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De Novo Treatment of Diffuse Large B-Cell Lymphoma With Rituximab, Cyclophosphamide, Vincristine, Gemcitabine, and Prednisolone in Patients With Cardiac Comorbidity: A United Kingdom National Cancer Research Institute Trial

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ABSTRACT

Purpose
The treatment of patients with diffuse large B-cell lymphoma (DLBCL) with cardiac comorbidity is problematic, because this group may not be able to receive anthracycline-containing chemoimmunotherapy. We designed a single-arm phase II multicenter trial of rituximab, gemcitabine, cyclophosphamide, vincristine, and prednisolone (R-GCVP) in patients considered unfit for anthracycline-containing chemoimmunotherapy because of cardiac comorbidity.

Patients and Methods
Sixty-one of 62 patients received R-GCVP, administered on day 1 with gemcitabine repeated on day 8 of a 21-day cycle. Median age was 76.5 years. All patients had advanced disease; 27 (43.5%) had left ventricular ejection fraction of $\leq$ 50%, and 35 (56.5%) had borderline ejection fraction of $>$ 50% but $\leq$ 55% and comorbid cardiac risk factors such as ischemic heart disease, diabetes mellitus, or hypertension. Primary end point was overall response rate at the end of treatment.

Results
Thirty-eight patients (61.3%; 95% CI, 49.2 to 73.4) achieved disease response (complete response [CR], n = 18; undocumented/unconfirmed CR, n = 6; partial response, n = 14). Two-year progression-free survival for all patients was 49.8% (95% CI, 37.3 to 62.3), and 2-year overall survival was 55.8% (95% CI, 43.3 to 68.4). Thirty-four patients experienced grade $\geq$ 3 hematologic toxicity. There were 15 cardiac events, of which seven were grade 1 to 2, five were grade 3 to 4, and three were fatal, reflecting the poor cardiac status of the study population.

Conclusion
Our phase II multicenter trial showed that the R-GCVP regimen is an active, reasonably well-tolerated treatment for patients with DLBCL for whom anthracycline-containing immunochemotherapy was considered unsuitable because of coexisting cardiac disease.

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INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the commonest type of non-Hodgkin lymphoma (NHL), with an incidence that increases with age to $>$ 100 cases per 100,000 in people age $>$ 80 years.[1] By the year 2015, the population age $>$ 65 years is predicted to rise by 22%, and that age $>$ 80 years by 50%,[2] indicating that many more patients will present with attendant comorbid illnesses, making curative treatment approaches problematic. In a series of 6,388 patients age $\geq$ 65 years with DLBCL, cardiac risk factors were common; 32% patients had diabetes mellitus (DM), and 73% had hypertension.[3] The treatment of choice for newly diagnosed patients with advanced DLBCL is R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone) chemoimmunotherapy, which results in 5-year survival among patients age $>$ 65 years in the region of 60%.[4] However, patients with concomitant cardiac comorbidities that precluded the use of anthracyclines were often excluded from the studies that proved the efficacy of chemoimmunotherapy.[5-7]

Doxorubicin is one of the key components of the R-CHOP regimen, but it is known to be associated with an increased risk of cardiac toxicity, particularly congestive heart failure, with increasing cumulative dose.[8] More recently, it was also shown in a large US study that the risk of cardiomyopathy is greatly enhanced by the attendant cardiac risk factor of hypertension.[3] As a result, patients with

pre-existing cardiac comorbidity are often excluded from treatment with R-CHOP and therefore may not receive curative therapy. However, there have been few, if any, studies that have prospectively recruited patients with DLBCL with cardiac comorbidities, thus reducing the chances of defining a curative treatment regimen for this group of patients. One potential way forward is to find another drug that can be substituted for doxorubicin. Gemcitabine is a chemotherapeutic drug that in combination with platinum and methylprednislone has shown promising efficacy in the setting of both relapsed/refractory NHL and HL.[9] Importantly, the drug seems to be associated with minimal cardiac adverse effects and seems safe in the setting of ischemic heart disease (IHD) and other cardiac risk factors such as DM and hypertension.

Therefore, we developed a trial for patients who were considered unfit for conventional curative treatment with R-CHOP chemoimmunotherapy on the basis of the presence of poor cardiac ejection fraction or borderline ejection with attendant comorbidities such as IHD, DM, or hypertension, where the drug doxorubicin was replaced by gemcitabine in the R-CHOP combination. The aim of the trial was to develop a regimen to treat this group of patients with a curative approach without causing cardiac toxicity.

PATIENTS AND METHODS

We performed a two-stage, multicenter, phase II, open-label, nonrandomized, single-arm trial. The trial was conducted in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice and was monitored by an independent data monitoring committee. All patients received information about the trial before providing written informed consent. The trial received ethical approval from the Royal Free Hospital and Medical School Research Ethics Committee.

To be included in the trial, patients age $\geq$ 18 years were required to have a diagnosis of previously untreated, histologically proven, CD20-positive DLBCL, including all of its morphologic variants, according to the 2008 WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues. Central review of histopathology was performed to confirm eligibility.

Patients were eligible if they were deemed unfit to receive anthracycline-based chemotherapy according to the following criteria: Initially, patients were eligible if there was a documented left ventricular ejection fraction (LVEF) $\leq$ 50%, as assessed by transthoracic echocardiogram or multigated acquisition nuclear medicine scan; in those with borderline ejection fractions and cardiac comorbid conditions, entry criteria were extended to include patients with LVEF $>$ 50% but $\leq$ 55%, provided they had documented cardiac comorbidities (hypertension, IHD, or DM) precluding anthracycline use according to the local investigator. Patients with nonbulky stage Ia disease were excluded, but those with all other stages of disease were eligible provided that disease was measurable. Patients had to have Eastern Cooperative Oncology Group performance status of 0 to 3 and adequate bone marrow (neutrophils $> 1.5 \times 10^9$/L; platelets $> 150 \times 10^9$/L), hepatic, and renal function. Patients with documented CNS or meningeal involvement, previous diagnosis of low-grade NHL, or HIV were excluded, as were pregnant or lactating women. Before initiation of therapy, all patients underwent clinical examination and staging with contrast-enhanced computed tomography (CT) scans of the neck, thorax, abdomen, and pelvis and bone marrow biopsy. Complete medical history was taken, and cardiac comorbidities and Eastern Cooperative Oncology Group performance status were recorded. ECG and transthoracic echocardiogram or multigated acquisition nuclear medicine scan were performed to document LVEF. Baseline laboratory tests to document hepatic, liver, and bone marrow function were performed.

Treatment consisted of six cycles of rituximab, gemcitabine, cyclophosphamide, vincristine, and prednisolone (R-GCVP) administered every 21 days. Gemcitabine was administered intravenously over 30 minutes on days 1 and 8 of each 21-day cycle. Dose of gemcitabine was 750 mg/m^2 in cycle one and was sequentially escalated to 875 mg/m^2 in cycle two and 1,000 mg/m^2 in cycle three, if tolerated with no evidence of hematologic toxicity; dose then remained at 1,000 mg/m^2 for all subsequent cycles. Rituximab 375 mg/m^2 was administered as an intravenous infusion on day 1 of each cycle, with appropriate premedication (acetaminophen 1 g and chlorphenramine 10 mg intravenously). Cyclophosphamide 750 mg/m^2 and vincristine 1.4 mg/m^2 (maximum dose 2 mg) were administered intravenously on day 1 of each cycle, and prednisolone 100 mg was administered orally for the first 5 days of each cycle. Growth factor support (pegfilgrastim 6 mg subcutaneously) was mandated for all patients and administered on day 9 of each cycle. Patients considered to be at high risk for CNS relapse received intrathecal methotrexate 12.5 mg for three cycles. Radiotherapy to residual masses or original sites of disease bulk was permitted according to local policies, but it was specified in the protocol that radiotherapy not be administered within 1 month of the last dose of gemcitabine.

The following dose reductions for gemcitabine, vincristine, and cyclophosphamide were advised in the event of hematologic toxicity: Gemcitabine was reduced to 75% dose, if absolute neutrophil count (ANC) 0.5 to 0.9 $\times$ 10^9/L or platelets 50 to 74 $\times$ 10^9/L on the day of treatment; day 1 dose was delayed if ANC $< 0.5 \times 10^9$/L or platelets $< 50 \times 10^9$/L; day 8 dose was omitted in this instance. In the event of dose-limiting hematologic toxicity, gemcitabine dose escalation did not proceed in subsequent cycles. Cyclophosphamide and vincristine doses were both reduced to 75% dose if ANC 0.5 to 0.9 $\times$ 10^9/L or platelets 50 to 74 $\times$ 10^9/L on the day of treatment, with delay of treatment if ANC $< 0.5 \times 10^9$/L or platelets $< 50 \times 10^9$/L.

Patients were assessed for adverse events and toxicity at each clinic visit. Interim response assessment was made after the third cycle of treatment with physical examination and contrast-enhanced CT scans of neck, thorax, abdomen, and pelvis. Final response assessment was made with physical examination and CT scan at end of treatment. In patients with bone marrow involvement at baseline, repeat bone marrow biopsy was performed at end of treatment. Patients underwent follow-up with regular clinical review, and CT scans of the neck, chest, abdomen, and pelvis were performed 3 and 12 months after treatment completion.

Response was assessed in accordance with the International Workshop on Standardized Response Criteria for NHL.[10] Overall response was defined as achievement of complete response (CR), CR undocumented/unconfirmed (CRu), or partial response (PR). Toxicities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0).

Primary end point was overall response rate (ORR) at end of treatment. ORR $\geq$ 60% would warrant further testing of this regimen in a randomized phase III trial, whereas ORR $\leq$ 40% would be of no interest for investigation in future trials. Sample size was calculated using Simon's optimal two-stage design,[11] with 10% level of significance and 90% power, giving a total sample

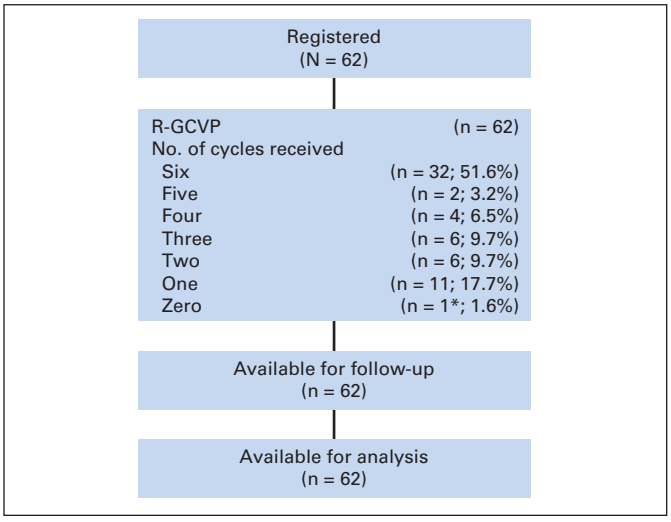

Fig 1. CONSORT diagram. R-GCVP, rituximab, gemcitabine, cyclophosphamide, vincristine, and prednisolone. (*) Died before study treatment as result of chest sepsis/lung abscess.

size of 46 (18 in initial stage) and requiring a minimum of 23 responders to indicate that the treatment was effective. Recruitment of a total of 60 patients for this phase II trial was planned to allow for nonevaluable patients. Secondary end points included progression-free (PFS) and overall survival (OS), estimated using the Kaplan-Meier method, and toxicities. Analyses were by intention to treat (ITT), unless otherwise specified. Subgroup analyses were not prespecified and were performed for exploratory purposes only.

RESULTS

Patient and Disease Characteristics

Sixty-two patients were recruited (April 2008 to July 2010) from 32 centers across the UK National Cancer Research Network. Figure 1 (CONSORT diagram) shows trial treatment information. Table 1 lists baseline characteristics. Median patient age was 76.5 years; 69.4% of patients had advanced (stage > III/IV) disease, and 71.0% had International Prognostic Index score ≥ 3. IHD was documented in 59.7%, hypertension in 48.4%, and DM in 22.6% of patients. Twenty-seven patients (43.5%) had cardiac ejection fraction ≤ 50%, and 35 (56.5%) had borderline ejection fraction > 50 but ≤ 55% plus the presence of comorbid cardiac risk factors such as IHD, DM, or hypertension.

Of the 27 patients with LVEF ≤ 50%, 25 (92.6%) had cardiac comorbidities in addition to poor ejection fraction, and 14 (51.9%) had multiple comorbidities. Comorbidities were hypertension (n = 12), DM (n = 6), IHD (n = 19), arrhythmias or conduction disorders (n = 4), and valvular heart disease (n = 1). All 35 patients with LVEF > 50% had documented cardiac comorbidities, and 23 (65.7%) had multiple comorbidities (Table 2).

Histologic diagnosis was confirmed by central review in 47 patient cases. Cells of origin[12] were germinal center derived in 16 patient cases (34.0%), nongerminal center cell type in 18 (38.3%), and not assessable in 13 (27.7%).

Table 1. Patient Demographic and Clinical Characteristics in ITT Population (n = 62)

Characteristic	No.	%
Age, years		
≤ 60	4	6.5
61 to 70	11	17.7
71 to 80	31	50.0
> 80	16	25.8
Median	76.5	
Range	52-90	
Sex		
Male	41	66.1
Female	21	33.9
ECOG PS		
0	10	16.1
1	21	33.9
2	22	35.5
3	9	14.5
4	0	0.0
Stage		
Bulky stage 1a	3	4.8
Ib	1	1.6
II	15	24.2
III	20	32.3
IV	23	37.1
B symptoms		
Present	29	46.8
Absent	33	53.2
IPI		
0	0	0.0
1	6	9.7
2	12	19.4
3	19	30.6
4	15	24.2
5	10	16.1
Histology		
Germinal center phenotype	16	34.0
Nongerminal center phenotype	18	38.3
Not assessable	13	27.7
Unavailable	15	
LVEF, %		
≤ 50	27	43.5
> 50	35	56.5

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; IPI, International Prognostic Index; ITT, intention to treat; LVEF, left ventricular ejection fraction.

Table 2. Patient Comorbidities by Group in ITT Population

Comorbidity	Group One: LVEF ≤ 50% (n = 27) No.	Group One: LVEF ≤ 50% (n = 27) %	Group Two: LVEF > 50% (n = 35) No.	Group Two: LVEF > 50% (n = 35) %
No. of comorbidities*				
0	2	7.4	0	0.0
1	11	40.7	12	34.3
2	9	33.3	17	48.6
3	4	14.8	3	8.6
4	1	3.7	2	5.7
5	0	0.0	1	2.9
Type of comorbidity				
Hypertension	12	44.4	18	51.4
DM	6	22.2	8	22.9
IHC	19	70.4	18	51.4
Other cardiac disorder	5	18.5	14	40.0
Other medical disorder†	3	11.1	10	28.6
Other cardiac disorders				
Valvular heart disease	1		3	
Conduction disorders‡	4		7	
Contractility disorders	—		2	
Combined valvular and conduction	—		1	
Previous cardiac transplantation	—		1	
Other medical disorders				
Stroke (CVA/TIA)	1		4	
COPD	1			
COPD and pulmonary hypertension			1	
Pulmonary fibrosis	1			
Pulmonary hypertension			2	
Pulmonary fibrosis and pulmonary hypertension			1	
Aortic aneurysm			1	
Combined stroke and abdominal aortic aneurysm			1	

Abbreviations: COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; DM, diabetes mellitus; IHC, ischemic heart disease; ITT, intention to treat; LVEF, left ventricular ejection fraction; TIA, transient ischemic attack.
*No. of comorbidities in addition to reduced LVEF.
†Other comorbidities precluding use of anthracycline.
‡Conduction disorders: atrial fibrillation, arrhythmias, other conduction disorders, or pacemaker in situ.

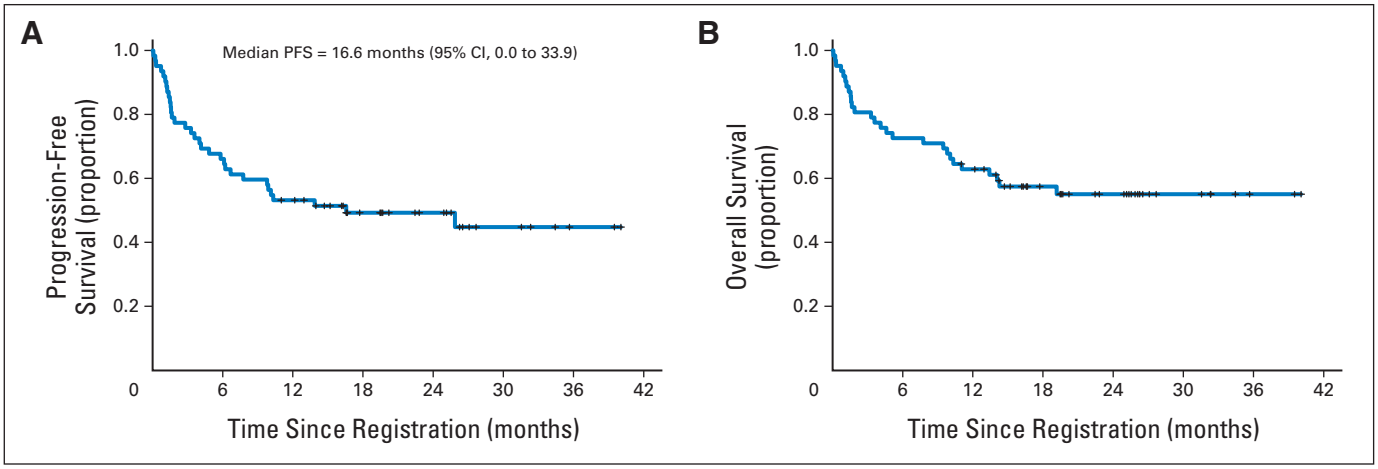

Fig 2. (A) Progression-free survival (PFS) and (B) overall survival curves for intention-to-treat population.

Efficacy

ORR at end of treatment for all patients was 61.3%; 38 patients achieved disease response (CR, n = 18 [29.0%]; CRu, n = 6 [9.7%]; PR, n = 14 [22.6%]), exceeding the minimum response rate required to indicate that the treatment was effective (Simon's design required 23 responders among 46 patients). Ten patients (16.1%) did not achieve disease response (stable disease [SD], n = 4 [6.5%]; progressive disease [PD], n = 6 [9.7%]). Fourteen patients (22.6%) were nonevaluable because of death (cardiac, n = 3; respiratory infection, n = 3; treatment-related toxicity, n = 3; toxicity, n = 3; infection, n = 1; pneumonitis, n = 1).

Median follow-up was 24.9 months, censoring those who had died. Thirty-two patients (51.6%) died or had disease progression; 1-year PFS was 53.2% (95% CI, 40.8 to 65.7), and 2-year PFS was 49.8% (95% CI, 37.3 to 62.3). Twenty-seven patients (43.5%) died; 1-year OS was 62.9% (95% CI, 50.8 to 74.9), and 2-year OS was 55.8% (95% CI, 43.3 to 68.4). Causes of death were NHL (n = 14), treatment-related toxicity (n = 4), cardiac (n = 3), and other (n = 6). Figure 2 shows PFS and OS curves. Exploratory analyses indicated that patients with lower International Prognostic Index score may have had better survival rates (PFS: hazard ratio [HR], 0.75; 95% CI, 0.48 to 1.18; $P = .22$; OS: HR, 0.75; 95% CI, 0.49 to 1.14; $P = .18$). Figure 3 shows PFS and OS curves by LVEF group.

Group One: LVEF ≤ 50% (n = 27)

ORR at end of treatment for group one was 70.4%; 19 patients achieved disease response (CR, n = 12 [44.4%]; CRu, n = 2 [7.4%]; PR, n = 5 [18.5%]), three patients (11.1%) did not achieve disease response (SD, n = 0; PD, n = 3 [11.1%]), and five patients (18.5%) were nonevaluable.

Thirteen patients (48.1%) died or had disease progression in group one; 1-year PFS was 59.1% (95% CI, 40.6 to 77.7), and 2-year PFS was 54.9% (95% CI, 35.9 to 73.9). Nine patients (33.3%) died; 1-year OS was 70.4% (95% CI, 53.1 to 87.6), and 2-year OS was 65.7% (95% CI, 47.3 to 84.0).

Group Two: LVEF > 50% (n = 35)

ORR at end of treatment for group two was 54.3%; 19 patients achieved disease response (CR, n = 6 [17.1%]; CRu, n = 4 [11.4%]; PR, n = 9 [25.7%]), seven patients (20.0%) did not achieve disease response (SD, n = 4 [11.4%]; PD, n = 3 [8.6%]), and nine patients (25.7%) were nonevaluable. Nineteen patients (54.3%) died or had

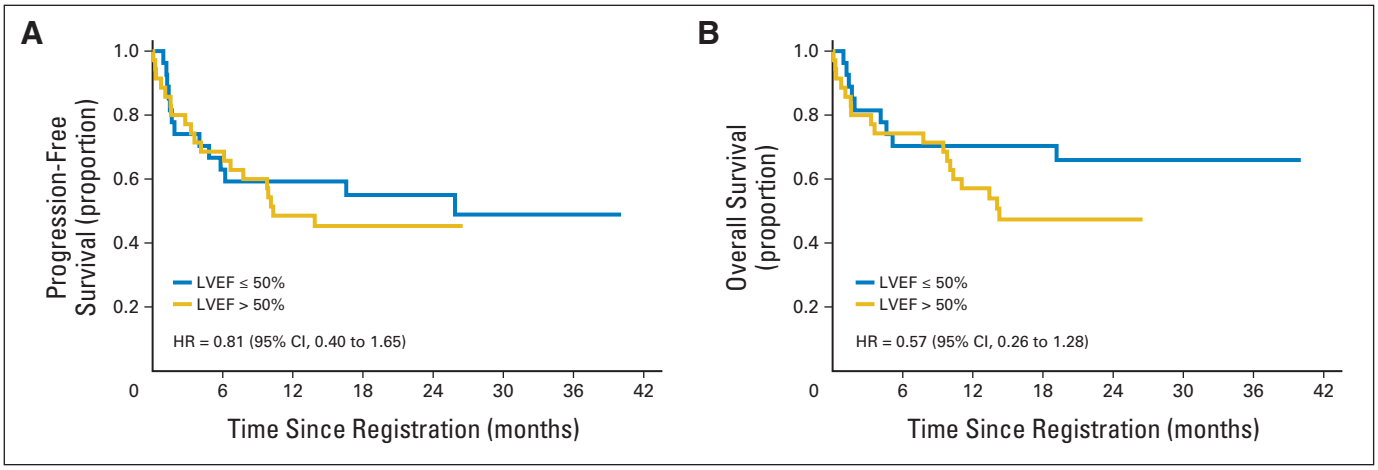

Fig 3. (A) Progression-free and (B) overall survival curves by left ventricular ejection fraction (LVEF) group for intention-to-treat population. HR, hazard ratio.

Table 3. Reported Grade ≥ 3 Toxicities by Cycle in Safety Population

Adverse Event	Cycle						Any Grade 3 to 5 (n = 61)
	One (n = 61)	Two (n = 50)	Three (n = 44)	Four (n = 38)	Five (n = 34)	Six (n = 32)	
Any hematologic	23	14	8	7	4	8	34
Neutropenia	23	10	5	1	3	5	29
Thrombocytopenia	10	5	4	6	1	4	19
Anemia	1	2	2	1	0	1	7
Any nonhematologic*	26	12	11	10	7	5	39
Infection	13	3	4	2	2	1	17
Fatigue	6	0	4	3	4	3	14
Cardiac	5	4	1	0	0	1	10
Neurologic	2	1	1	2	1	1	5
Diarrhea	2	1	1	1	0	0	4
Bone pain	1	1	1	1	0	0	4
Fever	3	0	1	0	0	0	4

*All reported toxicities included in summary; toxicities reported in > 5% of safety population detailed.

disease progression in group two; 1-year PFS was 48.6% (95% CI, 32.0 to 65.1), and 2-year PFS was 44.8% (95% CI, 28.0 to 61.6). Eighteen patients (51.4%) died; 1-year OS was 57.1% (95% CI, 40.7 to 73.5), and 2-year OS was 46.1% (95% CI, 28.7 to 63.4).

Toxicity

Sixty-one patients (98.4%) received at least one cycle of treatment, defined as the safety population. One patient died before starting treatment as a result of lung abscess. Median number of cycles administered was six. Forty-four patients (71.0%) received ≥ three cycles, and 32 (51.6%) received the full six cycles of treatment. Thirty-four patients were reported to have experienced grade ≥ 3 hematologic toxicity (55.7% of safety population). Hematologic toxicity was predominantly neutropaenia and thrombocytopenia and was not cumulative (Table 3). Grade ≥ 3 infection was reported in 17 patients (27.9%). Fifteen patients had reported cardiac adverse event of any grade (24.6%; highest grade 1 to 2, n = 5; highest grade 3 to 4, n = 7; fatal, n = 3). The three deaths recorded were the result of pulmonary edema in one patient with known IHD and hypertension after cycle one and myocardial infarctions in patients with known IHD after cycles one and three, respectively. One grade 3 cardiac adverse event, from which the patient recovered, occurred post-treatment.

DISCUSSION

In DLBCL, the treatment of patients with cardiac comorbidity is problematic, and often, patients are treated with palliative intent or with regimens that may not have the same degree of efficacy as anthracycline-containing chemotherapy. If suitable drugs with similar efficacy can be found to substitute for doxorubicin, one may expect to produce similar outcome results. The trial reported here achieved ORRs for all patients of 61.3% (n = 62) and 81.8% for those who received ≥ three cycles of treatment (n = 44); observed 2-year OS was 55.8% (95% CI, 43.3 to 68.4). Given the group of patients presented in this study were at high risk, as defined by poor ejection fraction or borderline ejection fraction plus presence of multiple cardiac risk factors, the results emphasize that it is still possible to offer such groups of patients treatment with curative intent.

In the published literature, there are few studies that define specific cardiac comorbid entry criteria, and as such, it is difficult to find comparative results. However, it is noteworthy that in selected studies of older patients that proved the efficacy of full-dose chemoimmunotherapy, contraindications usually included cardiac comorbid illnesses or those patients who had reduced ejection fraction.[5,6] These studies therefore selected atypical elderly populations, whereas in an unselected group, the incidence of cardiac comorbid illness approached 70% for cardiac risk factors such as hypertension.[3] During the development of this study in 2006, no previous studies were identified that had targeted patients with specific comorbidities, particularly with regard to detailed cardiac criteria precluding the use of anthracycline-containing chemotherapy.

Previous studies have shown that in patients with malignant disease, presence of comorbid illnesses result in excess morbidity and mortality.[13] Our study attempted to incorporate detailed cardiac inclusion criteria and cardiac risk factors such as presence of IHD, DM, and hypertension. More than half of the patients in each group had multiple cardiac risk factor comorbidities: 51.9% of patients with LVEF ≤ 50% and 65.7% of patients with LVEF > 50%. The most common comorbidity was IHD, followed by hypertension. In DLBCL, presence of hypertension is the most significant risk factor for development of congestive cardiac failure, when treatment with anthracyclines is administered.[3] In our study, prevalence of hypertension was 48.4%, but the observed incidence of cardiac failure during and after treatment was low.

Studies providing evidence of chemoimmunotherapy efficacy continue to be published; however, caution should be exercised when interpreting results, because comorbid conditions are often excluded, or no mention is made with regard to presence or absence of comorbid conditions, making it difficult to assess whether the study population reflects a typical population of patients with DLBCL. The study presented here directly addresses the issue of unsuitability for anthracycline-containing chemoimmunotherapy by outlining strict cardiac-directed inclusion criteria. In this high-risk cardiac group of patients, where 96.8% of patients displayed ≥ one cardiac risk comorbidity, and 59.7% displayed ≥ two, cardiac adverse events were reported in 15 patients, which resulted in cardiac-related deaths in three

patients (two of which occurred before second cycle of treatment). Hematologic toxicity was observed to be highest during the first (n = 23 of 61) and second cycles (n = 14 of 50), in line with previous studies,[14] and was not cumulative. In our study, use of granulocyte colony-stimulating factor, was mandated, and with this approach, incidence of hematologic toxicity was as expected and manageable.

It is difficult to find direct comparative studies, but a previous study predating the use of rituximab administered the CEPP (cyclophosphamide, etoposide, procarbazine, and prednisolone) regimen to patients for whom anthracyclines were contraindicated and reported 3-year OS of 50%.[15] A later trial published in abstract form reported 5-year OS of 49% using the R-CEOP (rituximab, cyclophosphamide, etoposide, vincristine, and prednisone) regimen, but detailed anthracycline contraindicating criteria were not presented, and the analysis was retrospective.[15a] Recent studies have reported on the utility of liposomal anthracycline derivatives, but these excluded patients with cardiac ejection fraction $< 50\%$.[16] Similarly, a recent article published on patients with DLBCL age ≥ 80 years treated with the R-miniCHOP (rituximab, reduced-dose cyclophosphamide, doxorubicin, vincristine, and prednisolone) regimen reported ORR of 73% and 2-year OS of 59%,[17] but no details were presented on whether patients had inherent anthracycline contraindications or displayed attendant cardiac comorbidities.

In summary, the issue of treatment-limiting comorbidities will become more critical in future studies as the number of elderly patients with DLBCL increases as a result of changing demographics. Risk stratification with particular reference to end-organ/system deficits will permit more patients to be treated with curative intent and be entered into relevant clinical trials. Further testing of the R-GCVP regimen is warranted to confirm its efficacy in a larger randomized clinical trial against novel R-CVP (rituximab, cyclophosphamide, vincristine, and prednisolone) regimens, with enhancement of either the chemotherapeutic or immunotherapeutic component.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. 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.
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Manuscript writing: All authors
Final approval of manuscript: All authors

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