Split-dose R-CHOP: a new approach to administer cytotoxic chemo-immunotherapy to elderly patients with DLBCL

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Background Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma. It is challenging to deliver standard rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) chemotherapy in the very elderly or elderly with comorbidities because of age-related changes in metabolism and performance.

Objectives To describe outcomes of a unique approach to the delivery of standard R-CHOP chemotherapy in split-doses for the treatment of elderly DLBCL patients.

Methods We performed a single center, retrospective analysis of all patients with DLBCL treated with split-dose R-CHOP during January 2007-April 2015. The patients received R-CHOP at a 50% dose reduction on days 1 and 15 of each 28-day cycle (split dose), with full dose rituximab on day 1 for up to 6 cycles. The total amount of chemotherapy delivered during each 28-day cycle of split-dose R-CHOP was equivalent to the cumulative dose in each 21-day cycle of standard R-CHOP.

Results We identified 22 patients who had been treated with split-dose R-CHOP (median age, 81 years). 10 patients had a Charlson Comorbidity Index score of ≥2, and 13 were aged ≥80. 12 patients completed their prescribed treatments, and 10 required further de-escalation or early termination owing to toxicity. All of the patients who completed therapy were in a complete remission at the end of treatment. The median overall survival for the entire cohort was 47 months, and median progression-free survival was 43 months.

Limitations Retrospective, single institution study, small cohort

Conclusions Split-dose R-CHOP allowed administration of curative-intent therapy in an elderly population with encouraging outcomes.

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Diffuse large B-cell lymphoma (DLBCL) is a form of high-grade non-Hodgkin lymphoma (NHL) with a high mortality rate if untreated. It is the most common form of NHL and its incidence increases with age with a median age of presentation of 70 years.[1,2] As a result of improved medical care, the population of octogenarians and older is growing, and consequently, there has been an increase in the number of cases of NHL in this specific age group.[3] However, despite this shifting demographic, the standard treatment approach for most patients with DLBCL or transformed DLBCL from underlying low-grade lymphoma remains immunotherapy with the anti-CD20 monoclonal antibody rituximab in combination with cytotoxic chemotherapy that includes cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) given in 21-day cycles.[4-6] Although that regimen has been established as the standard of care in patients up to the age of 80 years, maintaining dose density and intensity in geriatric patients may be difficult because of age-related changes in metabolism and comorbid conditions.[4,7] Given that 85% of patients over the age of 80 years will present with comorbidity, many of these patients do not receive curative intent chemotherapy.[8] Many providers are hesitant to prescribe multi-agent anthracycline-based chemotherapeutic regimens to this age group because of concerns about excessive therapy-related toxicity and poor hematologic reserve.[7,8] This is best exemplified by a SEER-Medicare database review that

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demonstrated only 42% of approximately 9,400 patients over the age of 65 with DLBCL received doxorubicin-based therapy.[9]

Although there are limited data to guide the treatment of geriatric patients diagnosed with DLBCL, the importance of offering treatment is clear, because the main cause of death in this population is progressive lymphoma.[8,10] Despite this, patients in the most vulnerable age group, ≥80, often do not receive combination therapy with curative intent.[10] A study comparing outcomes in the pre- and post-rituximab eras in DLBCL patients aged ≥80 found that curative intent chemotherapy was offered to only 21 of 40 patients (53%) in the post-rituximab era.[11] However, elderly patients who are offered the 21-day R-CHOP regimen (R-CHOP-21) often experience more toxicity than do their younger counterparts.[12] Although R-CHOP-21 is offered to all patients who are deemed to be candidates for this regimen, the only listed option for those aged ≥80 with comorbidities is the attenuated immunochemotherapy regimen, R-miniCHOP.[8,13] This regimen delivers about 50% of the dose of CHOP 21 and results in a 2-year progressive-free survival of less than 50%.

At our center, we have developed an alternative approach to deliver standard cumulative doses of R-CHOP-21 chemotherapy through split doses with a 50% dose reduction given over a 28-day cycle. By administering in this fashion with growth-factor support, we have been able to avoid significant cytopenias and are able to effectively administer the total dose of R-CHOP-21 chemotherapy in 24 instead of 18 weeks. We have used this method of chemotherapy delivery for the treatment of DLBCL or transformed large-cell lymphoma in the very elderly (≥80 years) or the elderly with comorbidities, and we have termed the regimen split-dose R-CHOP.[14-16] In this article, we report outcomes of elderly patients treated with this institutional regimen.

Materials and methods

Study design and data elements

We reviewed the charts of DLBCL patients treated with split-dose R-CHOP at the University of Pennsylvania Abramson Cancer Center. We evaluated all patients seen at the center with a diagnosis of either transformed or de novo DLBCL who were treated with split-dose R-CHOP chemotherapy during January 2007-April 2015. We included all patients who received at least 1 dose of split-dose R-CHOP for treatment. We excluded patients who had received more than 1 cycle of standard R-CHOP-21 before de-escalation to our split-dose regimen.

All of the data were abstracted from our inpatient and outpatient electronic medical records. Demographic data collected included age at diagnosis, sex, type of DLBCL (de novo or transformed), and disease stage. Laboratory values measured included white blood cell count (WBC), hemoglobin (Hgb), platelet count (PLT), serum creatinine (Cr), albumin (Alb), and lactate dehydrogenase (LDH). An albumin of <3.5 mg/dL was considered to be low, and a creatinine level of >1.5 mg/dL was classified as elevated for all patients. International Prognostic Index (IPI; range 0-5)[17] and Charlson Comorbidity Index (CCI),[18] excluding points for their lymphoma diagnosis, were calculated retrospectively for all patients. A CCI score of ≥2 was deemed to be a high-risk group based on previous literature demonstrating its value as an independent prognostic factor in the outcomes of elderly patients with DLBCL.[19] Response assessment was performed using the 2007 International Working Group criteria, and all patients had either a computed-tomography (CT) or positron-emission tomography-CT scan done at the end of treatment for response assessment.[20] This study was reviewed and approved by the institutional review board at the University of Pennsylvania.

Split-dose R-CHOP regimen
Each cycle is 28 days and consists of one A treatment on day 1, and one B treatment on day 15 for up to 6 cycles.

Day 1 (A part of cycle)
- Rituximab 375 mg/m2 IV
- Cyclophosphamide 375 mg/m2 IV
- Doxorubicin 25 mg/m2 IV
- Vincristine 1 mg IV
- Prednisone 50 mg (days 1-5) by mouth

Day 15 (B part of cycle)
- Cyclophosphamide 375 mg/m2 IV
- Doxorubicin 25 mg/m2 IV
- Vincristine 1 mg IV
- Prednisone 50 mg (Days 15-19) by mouth

FIGURE 1 Split-dose R-CHOP regimen[a]

R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone

[a]Filgrastrim or pegfilgrastim is given with each A and B treatment to prevent neutropenia

Split-dose R-CHOP regimen

In this regimen, patients receive CHOP chemotherapy at a 50% dose reduction on day 1 (A treatment) and day 15 (B treatment) of each 28-day cycle. Rituximab is given at full dose on day 1 of each cycle. The total amount of chemotherapy delivered during each 28-day cycle of split-dose R-CHOP is equivalent to full-dose R-CHOP-21, and patients receive up to a total of 6 A and 6 B cycles (Figure 1). Patients are supported with either granulocyte-colony stimulating factor (G-CSF) or pegylated G-CSF prophylactically after each half cycle, at the discretion of the provider.

TABLE Patient characteristics (N = 22)

Characteristic	Value
Median age, y (range)	81 (60-90)
DLBCL diagnosis, n (%)	
De novo	13 (59)
Transformed	9 (41)
Female, n (%)	16 (73)
Mean WBC, 10^3/uL (SD)	8.9 (3.7)
Mean Hgb, g/dL (SD)	11.8 (2.0)
Mean Plt, 10^3/uL (SD)	295 (118)
Mean Cr, g/dL (SD)	1.02 (0.36)
Elevated LDH, n (%)	16 (73)
Decreased albumin, n (%)	10 (45)
Did not complete therapy, n (%)	10 (45)
Disease stage ≥3, n (%)	15 (68)
IPI score ≥3, n (%)	14 (64)
CCI score ≥2, n (%)	10 (45)
Received 1 cycle of R-CHOP-21, n (%)	2 (9)
Received G-CSF or pegylated G-CSF, n (%)	22 (100)

Cr, serum creatinine; CCI, Charlson Comorbidity Index; DLBCL, diffuse large B-cell lymphoma; G-CSF, granulocyte-colony stimulating factor; Hgb, hemoglobin; IPI, International Prognostic Index; LDH, lactate dehydrogenase; Plt, platelet count; R-CHOP-21, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone – 21-day regimen; WBC, white blood cell count

Statistical analysis

Descriptive statistics were used to describe the demographics of the study population. Survival analyses using the Kaplan-Meier methodology were performed. A log-rank test was used to compare outcomes between patients with de novo and transformed DLBCL. Categorical outcomes were compared between patients who completed therapy and those who did not, using the Fisher exact test. The primary outcome for this study was overall survival (OS), which was estimated from the date of first treatment of split-dose R-CHOP to death or end of follow-up. Secondary outcomes included progression-free survival (PFS), rates of therapy completion, end-of-treatment response, and hospitalizations during chemotherapy. PFS was calculated from date of first treatment to relapse or death. All tests were 2-sided, and a *P*-value of <.05 was considered statistically significant. Analyses were performed using STATA (version 13.0) software.

Results

We identified 27 patients who received split-dose chemotherapy. Two of those patients had received split-dose R-CEOP (etoposide substituted for doxorubicin) and were excluded. Three patients had received more than 1 cycle of full-dose R-CHOP before de-escalation to split-dose R-CHOP and were also excluded. For our data analysis, we included 22 patients with either de novo DLBCL (n = 13) or transformed DLBCL (n = 9) from a low-grade lymphoma treated with the split-dose R-CHOP regimen. The median age at diagnosis for these patients was 81 years (range, 60-90 years; Table). Of the 9 patients with transformed DLBCL, 3 had received previous chemotherapy for indolent lymphoma with either single-agent rituximab or with bendamustine in combination with rituximab. In all, 73% of the patients (n = 16) were women, 68% (n = 15) had stage 3 or 4 disease at diagnosis, and LDH levels were elevated in 73% of patients (n = 16). Baseline albumin was decreased in 10 patients, and baseline creatinine was elevated in 3 patients. The mean WBC count was 8,900 µL, mean Hgb 11.9 g/dL, and mean platelet count 295,000 µL. The median CCI score was 1 (range, 0-5), and 45% of patients (n = 10) had a CCI score of ≥2. Fourteen patients had an advanced IPI score of ≥3, denoting intermediate-high or high-risk disease. All patients had a baseline echocardiogram that demonstrated adequate cardiac function (ejection fraction, ≥50%) before administration of anthracycline.

In all, 12 patients completed split-dose R-CHOP therapy as prescribed by the treating physician, and all of those patients achieved a complete response (CR) on post-treatment imaging. The remaining 10 patients did not complete split-dose R-CHOP as prescribed because of toxicity or disease progression. Of those 10 patients, 3 died during therapy and 3 relapsed shortly after early termination of split-dose R-CHOP. The causes of death in the 3 patients who died during therapy included pulmonary emboli (n = 1), progressive lymphoma (n = 1), and myocardial infarction (n = 1). The remaining 4 patients achieved a response even though they did not complete therapy, although some received treatments such as consolidative radiation or additional rituximab. Two patients in our cohort, of whom 1 died, experienced cardiotoxicity. A total of 12 patients (55%) were hospitalized during their treatments for varying toxicities, of whom 9 patients required further treatment de-escalation. Patients who were able to complete therapy were less likely to be hospitalized than those who could not complete therapy (25% vs 75%, respectively; $P < .01$) and trended toward having a CCI of <2 (75% vs 25%, $P = .08$). However, completion of therapy was not affected by age of ≥80, disease stage of ≥3, or IPI of ≥3 at presentation. The median OS for all patients was 47 months (Figure 2) and the median PFS was 43 months (Figure 2). The median OS was 25 months for patients with de novo DLBCL and 80 months for patients with transformed DLBCL, and this difference was statistically significantly ($P = .0498$).

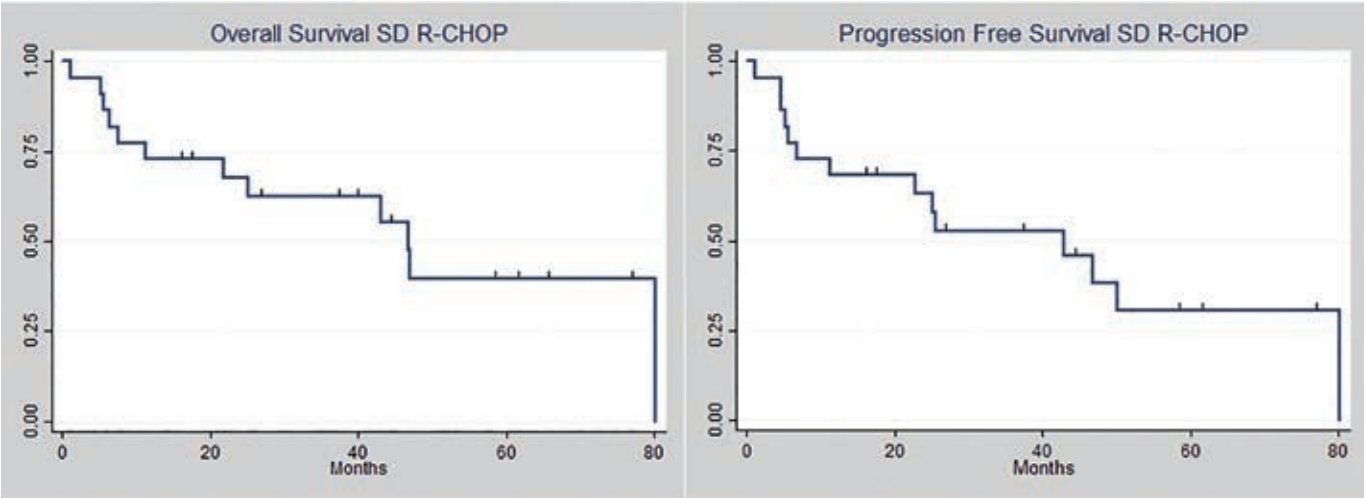

FIGURE 2 Progression-free survival and overall survival for split-dose R-CHOP

R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone

Discussion

The optimal treatment of DLBCL in the very elderly and the elderly with comorbidities remains controversial. At our institution, we have developed and used a regimen we have called split-dose R-CHOP in the treatment of this growing geriatric population. With this regimen, we have been able to offer patients the same cumulative dosage of chemotherapy as R-CHOP-21 in fractionated doses over an extended period (24 weeks vs 18 weeks), with the goal of limiting toxicity. In our population, all of the patients who were able to complete therapy as prescribed had excellent outcomes and achieved a CR on post-treatment imaging. However, despite this scheduling modification, not all of our patients were able to complete the prescribed treatments and a significant percentage of patients still required hospitalization as a result of treatment-related toxicities. In addition, this regimen may not be an option for all elderly patients because cardiac comorbidities may limit exposure to anthracycline therapy for some patients, and in such scenarios, alternative regimens are pursued. Although that consideration is beyond the scope of this study, in elderly patients with a contraindication to an anthracycline, we modify our split-dose R-CHOP regimen by substituting etoposide for doxorubicin (split-dose R-CEOP).[21]

Although DLBCL is a disease that is more common with increasing age, few studies have evaluated the optimal regimen for the very elderly population and many studies have excluded patients over the age of 80 years.[4,22] One group studied a novel regimen termed R-miniCHOP prospectively in the treatment of DLBCL, specifically in patients aged ≥80 years. This was an attenuated regimen with dose reductions of about 50% in all the drugs in R-CHOP-21, except for rituximab. In the single-arm study of R-miniCHOP, the median PFS was 21 months and median OS was 29 months, yet despite dose attenuation, there were 12 deaths (8%) attributed to treatment.[23] Although we cannot directly compare the aforementioned prospective study results with our retrospective findings, our improved PFS and OS are encouraging and worthy of further clinical investigation. The difference in OS in our study is possibly a result of the inclusion of transformed DLBCL, which carries with it a different prognosis than patients with de novo DLBCL. This was demonstrated in our study, with patients with transformed DLBCL having better OS, compared with patients with de novo DLBCL. However, a recent retrospective review compared outcomes of patients receiving R-CHOP for transformed follicular lymphoma with those with de novo DLBCL and found similar overall survival, suggesting that in the rituximab era, outcomes of these entities may be more similar.[24] Nevertheless, with the drug delivery modifications in our split-dose R-CHOP regimen, we allow for equivalent dose administration as R-CHOP-21 chemotherapy, albeit over a longer period. Hence, split-dose R-CHOP may be an intermediate option for physicians wanting to intensify the treatment regimen from R-miniCHOP without giving standard R-CHOP-21. Although the results of any retrospective study should be taken with caution, we feel that our findings warrant investigation in a prospective study.

In addition to R-miniCHOP, several other groups have described institutional modifications to R-CHOP chemotherapy for the treatment of elderly patients with DLBCL. One such regimen, R-split-CHOP, divided the administration of cyclophosphamide and doxoru-

bicin over 2 days to decrease toxicity. In a retrospective review of 30 patients, the 3-year OS was 61% with no treatment-related deaths in their cohort.[25] Another group reported its results with dose modifications of R-CHOP by age. Patients aged ≥70 received a 70% dose reduction, while those aged ≥80 received a 50% dose reduction, similar to R-miniCHOP. Based on toxicity, dose escalations could be made as tolerated. In this cohort, patients in the 70-79 age group had a 2-year OS of 75% and patients in the ≥80 age group had a 2-year OS of 65%.[26] All the aforementioned regimens, like ours, represent variations on the administration and dosing of R-CHOP chemotherapy. However, without a prospective clinical trial, the optimal regimen for elderly patients with DLBCL is not clear, and for all patients who are deemed able to tolerate R-CHOP-21, this should remain the standard of care. Our split-dose R-CHOP approach incorporates the benefits of many of these regimens by limiting toxicity through a 50% dose reduction with each treatment while maintaining intensity by delivering the equivalent dose of chemotherapy as R-CHOP-21. This potential benefit of split-dose R-CHOP does come at the inconvenience of a longer administration of chemotherapy.

Alternative regimens explored for the very elderly include non-anthracycline based therapies such as bendamustine-rituximab. In a Phase II study incorporating 14 patients ≥80 years with aggressive lymphomas felt not to be eligible for R-CHOP chemotherapy, the median OS with bendamustine-rituximab chemotherapy was 7.7 months with no treatment related mortality.[27] While this represents a reasonable option in select patients, anthracycline therapy has historically been a mainstay in the treatment of aggressive lymphomas with an overall survival benefit seen even in an elderly population.[28,29] However, this has been recently challenged by an evaluation of an elderly cohort from a Veterans Affairs database that suggested the inclusion of full-dose doxorubicin may add more toxicity than benefit after a high treatment-related mortality was seen in that study.[30] Although the cumulative dose of anthracycline given during chemotherapy is the most important predictor of anthracycline-related cardio-toxicity, previous study findings have demonstrated that lower-dose doxorubicin given more frequently results in less cardiotoxicity than does the standard every 3 week administration.[31-33] With our split-dose R-CHOP approach, doxorubicin is given at 50% dose reduction every 2 weeks, which may limit the cardiac toxicity to this population.[14]

With the advent of multiple new targeted therapies, there may be a role for the addition of a novel agent in combination with chemotherapy for the treatment of elderly DLBCL patients. Owing to the poorer historical response rate of DLBCL in elderly patients and the increased frequency of an activated B-cell phenotype in this population,[34,35] a phase 2 protocol, REAL07, studied the addition of lenalidomide in patients aged 60-80 years and found that it was a safe addition with impressive response rates.[22] However, with this regimen there was significant toxicity, with 55% of patients experiencing grade 4 neutropenia, which may not be as tolerable in population aged ≥80. Other agents with an encouraging safety profile that may have a role in improving outcomes in patients with DLBCL include the Bruton kinase inhibitor, ibrutinib. The combination of ibrutinib with R-CHOP has been studied in early-phase protocols that have demonstrated exciting results with limited additional toxicity.[36] Ibrutinib, like lenalidomide, has particular efficacy in the activated B-cell phenotype,[37] which may be of greater significance in the elderly population. However, the safety of ibrutinib or lenalidomide with R-CHOP has not been studied prospectively in a frail elderly population.

There are several limitations of this study design. A retrospective cohort study limits data collection to that available in the clinical record. As a single-center study from an academic institution, there are restrictions to generalizability and potential biases in the patient population. In addition, without a direct comparison group, we are not able to determine the relative effectiveness and toxicity of split-dose R-CHOP compared with R-CHOP-21. However, this report is the first detailed evaluation of delivering the same cumulative dosage as R-CHOP-21 in a de-escalated, prolonged fashion with split doses. We were also unable to assess the effect of patient level variables on overall survival because of the limited size of our cohort. Lastly, we did include patients who received up to 1 cycle of full-dose R-CHOP-21 before de-escalation to split-dose R-CHOP, which may have confounded our results, but as this was the case for only 2 patients, we felt it would not have an impact on the overall clinical outcomes.

The importance of developing appropriate treatments for the elderly population has never been more crucial. By 2030, nearly 20% of the US population will be over the age of 65 years, and the most rapidly growing population is for people aged ≥ 85 years.[38] Despite that, the elderly remain an underrepresented group in cancer research resulting in a lack of guidelines for a standard treatment approach in this patient population.[39] This has led to recent calls by the American Society of Clinical Oncology to modify clinical trial design and improve the participation of elderly patients so that optimal treatments can be defined.[40] Until such studies can be implemented and performed, retrospective reviews of regimens such as our split-dose R-CHOP will help provide options for physicians who are struggling to determine the best way to treat the very elderly patient or an elderly patient with comorbidities and DLBCL.

Conclusions

The treatment of DLBCL in elderly patients with curative intent remains a challenge in geriatric oncology. Although the current standard of care therapy for elderly DLBCL with comorbidities remains R-miniCHOP, a regimen that has been validated in a large phase 2 study, our split-dose R-CHOP approach offers an intermediate option for clinicians wanting to augment the intensity of chemotherapy in a frail elderly population without giving full-dose R-CHOP-21 chemotherapy. We hope to validate these results in a larger prospective trial of this regimen in the treatment of elderly patients with DLBCL.

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