Phase 2 study of CHOP-R-14 followed by ^{90}Y-ibritumomab tiuxetan in patients with previously untreated diffuse large B-cell lymphoma

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Received August 29, 2016; Accepted January 31, 2017

DOI: 10.3892/mco.2017.1169

Abstract. The aim of this open-label, single-center, phase 2 study was to assess the efficacy and safety of dose-dense CHOP-R-14 followed by ^{90}Y-ibritumomab radioimmunotherapy (RIT) in patients with previously untreated diffuse large B-cell lymphoma (DLBCL). A total of 20 patients, the majority presenting with high-risk characteristics, were enrolled to receive dose-dense cyclophosphamide, doxorubicin, vincristine, prednisone and rituximab every 14 days (CHOP-R-14), followed by ^{90}Y-ibritumomab tiuxetan consolidation. Sixteen patients completed RIT consolidation (rituximab 250 mg/m^2 on day 1 and day 7, 8, or 9, followed by a single injection of ^{90}Y-ibritumomab). Complete response (CR) rates of 75 and 95% were observed after treatment with CHOP-R-14 and RIT, respectively; 4 of the 5 patients who achieved a partial response after CHOP-R-14 converted to CR following treatment with RIT. With a median follow-up of 89.7 months, the progression-free and overall survival rates for the cohort were 75 and 85%, respectively. Hematological adverse events were common following CHOP-R-14 and RIT, but they were manageable with treatment interruption. Therefore, this regimen achieved promising survival outcomes in high-risk DLBCL on long term follow-up, with manageable toxicity.

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma (NHL), representing ~30-40% of all NHL cases (1), and is characterized by an aggressive phenotype. Although the incorporation of the monoclonal antibody rituximab into the treatment paradigm for DLBCL has resulted in improved complete response (CR), progression-free survival (PFS) and overall survival (OS) (2-6), there is a disparity in outcomes among patients with high-risk characteristics, calling for more effective first-line treatment strategies. Specifically, modification of treatment strategies must be considered in patients with activated B-cell (ABC) origin and/or secondary extranodal involvement, entities representing different aggressive biological subsets that manifest altered clinical behavior (7-9).

One such strategy is the use of dose-dense induction chemotherapy, which was investigated in patients with DLBCL prior to the design of the present study, with a reported benefit (10). A number of trials have since reported comparable results for cyclophosphamide, doxorubicin, vincristine, prednisone, and rituximab every 14 days (CHOP-R-14) vs. CHOP-R-21, suggesting the need for more effective alternative approaches, such as consolidation therapy (11,12). Consolidation with the radioimmunoconjugate ^{90}Y-ibritumomab tiuxetan (^{90}Y-ibritumomab; Zevalin®; Biogen IDEC, Weston, MA, USA and Spectrum Pharmaceuticals, Irvine, CA, USA) has yielded promising responses and survival outcomes in the first-line and salvage settings (2-year PFS and OS rates as high as 85 and 95%, respectively) in NHL, including DLBCL (13-18). An open-label phase 2 single-center pilot study was designed, with the objective of evaluating the efficacy and safety of the combination of CHOP-R-14 and ^{90}Y-ibritumomab in treatment-naive high-risk DLBCL patients. This is the first report of our results with a long-term follow-up.

Materials and methods

Patients. Eligible patients were aged ≥18 years, with previously untreated, confirmed CD20$^+$ DLBCL with measurable disease, a World Health Organization (WHO) performance status of 0-2, an International Prognostic Index (IPI) score of ≥2, and a life expectancy of ≥3 months. Acceptable organ function was required and defined as follows: Adequate hematological [absolute neutrophil count (ANC) ≥1,500/mm^3 and platelet count ≥150,000/mm^3], hepatic (total bilirubin ≤2.0 mg/dl),

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Key words: dose-dense chemotherapy, radioimmunotherapy, consolidation, large B-cell lymphoma, CHOP-R-14

renal (serum creatinine ≤2.0 mg/dl), and normal cardiac function. Patients were excluded if they had central nervous system (CNS) lymphoma, HIV/AIDS, pleural effusion, or any serious non-malignant disease or infection. Those who had received prior RIT, anthracyclines, or external beam radiation therapy (involved field or regional) to >25% of active bone marrow were also excluded. The patients were not permitted to receive rituximab 4 weeks prior to enrollment, or granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor within 2 weeks prior to treatment.

Study design. Patients were enrolled between September, 2004 and July, 2009. The treatment included 6 cycles of CHOP-R-14 chemotherapy every 2 weeks, with rituximab 375 mg/m^2 IV on day 1, cyclophosphamide 750 mg/m^2 on day 1, doxorubicin 50 mg/m^2 on day 1, vincristine 1.4 mg/m^2 (maximum 2 mg) on day 1, and prednisone 100 mg on days 1-5. Pegfilgrastim was administered at a fixed dose (6 mg subcutaneously) 24 h after each CHOP-R-14 cycle.

The patients were restaged after 4 cycles of CHOP-R-14. Those with documented response [CR or partial response (PR)] continued therapy with an additional 2 cycles of chemo-immunotherapy. Within 4-6 weeks after the sixth cycle of CHOP-R-14, the patients who maintained a CR or PR with <25% lymphoma burden in the marrow and adequate hematological reserve, received one course of ^{90}Y-ibritumomab; the dose was adjusted according to the platelet count (0.4 mCi/kg for platelet counts ≥150,000/mm^3; and 0.3 mCi/kg for platelet counts 100,000-149,000/mm^3; maximum dose of 32 mCi). The course of ^{90}Y-ibritumomab consisted of an initial infusion of rituximab 250 mg/m^2 on day 1, another infusion of rituximab 250 mg/m^2 on day 7, 8, or 9, followed by a weight-based dose of ^{90}Y-ibritumomab.

All the patients provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki and approved by our Institutional Review Board, as well as the Food and Drug Administration (IND # BB-IND 11065). Registration with ClinicalTrials.gov was not required at the time of study initiation.

Response evaluations and outcome measures. The baseline assessments performed within 4 weeks prior to patient registration included medical history, physical examination, clinical laboratory tests [complete blood count (CBC) and serum chemistries] and computed tomography (CT) scans. Bilateral bone marrow biopsy and aspirates were obtained within 6 weeks of patient registration to stage the patient. Lymphomas with dominant lymph node and/or spleen involvement were considered as primary nodal (PN). Those with disease involving nodal as well as extranodal sites (including the bone marrow) were considered as PNs with secondary extranodal (SEN) involvement. Lymphomas with minor or no lymph node involvement arising in extranodal organs other than the spleen were considered as primary extranodal (PEN). Baseline assessments were repeated for restaging at the end of the CHOP-R-14 treatment period and at 1 month after treatment with ^{90}Y-ibritumomab. Tumor response was based on International Workshop Criteria (19) and did not require positron emission tomography (PET) scans. Disease status was monitored in the follow-up period every 3 months for the first year and every 6 months thereafter, for a total of 4 years on study. The primary endpoints of the study included response [CR, PR and overall response rate (ORR)] and safety of administering CHOP-R-14 and ^{90}Y-ibritumomab to patients with previously untreated DLBCL. Using the Hans criteria, germinal center (GC) vs. ABC origin was defined retrospectively based on immunohistochemical staining for CD10, B-cell lymphoma-6 and multiple myeloma oncogene-1 (20).

Toxicity evaluations. During active treatment, hematological toxicities were assessed weekly. Dose-limiting hematological values included an ANC <1,500/mm^3 and/or hemoglobin level <10 g/dl and/or platelet count <100/mm^3. Hematological and non-hematological toxicities were graded using the National Cancer Institute (NCI) Toxicity Criteria. A CBC was obtained weekly for the first 12 weeks following administration of ^{90}Y-ibritumomab and at 6-month intervals thereafter for the duration of the patient's life. During this time, serious adverse events (AEs) and any new or worsening drug-related AEs were reported. AEs occurring after the initiation of subsequent anticancer therapy were not reported, unless the AE occurred within 30 days of ^{90}Y-ibritumomab administration, or the event was likely to be related to RIT.

Statistical analysis. This study was powered to ensure the safety of the combined CHOP-R-14 and ^{90}Y-ibritumomab regimen based on the most likely dose toxicity, which was estimated to be hematological. Using a Simon 2-stage design (21), 60% (p0) was set as the proportion of expected hematological toxicity. Patients with clinically significant grade 3/4 hematological toxicity with CHOP-R-14 (requiring dose delay, dose reduction, or resulting in any severe AEs) and/or with any grade 3/4 hematological toxicity after RIT counted toward the threshold of 80%, defined as an unacceptable proportion of toxicity (p1). Using these parameters with α=0.09 and β=0.2, accrual of 11 patients during stage 1 was required, with plans to terminate the study at the first stage should ≥7 patients experience grade 3 or 4 hematological toxicity, as defined above. With this model, the expected sample size was 18, with a 62% probability of terminating the study at the first stage.

Response rates (CR, PR, and ORR) were calculated for all the patients after treatment with CHOP-R-14, and again after treatment with ^{90}Y-ibritumomab. The ORR included patients with a PR or CR after treatment. Survival data were estimated using the Kaplan-Meier method with median estimates and 95% confidence intervals generated up to the time of the last event (22). PFS was calculated from the date of initiation of cycle 1 of CHOP-R-14 therapy to the date of documented relapse, disease progression, or death from any cause. OS was calculated from the date of initiation of cycle 1 of CHOP-R-14 therapy to the date of death from any cause. Survival outcomes in patients with GCB vs. ABC origin and PN/PEN vs. SEN disease were compared using *t*-tests, with statistical significance defined by a P-value of <0.05.

Results

Patient disposition. A total of 20 patients were enrolled at the Rush University Medical Center (Chicago, USA). The patient baseline characteristics are summarized in Table I. The

Table I. Patient demographics and baseline characteristics.

Parameters	Patients (n=20)
Male, n (%)	8 (40)
Age, years	
Median	60
Range	33-81
Race, n (%)	
Caucasian	12 (60)
Hispanic	4 (20)
Unknown	4 (20)
B symptoms, n (%)	
Yes	5 (25)
No	15 (75)
Performance status at diagnosis, n (%)	
0	18 (90)
1	2 (10)
LDH at diagnosis, n (%)	
≤240 IU/l	3 (15)
>240 IU/l	17 (85)
Stage at diagnosis, n (%)	
2	2 (10)
3	10 (50)
4	8 (40)[a]
Bone marrow involvement, n (%)	
Yes	4 (20)
No	16 (80)
Sites of disease, n (%)	
Primary nodal	14 (70)
Primary extranodal	6 (30)
Secondary extranodal (including bone marrow involvement)	9 (45)[b]
Cell origin, n (%)	
Germinal center	7 (35)
Activated B-cell	9 (45)
Unknown	4 (20)
Bulky disease, n (%)	
No	6 (30)
>5 cm	6 (30)
>10 cm	8 (40)
IPI score, n (%)	
2	9 (45)
3	11 (55)

[a]Deemed stage IV in case of extensive or multiplesite extranodal involvement, disease of the bone marrow and/or secondary involvement of the lung or liver parenchyma. [b]Includes 6 patients with primary nodal and 3 patients with primary extranodal sites. IPI, International Prognostic Index; LDH, lactate dehydrogenase.

majority of the patients exhibited characteristics conferring increased risk of relapse, with bulky disease in 14 (70%), an intermediate-high IPI score in 11 (55%), secondary extranodal disease in 9 (45%) and ABC origin in 9 (45%) patients. A total of 18 patients completed 6 cycles of CHOP-R-14 (1 patient withdrew consent after 5 cycles, and 1 patient with extranodal lung masses discontinued treatment after 5 cycles due to AEs). Of these 18 patients, 16 proceeded with RIT. One patient was excluded from receiving RIT due to bronchiolitis obliterans with organizing pneumonia (BOOP), and the other due to abnormal ^{111}Y-ibritumomab lung biodistribution without clinical or radiographical evidence of pathology. The median follow-up time for all patients (n=20) was 89.7 months (range, 22.9-128.2 months).

Efficacy and survival outcomes. Intent-to-treat analyses were used to determine efficacy and survival outcomes. After ≥4 cycles of CHOP-R-14, a response was achieved in all the patients, namely a CR in 15 patients (75%) and a PR in 5 patients (25%). A total of 16 patients (11 in CR and 5 in PR) subsequently received ^{90}Y-ibritumomab; of these 16 patients, 15 achieved a CR and 1 maintained a PR. Of note, among the 5 patients with a PR following chemo-immunotherapy induction, 4 patients (80%) converted to a CR after treatment with RIT. Those patients who did not proceed with RIT remain in CR, making the final CR rate in the entire cohort 95%.

A total of 5 patients relapsed, 3 of whom within 6 months after ^{90}Y-ibritumomab treatment; these patients had extensive secondary extranodal involvement and/or bulky disease. One of these patients achieved a CR to second-line chemotherapy followed by autologous stem cell transplantation, while the other 2 patients developed progressive disease refractory to second-line chemotherapy. The remaining 2 patients developed late (after 2 years) relapse in the CNS and achieved a CR with salvage therapy. Survival outcomes were determined at a median follow-up of 89.7 months: The PFS for the entire cohort was 75% (Fig. 1) and the OS for the entire cohort was 85% (Fig. 2). There was no difference in PFS or OS in patients with GC vs. ABC origin or those with PN/PEN vs. SEN involvement (P>0.4-0.8).

Safety. Hematological AEs were common in patients after CHOP-R-14 and ^{90}Y-ibritumomab treatment. The rates of grade 3 or 4 hematological toxicities with CHOP-R-14 were as follows: 60% with neutropenia (n=12), 25% with anemia (n=5) and 20% with thrombocytopenia (n=4). Of note, 4 of these patients had bone marrow involvement at diagnosis. Only 5 patients (25%) required dose delay/reduction, with 1 patient suffering a serious AE as a result of hematological toxicity (hospitalized with fever). Grade 3 neutropenic fever was reported in 4 patients (20%) undergoing CHOP-R-14 therapy. Assuming 120 anticipated cycles of chemotherapy to be delivered (6 cycles/patient for 20 patients), there was a delay in 14 cycles (12%) and 2 cycles were omitted (2%); not all delays/omissions were attributed to hematological toxicity. A total of 4 patients required erythrocyte-stimulating agents.

Of the 16 patients receiving RIT, 8 (50%) had grade 3 or 4 hematological toxicity (anemia in 1, neutropenia in 8 and thrombocytopenia in 2 patients). Of these 8 patients, 5 also developed grade 3 or 4 cytopenias with CHOP-R-14. After RIT, the median nadir of neutropenia was 930/mm^3 and no neutropenic fevers were reported. The incidence of hematological toxicity did not meet the criteria to terminate the study

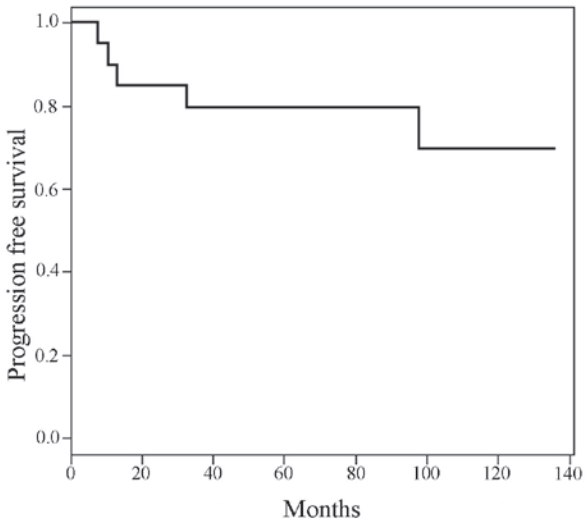

Figure 1. Progression-free survival in patients with diffuse large-cell B-cell lymphoma receiving ^{90}Y-ibritumomab tiuxetan consolidation after CHOP-R-14.

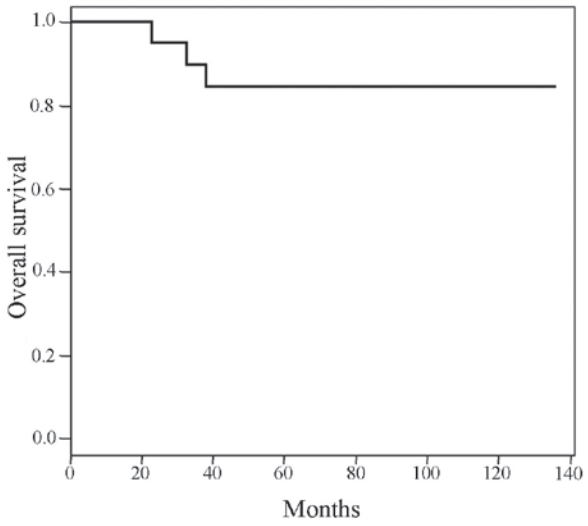

Figure 2. Overall survival of patients with diffuse large-cell B-cell lymphoma receiving ^{90}Y-ibritumomab tiuxetan consolidation after CHOP-R-14.

at the first stage (only 6 of the first 11 patients met criteria counted towards the stopping threshold). The most common non-hematological AEs occurring in >10% of the patients included gastrointestinal events, neuropathy and infections. All these AEs were more common after treatment with CHOP-R-14 rather than with RIT, the majority of which were of grade 1 or 2 severity. Four patients (20%) experienced grade 3 neuropathy after CHOP-R-14, persisting into the RIT phase of the trial, with no new cases reported. Infections were low-grade and occurred more commonly during CHOP-R-14 therapy (60%) than during subsequent ^{90}Y-ibritumomab therapy (38%).

No deaths occurred during the CHOP-R-14 or ^{90}Y-ibritumomab treatment periods. A total of 3 deaths were reported during follow-up: Two patients succumbed to disease progression after receiving RIT at 18.5 and 34 months, respectively; the third patient succumbed to BOOP 30 months after completing 5 cycles of CHOP-R-14 (and excluded from the RIT phase). There were no other serious AEs reported in patients during follow-up.

Discussion

Despite the survival advantage conferred by the addition of rituximab to chemotherapy for the treatment of DLBCL, the clinical course of patients with this type of lymphoma remains heterogeneous and unpredictable (1,23). Novel therapeutic strategies tailored to specific high-risk clinicopathological characteristics are required to optimize care. Our study investigated the efficacy and safety of first-line dose-dense CHOP-R-14 induction followed by ^{90}Y-ibritumomab consolidation in patients with high-risk clinical and biological characteristics. The results appeared to be promising as compared with those reported by the Groupe d'Etude des Lymphomes de l'Adulte (GELA) at 5 years of follow-up in patients receiving CHOP-R-21 (5-year PFS rates stratified according to IPI of 69 and 47% in low- and high-risk patients, respectively), maintained during a long-term follow-up of 89.7 months (24).

At the time of designing this study, the rationale for the use of CHOP-R-14 was based on German data demonstrating the superiority of CHOP-14 over CHOP-21, with improved 5-year event-free survival and OS rates (10). The RICOVER-60 trial has since established the synergistic effects of combining 6 cycles of dose-intensified CHOP-14 with rituximab in patients aged >60 years (25). However, in time, the relative benefit of dose-dense chemo-immunotherapy has not held up in head-to-head comparisons of standard CHOP-R-21 with CHOP-R-14: Cunningham *et al* demonstrated similar response rates [ORR, 88 vs. 91% (P<0.139) and CR/unconfirmed CR (CRu), 63 vs. 58% (P<0.183), respectively] and survival outcomes with CHOP-R-14 and CHOP-R-21 (11). These results were corroborated by GELA in elderly patients with DLBCL (12). By contrast, dose intensification with R-ACVBP has demonstrated a significant survival advantage in young patients with low- or low-intermediate-risk disease compared with CHOP-R-21, but with an associated significant increase in toxicity, raising questions of the generalizability of such a regimen (26). Similarly, in high-risk DLBCL, a subset analysis of the SWOG trial suggested a benefit to dose intensification via high-dose chemotherapy with stem cell rescue. This was, however, an unplanned analysis in a population that was heterogeneously treated with immunotherapy and not translatable to an older population (27). Taken collectively, these studies suggest that manipulation of chemo-immunotherapy induction alone is not optimal for improving clinical outcomes. Our study is innovative in investigating radioimmunotherapy consolidation with dose-dense chemo-immunotherapy as an alternative therapeutic strategy.

Over the last decade, RIT has emerged as a safe and effective consolidative strategy in indolent as well as aggressive lymphomas, most effective when administered earlier during the disease course. In patients with high-risk DLBCL, several studies have confirmed the benefit of first-line RIT consolidation following chemo-immunotherapy (Table II). For example, Zinzani *et al* administered ^{90}Y-ibritumomab consolidation after 4 cycles of CHOP-R-21 in 48 high-risk elderly (≥60 years)

Table II. Studies using RIT consolidation in the first-line setting in patients with highrisk DLBCL.

Study, year	N (number on RIT)	High-risk characteristics	Treatment regimen	Response rates with RIT	Survival	Refs.
Hamlin *et al*, 2010	63 (44)	Age >60 years-Age adjusted intermediate-high and high-risk IPI	CHOP-R-21 x6 → ^{90}Y-ibritumomab tiuxetan	PR or CRu →CR: 16% Final CR/CRu: 86%	Median f/u: 42 months PFS: 62% OS: 64%	(28)
Yang *et al*, 2009	20 (20)	Bulky disease	CHOP-R-21 x6 → ^{90}Y-ibritumomab tiuxetan	PR →CR: 67% Final CR: 90%	Median f/u: 17.5 months 2year PFS: 78.9±9.1% OS: NR	(29)
Zinzani *et al*, 2010	55 (48)	Age >60 years	CHOP-R-21 x4 → ^{90}Y-ibritumomab tiuxetan	PR →CR: 50% Final CR: 73%	Median f/u: 18 months 2-year PFS: 85% 2-year OS: 86%	(18)
Kraeber-Bodere *et al*, 2010	29 (23)	Age >60 years	CHOP-R-14 x6 → ^{90}Y-epratuzumab tetraxetan	PR →CR:30.7% Final CR: 56.5%	Median f/u: 12 months PFS: 75% OS: 83%	(30)
Friedberg *et al*, 2010	84 (50)	Bulky disease or advanced stage	CHOP-R-21 x6 → CHOP-21 x 2 → Iodine-131 tositumomab	PR →CR: NR Final CR: NR PR →CR: 80%	Median f/u: 12 months PFS: 75% OS: 83% Median f/u: 89.7 months	(31)
Karmali *et al*, present study	20 (16)	90% of patients with ≥1 highrisk characteristic: 55% IPI ≥3, 70% bulky disease, 45% SEN site, 45% nonGC origin	CHOP-R-14 x6 → ^{90}Y-ibritumomab tiuxetan	Final CR: 94%	PFS: 75% OS: 85%	

RIT, radioimmunotherapy; CR, complete response; CRu, unconfirmed CR; DLBCL, diffuse large B-cell lymphoma; f/u, follow-up; IPI, International Prognostic Score; NR, not reported; PR, partial response; OS, overall survival; PFS, progressionfree survival; CHOP-R, rituximab + cyclophosphamide, doxorubicin, vincristine and prednisone; SEN, secondary extranodal site; GC, germinal center.

patients with DLBCL. The CR rates improved from 58% after CHOP-R-21 to 73% after RIT, with a 50% PR to CR conversion rate after ^{90}Y-ibritumomab (18). After a median follow-up of 18 months, the estimated 2-year PFS and OS rates were 85 and 86%, respectively. Similar results with RIT have been published in comparable high-risk patient populations, including those with bulky disease (28-31). Although direct comparisons of these studies to our own cannot be made, our study demonstrated higher CR rates after dose-dense chemo-immunotherapy (75%) augmented by RIT (95% CR; 80% PR to CR conversion rate), with durable responses maintained over >7 years of follow-up.

Our study accrued a substantial number of patients with secondary extranodal involvement and bulky disease, other high-risk characteristics associated with late relapse (32). Consolidation with RIT was able to achieve reasonable survival outcomes in these patients, suggesting a role in eradicating minimal residual disease, a likely reason for late relapse. At best, given our small sample size, there were signals of activity of the immunomodulatory effects of RIT in GC and ABC patients. Targeted approaches to the underlying biology associated with cell of origin may be more effective, as demonstrated with early-phase trials with agents such as lenalidomide and ibrutinib, specifically for ABC-origin DLBCL (33,34).

Our small sample size and the inability to accrue 20 patients completing treatment in its entirety due to limited resources is a shortcoming that makes conclusions on toxicity difficult as well. For patients that did undergo therapy, toxicities were not unexpected, with an observed incidence and severity consistent with those of other studies using CHOP-R-14 and/or ^{90}Y-ibritumomab in patients with DLBCL (16,18,19,35). By the completion of this study, clinically significant grade 3/4 hematological toxicities after chemotherapy and/or any grade 3/4 toxicity after RIT was observed in 10 patients, with only 1 patient suffering a serious AE; all were manageable with treatment interruption and standard medical interventions. In the CHOP-R-14 phase of the trial, 87% of the cycles were delivered in a timely manner. A total of 18 patients completed all 6 cycles of CHOP-R-14 and the remaining 2 patients completed 5 cycles; only 3 patients had hematological toxicities accounting for cycle delays/omissions. There were no grade 3/4 infections or cases of neutropenic fever following RIT, despite a 56% rate of grade 3 or 4 neutropenia with consolidation. Neuropathy was the most common non-hematological toxicity following chemo-immunotherapy; a decrease in all grades of neuropathy post-RIT implicates CHOP-R-14 rather than RIT as the likely cause. A similar association between CHOP-R-14 and neuropathy was observed in the RICOVER-60 trial after the treatment of elderly patients with CHOP-R-14 (36).

In the present study, no cases of secondary AML/MDS were reported. Despite these reassuring findings, longer follow-up is required to definitively determine the risk of development of therapy-related myelodysplastic syndrome/acute myeloid leukemia attributed to combinations of RIT and anthracyclines/alkylators.

Several large randomized controlled trials have evaluated the safety and efficacy of dose-dense chemo-immnunotherapy in DLBCL with equivocal results, suggesting the need for alternative strategies. To the best of our knowledge, our trial is the first designed to investigate the efficacy of combining dose-dense CHOP-R-14 with RIT consolidation and the first to report survival outcomes with the longest follow-up post-RIT consolidation in DLBCL to date. Our high-risk patients achieved durable responses with acceptable toxicities in the first-line setting. There were several limitations to our study, including the small sample size and incomplete accrual; thus, our results on efficacy must be interpreted with caution. Additionally, our study predates the PET era. Nonetheless, our long-term follow-up provides a reliable measure of response, with evidence of benefit in patients with high-risk characteristics. In an era of targeted therapies, we consider that closer investigation of RIT consolidation should not be entirely abandoned as a potential treatment option in DLBCL.

Acknowledgements

The authors wish to thank the staff of the Rush University Cancer Center for their assistance in conducting this study, the patients for their participation, and Dr Amjad Ali (Department of Diagnostic Radiology and Nuclear Medicine) for his active involvement in the study. This study was supported by Biogen IDEC (Weston, MA, USA) and Spectrum Pharmaceuticals, Inc. (Irvine, CA, USA). Dr Stephanie A. Gregory has received research support from Biogen IDEC and is on the Advisory Panel for Spectrum Pharmaceuticals. Dr Venugopal participated in the speaker's bureau with and received research support from Biogen IDEC. Teresa O'Brien was a consultant and participated in the speaker's bureau with Biogen IDEC.

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