Published in final edited form as:

Clin Lymphoma Myeloma Leuk. 2015 May ; 15(5): 270–277. doi:10.1016/j.clml.2014.12.011.

Efficacy and Tolerability of Anthracycline-Based Therapy in Elderly Patients With Diffuse Large B-Cell Lymphoma

Christine C. Davis, Jonathon B. Cohen, Katherine S. Shah, Don A. Hutcherson, Minal J. Surati, Kelly Valla, Elyse H. Panjic, Caitlin E. Handler, Jeffrey M. Switchenko, and Christopher R. Flowers

Emory University Healthcare and Winship Cancer Institute, Atlanta, GA

Abstract

We examined treatment with or without anthracyclines in 72 elderly diffuse large B-cell lymphoma patients (age ≥ 65 years) in a retrospective cohort analysis. Factors leading to treatment without an anthracycline included age and ejection fraction, whereas markers of tolerability were similar between groups. This study highlights the details of anthracycline tolerability in elderly lymphoma patients.

Introduction—Although diffuse large B-cell lymphoma (DLBCL) can be cured with rituximab and anthracycline-based therapy, within the elderly population there are additional factors to consider in selecting a treatment regimen including comorbid conditions, decreased drug metabolism, decreased hematologic reserve, reduced performance status, and regimen-related toxicity.

Patients and Methods—We performed a retrospective cohort analysis of patients with DLBCL aged ≥ 65 years at time of diagnosis treated with either an anthracycline-containing regimen (ACR; n = 59) or a non-ACR (n = 13) to assess factors that led to treatment selection, tolerability, and outcomes.

Results—The mean age was 73 years in the ACR and 77 years in the non-ACR group ($P = .009$), and median left ventricular ejection fraction (LVEF) at diagnosis was 60% in the ACR group and 45% in the non-ACR group ($P < .001$). With an ACR, elderly DLBCL patients had a median overall survival of 28 months and a 2-year progression-free survival (PFS) of 64%. After an ACR, 14 patients [24%] (out of 59 total patients) had a decrease in LVEF, 7 patients [15%] (% is based off of those who we had the data collected, so this is out of 45 with this specific data) required a dose reduction of the anthracycline, and 15 patients [33%] (% is based off of those who we had the data collected, so this is out of 45 with this specific data) could not complete the regimen as planned. Hospitalization due to toxicity occurred in 20 patients [44%] (% is based off of those who we had the data collected, so this is out of 45 with data) of patients in the ACR group and 3 patients [75%] (% is based off of those who we had the data collected, so this is out of 4 with this specific data) in the non-ACR group, and was the only predictor of overall survival.

Address for correspondence: Christine C. Davis, PharmD, PGY-2 Hematology/Oncology Pharmacy Resident, Emory University Hospital, 1364 Clifton Road NE, B712, Atlanta, GA 30322; contact: christine.davis@emoryhealthcare.org.

Disclosure: The authors have stated that they have no conflicts of interest.

Conclusion—Results of this study suggest that elderly patients with DLBCL experience meaningful PFS with ACRs, but a third experience toxicity requiring therapy modification. Future studies should examine larger patient populations and define treatments with outcomes similar to ACR that also decrease toxicity and hospitalization in the elderly DLBCL population.

Keywords

Chemotherapy; Hospitalization; non-Hodgkin lymphoma; Tolerability; Toxicity

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma (NHL) and accounts for approximately 30% of cases.¹ DLBCL is largely a disease of elderly patients, with a median age at presentation of 66 years according to the Surveillance, Epidemiology, and End Results (SEER) database. Increased patient age at diagnosis is associated with decreased overall survival (OS), with the 5-year OS of DLBCL patients decreasing from 62% for ages 50 to 59 years, to 51% for ages 60 to 69 years, and 34% for ages older than 70 years.^{2,3}

The proportion of the US population aged ≥ 65 years who are potentially eligible for Medicare coverage is projected to increase from 14.8% in 2015 to 20.3% in 2030.⁴ It is expected that rates of NHL will continue to increase with the aging population. Although DLBCL can be curable with aggressive treatment, in elderly patients there are additional factors to consider when choosing a treatment regimen including comorbid conditions, decreased drug metabolism, decreased hematologic reserve, and reduced performance status (PS).⁵ Data from the Eindhoven Cancer Registry indicate that nearly 80% of patients older than the age of 60 years with aggressive NHL have at least 1 comorbid condition at presentation, including hypertension (22%), heart and vascular disease (19%), and previous malignancies (15%).⁶ Although data sets that link SEER registry and Medicare claims data for patients with DLBCL can provide information about comorbidities and lymphoma outcomes, these resources lack the clinical data needed to provide meaningful details regarding the toxicity of anthracyclines and other therapies in this population.

First-line induction therapy for fit patients with DLBCL is 3 to 4 or 6 cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) with or without radiation depending on the stage and tumor bulk.¹ R-COEP (rituximab, cyclophosphamide, etoposide, vincristine, and prednisone) and R-CVP (rituximab, cyclophosphamide, vincristine, and prednisone) have been used in patients in whom an anthracycline-containing regimen (ACR) is deemed too toxic.^{6,7} However, the efficacy and toxicity of these regimens in elderly patients with DLBCL has rarely been described.

In a study that examined elderly patients treated with an ACR or a non-ACR, both without rituximab, complete response (CR) was achieved in 47% of patients who received an ACR and in 32% of patients who received a non-ACR ($P = .0001$), and 5-year survival rates were 26% in patients treated with an ACR and 19% in patients treated with a non-ACR ($P < .5$).⁸ A more recent analysis of SEER–Medicare data in elderly patients with DLBCL found a median OS of 27.7 months and after adjusting for patient covariates; the greatest 3-year OS

was observed in patients treated with rituximab and an ACR of 63%, followed by a comparable survival for ACR treatment without rituximab of 52%, and non-ACR treatment with rituximab of 52%.⁹ Although treatment with an ACR is associated with improved response rates and progression-free survival (PFS) in elderly patients compared with non-ACR treatment, the associated toxicities including myelosuppression, febrile neutropenia, mucositis, and cardiomyopathy might exclude many elderly patients from such aggressive treatment.^{8,10} We performed a retrospective cohort analysis of patients with DLBCL aged 65 years at diagnosis treated with either an ACR or a non-ACR to examine clinical factors that led to treatment selection and assess toxicity and outcomes for a population of DLBCL that was comparable to SEER–Medicare studies but included clinical data suitable for detailed exploration of anthracycline effects on cardiac function and treatment modification.

Patients and Methods

Study Population

We used published methods^{11,12} to identify patients diagnosed with DLBCL based on previous pathology review and the World Health Organization *Classification of Tumours of Haematopoietic and Lymphoid Tissues*.¹³ Patients with DLBCL who received care within the Emory University Healthcare system between January 1, 2003 and August 13, 2013 were included in the study. Cases were included if there was a diagnosis of DLBCL confirmed in a record review and available information on date of diagnosis, date of last contact, or date of death, and known first course of treatment. This single-center, retrospective review of electronic medical records focused on elderly patients 65 years of age at the time of diagnosis. Although age 60 years and age 70 years have been used as cutoffs for patients with poor prognosis in the International Prognostic Index (IPI) and the elderly-IPI respectively, our study population was limited to patients aged 65 years and older to allow comparisons with population-based studies using SEER–Medicare data.^{3,9,14,15} Patients were excluded if they had incomplete records, coexistent active malignancy, or primary central nervous system (CNS) lymphoma. Incomplete records were defined as patients without documentation of a first-line management strategy and at least 1 follow-up encounter. This time period was chosen to include the period when rituximab was included in front-line regimens after the publication of randomized controlled trial results demonstrating the benefits of rituximab with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone).¹⁶ Standard practice at Emory during this period was to withhold anthracyclines in patients with a left ventricular ejection fraction (LVEF) < 45% and in patients the treating clinician considered to be at unacceptably high risk for toxicity. Figure 1 depicts the selection of DLBCL cases included in the analyses.

Data Collection

Clinical data were collected at the time of diagnosis, during treatment, and at follow-up. Baseline demographic characteristics and clinical variables evaluated at the time of diagnosis included: age, Eastern Cooperative Oncology Group PS, Ann Arbor stage, serum lactate dehydrogenase level, IPI score and risk category, age-adjusted IPI, and LVEF. Although the Medication-Based Disease Burden Index (MDBI), the Geriatrics Index of Comorbidity (GIC), and the Cumulative Illness Rating Scale for Geriatrics (CIRS-G)

provide useful geriatric-specific evaluation measures for elderly cancer patients, because of the limitation in available data for these measures of fitness and the retrospective nature of our chart review, complete collection of these data was not possible.¹⁷⁻¹⁹ We captured data to calculate the modified Charlson Comorbidity Index (CCI), a common measure of comorbidity that was adapted for an oncology patient population and previously assessed in similar studies with DLBCL patients.¹⁰ Other data collected included initial treatment regimen, tolerability, response to therapy, date of progression, and date of death.^{20,21} Tolerability data included any documentation of decrease in LVEF, removal or dose reduction of the anthracycline, removal or dose reduction of any treatment, treatment delay, treatment discontinuation, reduction in PS at completion of therapy, and hospital admission due to known regimen-related toxicity. Further information regarding hospitalization including reasons for admission and length of stay were also collected. Common Terminology Criteria for Adverse Events version 3.0 (CTCAE) was used to grade all toxicities.²² Date of last contact and date of death from any cause were collected and the date of death was verified using the Social Security Death Index. Despite other studies that indicated methods for obtaining cause of death, an accurate depiction of treatment toxicity-related deaths were not consistently available and analysis in this small cohort would have been biased and therefore these data were not collected.^{23,24} This study was approved by the Winship Cancer Institute Clinical and Translational Research Committee and the Emory University Institutional Review Board.

Statistical Analysis

The primary objective of this study was to examine PFS for patients who received ACR and too compare outcomes in patients who received a non-ACR. Secondary objectives included examination of the rates of OS, CR, partial response (PR), and to describe overall tolerability of ACR based on CTCAE.

Data were analyzed using analysis of variance for numerical covariates and the χ^2 test or Fisher exact test for categorical covariates when appropriate. PFS and OS were analyzed using Cox proportional hazards models and log rank tests. Patients were censored at the time of last follow-up. For PFS, disease progression and death were considered events. Significance was assessed at the 0.05 level. The statistical analysis was performed using SAS version 9.3.

Results

Patient Population and Baseline Characteristics

Among 155 patients diagnosed with DLBCL at age 65 years, patients with incomplete data (n = 79), primary CNS lymphoma (n = 3), and with a coexistent active malignancy (n = 1) were excluded, yielding a cohort of 72 patients (Figure 1). The eligible patients were treated with an ACR (n = 59) or a non-ACR (n = 13). In Table 1, baseline characteristics at the time of diagnosis of the ACR and non-ACR groups are compared. Patients who received an ACR were significantly younger (median age 73 years vs. 77 years; $P = .009$). Mean baseline LVEF was decreased in the non-ACR (43%) compared with the ACR group (59%;

$P < .001$). Other baseline demographic and disease-related characteristics, and comorbidities were similar between the groups.

First Course of Treatment

First-line regimens for patients are listed in Table 2. The ACR group included patients treated with R-CHOP ($n = 48$), rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin (R-EPOCH) ($n = 6$), rituximab, cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate, and cytarabine (R-HyperCVAD) ($n = 3$), or R-CHOP with or without investigational agents ($n = 2$). Patients in the non-ACR group received regimens including R-COEP ($n = 3$), R-CVP ($n = 1$), rituximab and radiation ($n = 1$), rituximab alone ($n = 1$), hospice care with or without palliative radiation ($n = 3$), or no treatment or alternative herbal treatment ($n = 3$).

Survival and Response

Patients were followed for a median of 4.5 years. Median PFS in the ACR group was 24 months versus 13 months in the non-ACR group (Figure 2A; hazard ratio [HR], 1.62; 95% confidence interval [CI], 0.64- 4.11; $P = .665$). Median OS was 28 months in the ACR group and 13 months in the non-ACR group (Figure 2B; HR, 0.46; 95% CI, 0.21- 1.01; $P = .475$). One-year PFS was 77% in the ACR group and 80% in the non-ACR group. Two-year PFS was 64% in the ACR group and 55% in the non-ACR group. For patients 65 years of age who received R-CHOP, the median PFS and OS were 39 months and 41 months, respectively, and the two-year PFS and OS were 72% and 63%. Within the same subset, 5-year PFS was 35% and 5-year OS was 43%.

Complete response was obtained in 38 patients [68%] (% is based off of those who we had the data collected, so this is out of 56 with this specific data) of patients in the ACR group and 4 patients [50%] (% is based off of those who we had the data collected, so this is out of 8 with this specific data) of patients in the non-ACR group; however this difference was not statistically significant (Table 3; $P = .246$). A univariate analysis of OS showed that CR predicted improved OS (HR, 0.21; 95% CI, 0.095-0.47), and hospital admission due to toxicity was associated with a decrease in OS (HR, 3.22; 95% CI, 1.02-10.1). CCI scores and radiation were not predictive of OS ($P = .093$ and $P = .791$). The univariate analysis of PFS showed no significant predictors of PFS among the variables analyzed, including CCI risk category and radiation ($P = .143$ and $P = .772$). In a univariate analysis of the cumulative incidence of progression in all patients, the only statistical predictors of progression were increased age-adjusted IPI score ($P = .015$) and Ann Arbor staging ($P = .042$).

Regimen-Related Toxicity

Figure 3 depicts overall tolerability of the anthracyclines in elderly patients who received an ACR. Among elderly DLBCL patients who received an ACR, 14 patients [24%] (out of 59 patients) had a decrease in LVEF, with a majority (10 patients [17%] (out of 59 total patients)) of these a decrease of only 5% to 10%. In addition, only 7 patients [12%] (out of 59 patients) of patients had the anthracycline dose reduced or removed from the regimen. In a comparison of other markers of tolerability between the 2 groups, the only statistical difference was an overall reduction in PS at completion of treatment (Figure 4). In the non-

ACR group, 4 patients [80%] (out of 5 patients with data collected) of patients had a reduction in PS compared with 5 patients [13%] (out of 39 patients with this data) of patients in the ACR group ($P = .004$). Of note, CCI and radiation were not predictors of toxicity. A subgroup analysis of patients aged older than 70 years, with 12 patients in the non-ACR group and 37 patients in the ACR group, showed the only statistical difference was a greater reduction in PS in the non-ACR group ($P = .035$). In patients who received an ACR, 15 patients [33%] (out of 45 patients with this data) were not able to complete the regimen as initially planned, which includes patients who required a dose reduction or treatment delay (13 patients [28%]) and patients who stopped treatment (2 patients [5%]).

Additionally, 20 patients [44%] (out of 45 patients with this data) of patients who received an ACR and 3 patients [75%] (out of 4 with this data) of patients who received a non-ACR were admitted to the hospital with a treatment related toxicity; however this was not a statistically significant difference ($P = .330$). Of 72 patients, 23 had 1 hospital admission (20 in the ACR group, 3 in the non-ACR group), 26 had < 1 hospital admission, and data regarding hospitalization was not available in 23 patients. Unavailable data included patients who were treated with their first line of therapy at an outside facility with limited records which differed from patients who were consistently followed at Emory with documentation during treatment stating the patient had no complications during treatment. A total of 34 hospital admissions related to treatment occurred during first-line therapy in 23 patients. The reason for admissions included febrile neutropenia (11 admissions [32%]), documented infection (8 admission [24%]), gastrointestinal toxicity (7 admission [21%]), pulmonary toxicity (3 admissions [9%]), and other (5 admission [15%]). Other consisted of 1 admission each due to decreased ejection fraction, allergic reaction to rituximab, subdural hematoma, altered mental status, and electrolyte abnormalities. The median length of stay for the ACR group was 5 days (range, 2-26 days) versus 5 days (range, 2-9 days) for the non-ACR group with 5 patients in the ACR group hospitalized for > 10 days. In a univariate analysis of predictors of the need for hospital admission for toxicity, it was found that increased IPI score ($P = .009$), a need for dose reduction or discontinuation of an agent ($P = .002$), treatment delay > 7 days ($P = .007$), and reduction in PS ($P = .014$) were all associated with an increased risk of hospital admission.

Discussion

In this academic center-based retrospective study, we found that 59 patients [82%] of elderly patients received R-CHOP or a similar anthracycline-based regimen of higher intensity as first-line therapy for DLBCL. Patients who received non-ACR were older and more likely to have a depressed baseline LVEF. Because of the limitations of a retrospective study, the only feasible geriatric evaluation was the CCI, despite previous studies that showed the benefit of more comprehensive evaluations such as the MDBI, GIC, or CIRS-G.¹⁷⁻¹⁹ Notably, in this study no relationships were observed between CCI-measured comorbid diseases and the type of treatment that patients received or in survival. However, our retrospective analysis was hampered by substantial numbers of elderly patients with incomplete data, which rendered a small population of patients treated with non-ACR, thus limiting our statistical comparisons to only the variables of the greatest interest and highlights the significant need

for prospective observational and intervention studies in elderly DLBCL patients, ideally using a more comprehensive geriatric evaluation.

Although there was no difference in PFS or OS for patients who received ACR and those who did not, too few patients received non-ACR to perform meaningful comparisons. Interestingly, tolerability was similar between the 2 groups aside from a greater incidence of decrease in PS during therapy in the non-ACR group. Although there was not a statistical difference in PS at diagnosis, 3 patients [30%] of patients in the non-ACR group had a baseline PS of > 1 compared with only 5 patients [9%] of patients in the ACR group, which might have contributed to the significant difference in reduction of PS with treatment observed. Together these data indicate that elderly patients at an academic medical center are not routinely excluded from standard of care chemotherapy regimens because of age alone and that patients treated in this manner did not experience worse treatment-related toxicity.

The only significant predictor of OS in both groups was hospitalization due to toxicity in the ACR group in which 20 patients [44%] of patients were hospitalized because of toxicity compared with 3 patients [75%] in the non-ACR group. The most common reasons for hospitalization included febrile neutropenia with or without a documented infection or documented infection. Median length of stay of 5 days was similar between groups. Patient factors that were associated with hospitalization due to toxicity included increased IPI score of 4 or 5, a need for dose reduction or discontinuation of an agent, treatment delay > 7 days, and reduction in PS, which provided provocative intermediate end points that can be investigated in future studies. These data also suggest that elderly patients with poor-risk features that make them ineligible for an ACR should be monitored closely and adverse events need to be addressed aggressively to avoid the risks of hospitalization and death.

To accurately interpret the findings of this study, several limitations must be taken into account. This was a retrospective, single-institution study that resulted in a small sample size because of missing data and the limited size of this patient population. Because several patients did not follow-up at Emory or presented with relapsed disease with limited outside hospital records of initial treatment and the limitation of the electronic medical records in the earlier time periods, some data elements were incomplete. In addition, this study inherently had a selection bias with physician clinical judgement used to determine the patients who received an ACR and those did not. Because more favorable patients were likely selected to receive an ACR, this might have produced a trend toward increased OS in the ACR group.

In a related study using the SEER–Medicare database in patients aged > 65 years, it was found that 3-year OS adjusted for covariates was highest in the group that received ACR with rituximab. Similar 3-year OS was identified for patients who received an ACR without rituximab and those who received a non-ACR with rituximab.⁹ This study also showed a common avoidance of ACR in elderly patients especially among those with congestive heart failure, chronic obstructive pulmonary disease, or chronic kidney disease.⁹ An earlier SEER database study with patients aged > 65 years that examined patients between 1999 and 2002 found similar results with patients treated with rituximab and a non-ACR having survival comparable with those treated without rituximab and with an ACR.³ The larger populations

of these studies provide a sufficient sample size to detect clinically meaningful differences between the ACR and non-ACR groups. However, these studies used claims data to capture treatment course and outcomes. Our study benefited from capturing specific clinical data on individual patient treatment regimens, toxicities, response, and progression events, which were not included in the SEER–Medicare database studies.

Another study in elderly patients aged ≥ 75 years demonstrated that only 46% received an ACR and only 26% of those patients completed 6 cycles of treatment.²⁵ In our study, we observed an increased completion of ACR therapy up to 57%, which is likely because of inclusion of younger patients. In a study that used an attenuated version of R-CHOP (ie, R-miniCHOP) in patients aged ≥ 80 years, it was found that an ACR with reduced doses resulted in a 2-year PFS of 47% with 21% of deaths attributed to toxicity.²⁶ The data on toxicity with R-miniCHOP includes hospitalization with a median length of stay of 2 days (range, 0–46 days) during the first cycle and 0 (range, 0–17 days) during the next 5 cycles.²⁶ The most common serious adverse events were infection, general disorders, and respiratory and mediastinal disorders. Febrile neutropenia occurred in 8% of patients compared with 7% of patients in our study who received a non-ACR and 17% in patients who received an ACR.²⁶ These data suggest that R-miniCHOP offers a compromise between efficacy and safety.²⁶

Bendamustine and rituximab (BR) has also been studied in an open-label phase II study with 14 patients aged ≥ 80 years, a population significantly older than in this analysis.²⁷ The primary outcome of overall response occurred in 69% of patients with 54% obtaining a CR with 4 of the patients alive without disease for at least 4 years. Secondary efficacy end points included OS of 7.7 months and a median PFS of 7.7 months.²⁷ The most common toxicity was 23% Grade 3 or 4 neutropenia with only 2 patients who required secondary prophylaxis with growth colony stimulating factor (G-CSF).¹⁹ No nonhematologic Grade 4 toxicities occurred and Grade 3 toxicities were rare.²⁷ A retrospective analysis of BR as first-line therapy in 15 patients with a median age of 69 years (range, 68–92 years) found either a CR or PR in 62% of patients, a PFS of 6 months, and OS of 9 months.²⁸ Toxicity data from this retrospective study was not routinely reported, however at least 26% of patients had infectious complications.²⁸ A more recently published study with BR in relapsed/refractory DLBCL in 28 patients with a median age of 71 years (range, 54–82 years) reported low toxicity with only 7% of patients requiring 1 dose reduction to 70 mg/m² and 7% of patients who discontinued treatment for prolonged Grade 4 neutropenia, and did not respond to G-CSF.²⁹ These studies conclude that for patients not eligible for standard treatment with R-CHOP, BR might be considered.

Recently, treatment of DLBCL patients aged ≥ 75 years was described in an observational study in which 70% received an ACR, approximately 50% of the patients completed therapy, and 70% of those who completed therapy had survived at 2 years; however, 69% were hospitalized because of toxicity.³⁰ The hospitalization in this study was likely greater than the observations in our study because of the older population. Overall, evidence from larger studies demonstrate the survival benefit of an ACR, however with either an ACR or non-ACR clinicians must be cautious in preventing and treating toxicities in the elderly population, because toxicities that lead to hospitalization appear to lead to excess mortality.

Conclusion

Our data and the findings of others support the use of aggressive therapy in eligible elderly patients with DLBCL because a substantial portion of these patients will achieve a durable remission. However, assessment of comorbidities and PS should be used when choosing an optimal induction regimen because age does not appear to be an absolute determinant of outcome. Based on similar findings in other disease states, age is less commonly used as a singular exclusion criteria for management of patients with acute myeloid leukemia and those who require a stem cell transplant because well-selected patients can be safely treated at older ages.³¹⁻³³ Because of the limited sample size, we were unable to predict OS or PFS in our cohort based on pretreatment factors, including the CCI, but future multicenter studies should focus on pretreatment characteristics outside of age that predict poor response to therapy and poor tolerability. Based on our findings of hospitalization as a predictor of OS, our current management of elderly patients will continue to ensure treatment with G-CSF and close monitoring for fever to decrease incidence of febrile neutropenia and need for hospitalization. Subsequent studies should consider collecting reasons for hospitalization and analyze the data for correlation with outcomes because there might be potential to highlight particular toxicities, such as febrile neutropenia. Because of the increasing portion of the population that will be aged ≥ 65 years and the increasing incidence of lymphoma and other cancers, a more comprehensive approach to evaluation and management of elderly patients is needed.

Acknowledgments

Research reported in this publication was supported in part by the Biostatistics and Bioinformatics Shared Resource of Winship Cancer Institute of Emory University and National Institutes of Health/National Cancer Institute under award number P30CA138292 and by Dr. Flowers' National Cancer Institute R21 CA158686. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

References

1. National Comprehensive Cancer Network. [Accessed August 13, 2013] Non-Hodgkin's Lymphomas Version 1. 2013. Available at: www.nccn.org
2. Howlader, N.; Noone, AM.; Krapcho, M., et al., editors. National Cancer Institute. [Accessed May 26, 2014] SEER Cancer Statistics Review, CSR 1975-2011. Available at: http://seer.cancer.gov/csr/1975_2011/
3. Link BK, Brooks J, Wright K, et al. Diffuse large B-cell lymphoma in the elderly: diffusion of treatment with rituximab and survival advances with and without anthracyclines. *Leuk Lymphoma*. 2011; 52:994–1002. [PubMed: 21338277]
4. United States Census Bureau. [Accessed May 12, 2014] Population Projections. 2012 National Population Projections: Summary Tables. Table 12. Projections of the Population by Age and Sex for the United States: 2015 to 2060. Available at: <http://www.census.gov/population/projections/data/national/2012/summarytables.html>
5. Nastoupil LJ, Sinha R, Flowers CR. Management strategies for elderly patients with diffuse large B-cell lymphoma. *Eur Oncol Haematol*. 2012; 9:123–6. [PubMed: 23805375]
6. Hainsworth JD, Flinn IW, Spiegel DR, et al. Brief-duration rituximab/chemotherapy followed by maintenance rituximab in patients with diffuse large B-cell lymphoma who are poor candidates for R-CHOP chemotherapy: a phase II trial of the Sarah Cannon Oncology Research Consortium. *Clin Lymphoma Myeloma Leuk*. 2010; 10:44–50. [PubMed: 20223728]

7. Moccia A, Schaff K, Hoskins P, et al. R-CHOP with etoposide substituted for doxorubicin (R-CEOP): excellent outcome in diffuse large B cell lymphoma for patients with a contraindication to anthracyclines (abstract 408). *Blood*. 2009; 114(suppl 1) Available at: <http://abstracts.hematologylibrary.org/cgi/content/abstract/114/22/408>.
8. Bastion Y, Blay JY, Devine M, et al. Elderly patients with aggressive non-Hodgkin's lymphoma: disease presentation, response to treatment, and survival—a Groupe d'Etude des Lymphomes de l'Adulte study on 453 patients older than 69 years. *J Clin Oncol*. 1997; 15:2945–53. [PubMed: 9256139]
9. Tien, YY.; Link, BK.; Brooks, JM., et al. Treatment of diffuse large B-cell lymphoma in the elderly: regimens without anthracyclines are common and not futile. *Leuk Lymphoma*. Published online April 22, 2014. <http://dx.doi.org/10.3109/10428194.2014.903589>
10. Fields PA, Linch DC. Treatment of the elderly patient with diffuse large B-cell lymphoma. *Br J Haematol*. 2012; 157:159–70. [PubMed: 22463486]
11. Graiser M, Moore SG, Victor R, et al. Development of query strategies to identify a histologic lymphoma subtype in a large linked database system. *Cancer Inform*. 2007; 3:149–58. [PubMed: 19455241]
12. Huang T, Shenoy PJ, Sinha R, et al. Development of the Lymphoma Enterprise Architecture Database: a caBIG Silver level compliant system. *Cancer Inform*. 2009; 8:45–64. [PubMed: 19492074]
13. A predictive model for aggressive non-Hodgkin's lymphoma. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. *N Engl J Med*. 1993; 329:987–94. [PubMed: 8141877]
14. Advani RH, Chen H, Habermann TM, et al. Comparison of conventional prognostic indices in patients older than 60 years with diffuse large B-cell lymphoma treated with R-CHOP in the US Intergroup Study (ECOG 4494, CALGB 9793): consideration of age greater than 70 years in an elderly prognostic index (E-IPi). *Br J Haematol*. 2010; 151:143–51. [PubMed: 20735398]
15. Jaffe ES. The 2008 WHO classification of lymphomas: implications for clinical practice and translational research. *Hematology Am Soc Hematol Educ Program*. 2009:523–31. [PubMed: 20008237]
16. 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; 346:235–42. [PubMed: 11807147]
17. Nabhan C, Smith SM, Helenowski I, et al. Analysis of very elderly (> 80 years) non-Hodgkin lymphoma: impact of functional status and co-morbidities on outcome. *Br J Haematol*. 2012; 156:196–204. [PubMed: 22084970]
18. Zekry D, Loures Valle BH, Lardi C, et al. Geriatrics index of comorbidity was the most accurate predictor of death in geriatric hospital among six comorbidity scores. *J Clin Epidemiol*. 2010; 63:1036–44. [PubMed: 20236800]
19. Beloosesky Y, Weiss A, Mansur N. Validity of the Medication-based Disease Burden Index compared with the Charlson Comorbidity Index and the Cumulative Illness Rating Scale for geriatrics: a cohort study. *Drugs Aging*. 2011; 28:1007–14. [PubMed: 22117098]
20. 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; 17:1244. [PubMed: 10561185]
21. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. *J Clin Oncol*. 2007; 25:579–86. [PubMed: 17242396]
22. [Accessed August 13, 2013] Common Terminology Criteria for Adverse Events, Version 3.0 (CTCAE). Available at: http://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v3.pdf
23. Johnson CJ, Weir HK, Fink AK, et al. The impact of National Death Index linkages on population-based cancer survival rates in the United States. *Cancer Epidemiol*. 2013; 37:20–8. [PubMed: 22959341]
24. Weinstock MA, Reynes JF. Validation of cause-of-death certification for outpatient cancers: the contrasting cases of melanoma and mycosis fungoides. *Am J Epidemiol*. 1998; 148:1184–6. [PubMed: 9867264]

25. van de Schans SA, Wymenga AN, van Spronsen DJ, et al. Two sides of the medallion: poor treatment tolerance but better survival by standard chemotherapy in elderly patients with advanced-stage diffuse large B-cell lymphoma. *Ann Oncol.* 2012; 23:1280–6. [PubMed: 21948810]
26. Peyrade F, Jardin F, Thieblemont C, et al. Attenuated immunochemotherapy regimen (R-miniCHOP) in elderly patients older than 80 years with diffuse large B-cell lymphoma: a multicenter, single-arm, phase 2 trial. *Lancet Oncol.* 2011; 12:460–8. [PubMed: 21482186]
27. Weidmann E, Neumann A, Fauth R, et al. Phase II study of bendamustine in combination with rituximab as first-line treatment in patients 80 years or older with aggressive B-cell lymphomas. *Ann Oncol.* 2011; 22:1839–44. [PubMed: 21257672]
28. Walter E, Schmitt T, Dietrich S, et al. Rituximab and bendamustine in patients with CD20+ diffuse large B-cell lymphoma not eligible for cyclophosphamide, doxorubicin, vincristine and prednisone-like chemotherapy. *Leuk Lymphoma.* 2012; 53:2290–2. [PubMed: 22475324]
29. Merchionne F, Quintana G, Gaudio F, et al. Bendamustine plus rituximab for relapsed or refractory diffuse large B cell lymphoma: a retrospective analysis. *Leuk Res.* 2014; 38:1446–50. [PubMed: 25455656]
30. Boslooper K, Kibbelaar R, Storm H, et al. Treatment with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone is beneficial but toxic in very elderly patients with diffuse large B-cell lymphoma: a population-based cohort study on treatment, toxicity and outcome. *Leuk Lymphoma.* 2014; 55:526–32. [PubMed: 23734653]
31. Devine SM, Owzar K, Blum W, et al. A Phase II Study of Allogeneic Transplantation for Older Patients with AML in First Complete Remission Using a Reduced Intensity Conditioning Regimen: Results From CALGB 100103/BMT CTN 0502 (abstract). *Blood (ASH Annual Meeting Abstracts).* 2012; 120 Abstract 230.
32. Hailemichael E, Kaufman JL, Flowers CR, et al. Do elderly myeloma patients benefit from high dose therapy (HDT) and autologous stem cell transplant (ASCT)? A comparative survival analysis using SEER Registry (abstract). *Blood.* 2012; 120 Abstract 2072.
33. Sorror ML, Sandmaier BM, Storer BE, et al. Long-term outcomes among older patients following nonmyeloablative conditioning and allogeneic hematopoietic cell transplantation for advanced hematologic malignancies. *JAMA.* 2011; 306:1874–83. [PubMed: 22045765]

Clinical Practice Points

- An ACR with rituximab is the treatment of choice for DLBCL based on evidence that demonstrated increased OS; however, in elderly patients, comorbid conditions, decreased drug metabolism, decreased hematologic reserve, and reduced PS can increase the risk of toxicities.
- There are no specific strategies recommended to identify which elderly patients will tolerate anthracyclines.
- In this study predictors of treatment choice were found to include a non-ACR with increased age and decreased LVEF.
- Among elderly DLBCL patients who received an ACR, 14 patients [24%] (out of 59 patients) had a decrease in LVEF, with most (10 patients [17%]) of these only 5% to 10% decreases.
- In patients who received an ACR, 15 patients [33%] (out of 45 patients with this data) were unable to complete treatment as planned.
- Hospitalization was a significant predictor of decreased survival with the most common reason for hospitalization being febrile neutropenia. Patient factors that were associated with hospitalization because of toxicity included increased IPI score of 4 or 5, a need for dose reduction or discontinuation of an agent, treatment delay > 7 days, and reduction in PS.
- Results of this study highlight the significant need for prospective observational and intervention studies in elderly DLBCL patients. Future multicenter studies should focus on pretreatment characteristics outside of age that predict poor response to therapy and poor tolerability, and analyze specific toxicities that lead to hospitalization and their potential effects on outcomes.

Figure 1. Selection of Study Cohort: Overview of the Study Cohort With Reasons for Inclusion/Exclusion Through the Selection Process

Abbreviations: ACR = Anthracycline-Containing Regimen; CNS = Central Nervous System; DLBCL = Diffuse Large B-Cell Lymphoma.

Figure 2.

Kaplan–Meier Survival Curves of DLBCL Patients. (A) Progression PFS Curves of Patients Who Received Either ACR or Non-ACR. (B) OS Curve of Patients Who Received Either ACR or Non-ACR

Abbreviations: ACR = Anthracycline-Containing Regimen; DLBCL = Diffuse Large B-Cell Lymphoma; OS = Overall Survival; PFS = Progression-Free Survival.

Figure 3. Tolerability of Anthracyclines in the ACR Group (n = 59): (A) Decrease in LVEF; (B) Anthracycline Dose Reduction or Removal

Abbreviations: ACR = Anthracycline-Containing Regimen; LVEF = Left Ventricular Ejection Fraction.

Figure 4. Other Markers of Tolerability

Abbreviations: ACR = Anthracycline-Containing Regimen; PS = Performance Status.

Table 1
Patient Demographic Characteristics

Characteristic	ACR	Non-ACR	P
Total Number of Patients (%)	59 (82)	13 (18)	
Age at Diagnosis, Years			.009
Mean	73	77	
Range	65-85	68-92	
Age >70	37 (62)	12 (92)	
Age >80	8 (14)	4 (31)	
Male Sex	36 (61)	7 (52)	.633
White Race	44 (78)	10 (83)	1.000
BSA, m²			.152
Mean	1.88	1.76	
Range	1.43-2.49	1.43-2.08	
ECOG Performance Status			.116
0-1	48 (91)	7 (70)	
2	4 (8)	2 (20)	
3	1 (2)	1 (10)	
Ann Arbor Staging			.471
I/II	16 (32)	4 (44)	
III/IV	34 (68)	5 (56)	
IPI Range			.290
0-1	10 (21)	4 (50)	
2-3	22 (46)	2 (25)	
4-5	16 (33)	2 (25)	
Modified Charlson Risk Category			.599
Low (0, 1, 2)	45 (90)	9 (81)	
Intermediate (3, 4)	5 (10)	2 (18)	
Baseline LDH > ULN	24 (50)	4 (40)	.825
Baseline LVEF			<.001
Mean	60	45	
Range	46-75	30-55	

Abbreviations: ACR = anthracycline containing regimen; BSA = body surface area; ECOG = Eastern Cooperative Oncology Group; IPI = International Prognostic Index; LDH = lactate dehydrogenase; LVEF = left ventricular ejection fraction; ULN = upper limit of normal.

Table 2**Treatments**

ACR	n (%)
CHOP	48 (81)
EPOCH	6 (10)
HyperCVAD	3 (5)
Other	2 (3)
Rituximab	58 (98)
Initial G-CSF	27 (46)
Radiation	12 (20)
IT chemotherapy	12 (20)
Non-ACR	
COEP	3 (23)
CVP	1 (8)
Other	5 (38)
Rituximab	8 (61)
Initial G-CSF	1 (8)
Radiation	6 (46)
IT chemotherapy	1 (8)

Abbreviations: ACR = anthracycline containing regimen; CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; COEP = cyclophosphamide, vincristine, etoposide, prednisone; CVP = cyclophosphamide, vincristine, prednisone; EPOCH = etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin; G-CSF = growth colony stimulating factor; HyperCVAD = dexamethasone, cyclophosphamide, vincristine, doxorubicin, methotrexate, cytarabine; IT = intrathecal.

Table 3
Response Rates at Completion of Initial Regimen

Response	ACR, n (%)	Non-ACR, n (%)	<i>P</i>
Complete Response	38 (68)	4 (50)	.246
Partial Response	9 (16)	1 (13)	
Stable Disease	3 (5)	0	
Progressive Disease	5 (9)	3 (38)	
Mixed Response	1 (2)	0	

Abbreviation: ACR = anthracycline containing regimen.