12. Pfreundschuh M, Schubert J, Ziepert M, et al. Six versus eight cycles of bi-weekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas: a randomised controlled trial (RICOVER-60). *Lancet Oncol.* 2008 Feb; 9(2):105–116. PMID: 18226581. [PubMed: 18226581]
13. Delarue R, Tilly H, Mounier N, et al. Dose-dense rituximab-CHOP compared with standard rituximab-CHOP in elderly patients with diffuse large B-cell lymphoma (the LNH03-6B study): a randomised phase 3 trial. *Lancet Oncol.* 2013 May; 14(6):525–533. PMID: 23578722. [PubMed: 23578722]
14. Aviles A, Neri N, Castaneda C, Talavera A, Huerta-Guzman J, Gonzalez M. Pegylated liposomal doxorubicin in combination chemotherapy in the treatment of previously untreated aggressive diffuse large-B-cell lymphoma. *Med Oncol.* 2002; 19(1):55–58. PMID: 12025891. [PubMed: 12025891]
15. Tsavaris N, Kosmas C, Vadiaka M, et al. Pegylated liposomal doxorubicin in the CHOP regimen for older patients with aggressive (stages III/IV) non-Hodgkin's lymphoma. *Anticancer Res.* 2002 May-Jun; 22(3):1845–1848. PMID: 12168880. [PubMed: 12168880]
16. Martino R, Perea G, Caballero MD, et al. Cyclophosphamide, pegylated liposomal doxorubicin (Caelyx), vincristine and prednisone (CCOP) in elderly patients with diffuse large B-cell lymphoma: results from a prospective phase II study. *Haematologica.* 2002 Aug; 87(8):822–827. PMID: 12161358. [PubMed: 12161358]
17. Schmitt CJ, Dietrich S, Ho AD, Witzens-Harig M. Replacement of conventional doxorubicin by pegylated liposomal doxorubicin is a safe and effective alternative in the treatment of non-Hodgkin's lymphoma patients with cardiac risk factors. *Ann Hematol.* 2012 Mar; 91(3):391–397. PMID: 21850390. [PubMed: 21850390]
18. Levine AM, Tulpule A, Espina B, et al. Liposome-encapsulated doxorubicin in combination with standard agents (cyclophosphamide, vincristine, prednisone) in patients with newly diagnosed AIDS-related non-Hodgkin's lymphoma: results of therapy and correlates of response. *J Clin Oncol.* 2004 Jul 1; 22(13):2662–2670. PMID: 15226333. [PubMed: 15226333]
19. Zaja F, Tomadini V, Zaccaria A, et al. CHOP-rituximab with pegylated liposomal doxorubicin for the treatment of elderly patients with diffuse large B-cell lymphoma. *Leuk Lymphoma.* 2006 Oct; 47(10):2174–2180. PMID: 17071492. [PubMed: 17071492]

20. Levine AM, Noy A, Lee JY, et al. Pegylated liposomal doxorubicin, rituximab, cyclophosphamide, vincristine, and prednisone in AIDS-related lymphoma: AIDS Malignancy Consortium Study 047. *J Clin Oncol*. 2013 Jan 1; 31(1):58–64. PMID: 23169503. [PubMed: 23169503]
21. Tulpule A. Multidrug resistance in AIDS-related lymphoma. *Curr Opin Oncol*. 2005 Sep; 17(5): 466–468. PMID: 16093797. [PubMed: 16093797]
22. Visani G, Ferrara F, Alesiani F, et al. R-COMP 21 for frail elderly patients with aggressive B-cell non-Hodgkin lymphoma: a pilot study. *Leuk Lymphoma*. 2008 Jun; 49(6):1081–1086. PMID: 18569635. [PubMed: 18569635]
23. Hequet O, Le QH, Moullet I, et al. Subclinical late cardiomyopathy after doxorubicin therapy for lymphoma in adults. *J Clin Oncol*. 2004 May 15; 22(10):1864–1871. PMID: 15143078. [PubMed: 15143078]

	Baseline n=80	Mid therapy n=65	End of therapy n=38
Median	63%	63%	63%
Mean	63%	61%	60%
p-value (from baseline)		P=0.03	P=0.02
Grade 2 (LVEF decrease 10-19%)		6 (9%)	4 (11%)
Grade 3 (LVEF decrease 20-29%)		2 (3%)	1 (3%)
Grade 4 (LVEF <20%)		0	0
Measured by Echo	69 (86%)	61 (94%)	37 (97%)

Figure 1.
Change in left ventricular ejection fraction during and after therapy

Figure 2.
Kaplan Meier Curve of Event-Free Survival (n=79)

Figure 3.
Kaplan Meier Curve of Overall Survival (n=79)

Table 1**Patient and Disease Characteristics (N = 80)**

Characteristic	No.	%
Age at diagnosis, years		
61–70	49	61
71–80	21	26
81–90	9	11
91	1	1
Performance Status		
0 or 1	64	80
2	16	20
Serum Lactate Dehydrogenase Level		
Normal	41	51
High	39	49
Number of extranodal disease sites		
0 or 1	55	69
2	25	31
Ann Arbor stage		
II	18	23
III	20	25
IV	42	53
International Prognostic Index		
1	9	11
2	24	30
3	29	36
4	12	15
5	6	8
Histology		
DLBCL	79	99
SLL (not eligible)	1	1
Cardiac risk factors		
Obesity (BMI ≥ 30)	32	40
Diabetes mellitus	27	34
History of coronary artery disease	20	25
History of hypertension	73	91
History of hyperlipidemia	45	56
History of hypothyroidism	21	26
History of smoking tobacco	35	44
None of the above 6 cardiac risk	2	3
Cardiac evaluation prior to treatment		
Nuclear cardiac scan	53	66
Echocardiography	67	84

Characteristic	No.	%
LVEF < 50%	0	0

Abbreviations: BMI, body mass index; DLBCL, diffuse large B-cell lymphoma; FBS, fasting blood glucose; LVEF, left ventricular ejection fraction; SLL, small lymphocytic lymphoma

Table 2

Grade 3 to 5 Toxicity During Treatment (N = 80)

Toxicity	Grade 3				Grade 4				Grade 5			
	N	%	N	%	N	%	N	%	N	%	N	%
General												
Dizziness	4	5	2	3								
Syncope	2	3										
Fatigue	20	25	4	5								
Insomnia	1	1										
Rigor	2	3										
Dehydration	2	3										
Anorexia	3	4										
Pain	14	18	1	1								
Gastrointestinal												
2 Nausea	1	1	1	1								
Constipation	4	5	1	1								
Elevated serum AST	1	1										
Pulmonary												
Dyspnea	10	13	2	3								
Hypoxia	1	1	1	1								
Pneumonitis	6	8	1	1								
Cardiac												
Congestive heart failure					1	1	1	1				
Atrioventricular block			1	1								
Atrial fibrillation	1	1										
Decrease in LVEF (Figure 1)	8	10	3	4								
Neurologic												
Neuropathy	5	6	1	1								
Vision change	2	3										
Mental status change	3	4										
Musculoskeletal	6	8										

Toxicity	Grade 3		Grade 4		Grade 5	
	N	%	N	%	N	%
Metabolic						
Hyperglycemia	7	9	1	1		
Hypokalemia	4	5				
Hypomagnesemia	1	1				
Hyponatremia	3	4				
Renal/genitourinary						
Increased creatinine	2	3				
Urinary retention	1	1				
Dermatologic						
Hand-foot syndrome	3	4				
Other rash	2	3	1	1		
Infection						
Febrile neutropenia	10	13			1	1
Other infection	11	14			1	1
Hematologic						
Anemia	9	11	1	1		
Neutropenia	12	15	19	24		
Thrombocytopenia	3	4	5	6		
Thromboembolic event	7	9				
Hemorrhage	2	3				

AST indicates aspartate aminotransferase; LVEF, left ventricular ejection fraction

* Patients with congestive heart failure were symptomatic and also were included in decrease in LVEF, grade 4.

Table 3

Response to Therapy (N = 79)

	IWG 1999 ⁶		IWG 2007 ⁷	
	No.	%	No.	%
CR	56	71	59	75
CRU	6	8		
PR	6	8	9	11
SD	2	3	2	3
PD	3	4	3	4
Not evaluable [†]	6	8	6	8

CR indicates complete response; CRU, complete response unconfirmed; progressive disease; PR, partial response; SD, stable disease.

[†] Response not evaluated because of initiation of unplanned alternative treatment (n = 4) or no response evaluation performed because of deterioration of patients' medical condition (n = 2), or other reasons.

Table 4

Events observed in this clinical trial (N = 79)

Endpoint	No.
Total events	34
Progression	20
Unplanned new treatment due to treatment toxicity	3
Discontinued trial and changed to standard chemotherapy	2
Discontinued trial and changed to radiation	1
Death without lymphoma progression	11
Infection during treatment	2
Heart failure	1
Secondary acute myelodysplasia/myelogenous leukemia	1
Unrelated cause	4
Unknown cause	3
No event	45

Table 5

Comparison of large scale studies

	RCHOP LNH98-5 (10)	RICOVER-60 RCHOP (12)	LNH03-6B RCHOP14 vs 21 (13)	DRCOP current study
Study population	DLBCL, age >60	DLBCL, age >60	DLBCL, age 60	DLBCL, age >60
% patients with cardiac risk factor(s) *	NR	NR	NR	98%
Grade 3 or 4 cardiac toxicity	8%	Arrhythmia 4% Cardiac dysfunction 2%	1 and 3%, respectively	Symptomatic toxicity 4% Asymptomatic LVEF decrease 11%
CR/CRu CR by PET scan	77% NR	75% NR	71 and 74%, respectively NR	78% 75%
3-year EFS 3-year OS		69–72% [†] 79–83% [†]	60 and 62%, respectively 69 and 72%, respectively	60% 74%
5-year EFS 5-year OS	47% 58%		49 and 53%, respectively 66 and 60%, respectively	53% 70%

* Cardiac risk factors: obesity (body mass index ≥ 30), diabetes mellitus, coronary artery disease, hypertension, hyperlipidemia, and/or hypothyroidism.

** One patient had both arrhythmia (atrioventricular block) and cardiac dysfunction. Thus, the incidence per patient was 5%.

[†] 8 cycles and 6 cycles of treatment, respectively.

CR indicates complete response; CRu, complete response unconfirmed; progressive disease; PR, partial response; SD, stable disease.

NR indicates not reported. RCHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and predonisone