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Disease Characteristics, Patterns of Care, and Survival in Very Elderly Patients with Diffuse Large B-Cell Lymphoma

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An abstract of
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Abstract

Disease Characteristics, Patterns of Care, and Survival in Very Elderly Patients with Diffuse Large B-Cell Lymphoma
By Jessica Nicole Williams

Background: Patients >80 years old have the highest incidence of diffuse large B-cell lymphoma (DLBCL), but are rarely included in DLBCL studies. Although rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) is considered standard therapy for DLBCL, patterns of R-CHOP use and its impact on survival in patients >80 years old are less clear.

Methods: We used the Surveillance, Epidemiology, and End Results (SEER)-Medicare database to characterize presentation, treatment, and survival patterns in elderly DLBCL patients diagnosed from 2004-2009. Chi-squared tests compared characteristics and initial treatments of DLBCL patients >80 years old versus patients aged 66-80 years. Multivariable logistic regression models examined factors associated with treatment selection in patients >80 years old; multivariable Cox proportional hazards models examined the relationship between treatment regimen and survival.

Results: Among 3,513 elderly patients with DLBCL, 922 (26%) were >80 years old. Patients >80 years old were less likely to receive R-CHOP and more likely to be observed or receive cyclophosphamide, vincristine, and prednisone (CVP) with or without rituximab. Marital status, performance status, and disease site were associated with initial receipt of R-CHOP in patients >80 years old. In multivariable Cox proportional hazards models that used observation as the reference category, R-CHOP for >4 cycles was associated with the most favorable overall survival (hazard ratio 0.39; 95% confidence interval 0.28-0.54).

Conclusions: Although DLBCL patients >80 years old were less likely to receive R-CHOP, this regimen conferred the most optimal overall survival and should be considered for this population. Future studies should aim to characterize the impact of DLBCL treatment on quality of life in this age group.

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INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma (NHL) in the western world (1). It is also a disease of the elderly, with a median age at diagnosis of 70 years (2) and an incidence that rises with increasing age (3). As the United States (U.S.) population ages, the percentage of persons over 64 years of age is projected to increase from 14.8% in 2015 to 20.3% in 2030 (4). Moreover, the number of people aged at least 80 years in the U.S. is expected to increase from 11.5 million in 2010 to 12.8 million by 2020 (5). An older population coupled with an age-associated increase in DLBCL incidence will lead to a greater clinical need for management of DLBCL in the very elderly, defined in this study as individuals older than 80 years.

This expected increase in DLBCL in the very elderly warrants a determination of current treatment patterns and the most effective management strategies for this population. Although DLBCL patients >80 years old are rarely included in clinical trials or epidemiological studies, there is some evidence that the standard-of-care regimen of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) recommended for younger patients should also be used for this age group (6-13). Previous studies have identified DLBCL treatment disparities based on race and insurance status (14, 15), but age-related disparities have not been studied comprehensively.

The goal of the present study was to address existing knowledge gaps by assessing presentation, treatment, and survival patterns in a large U.S. population-based cohort of elderly DLBCL patients. This involved comparing characteristics and initial treatment

regimens of patients aged >80 years old versus those aged 66-80 years. Additionally, we examined determinants of treatment selection and survival in DLBCL patients aged >80 years old.

METHODS

Data Source

We used data from the National Cancer Institute's (NCI) Surveillance, Epidemiology, and End Results (SEER) program linked to Medicare claims from 2004 through 2009. The SEER program collects and reports cancer incidence and survival data on approximately 28% of the U.S. population (16). The program started in 1973 with 9 registries and gradually expanded to its current size of 18 SEER sites, which collect information on patient demographics, tumor histopathology, disease stage, primary site of tumor, initial surgical and radiation treatment, and both date and cause of death. The main disadvantage of SEER data is a lack of information on chemotherapy; however, this limitation can be addressed by linking cancer registry information with Medicare claims.

Among persons at least 65 years of age, 97% are Medicare-eligible and 93% of SEER cases in this age category are linked to the Medicare enrollment files (17). At the time of this study, the linked database included all Medicare-eligible individuals who appeared in SEER through 2009, and their Medicare claims through 2010. Since the SEER-Medicare database does not include patient identifiers, this study did not require Institutional Review Board approval; however, a data use agreement was signed prior to initiating the analyses.

Eligibility Criteria

Patients were eligible for analysis if they were diagnosed with DLBCL between January 1, 2004 and December 31, 2009, and were aged at least 66 years at diagnosis. The minimum required age was 66 years in order to ensure that patients had been enrolled in Medicare for at least 12 months prior to diagnosis. DLBCL cases were identified using the World Health Organization (WHO) International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) histology codes 9680 and 9684 (18). The following regimens within 6 months of diagnosis were evaluated in this study: CVP (cyclophosphamide, vincristine, and prednisone), R-CVP (rituximab plus CVP), CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), R-CHOP, and no recorded treatment (observation). Cases were excluded if they were identified from autopsy or death certificates, had conflicting SEER and Medicare dates of death, died within 6 months of diagnosis, had therapy initiated >45 days before reported diagnosis, had interrupted Medicare coverage, or were enrolled in a health maintenance organization (HMO) from 12 months before to 6 months after diagnosis.

Patient Characteristics

The study population was divided into two groups based on age at diagnosis (66-80 years old vs. >80 years old). Race was classified as Caucasian or non-Caucasian. The non-Caucasian group consisted of African-Americans and those of "other" race; in SEER data, "other" refers to Asians, Native Americans, Pacific Islanders, or Alaska Natives (19). Although individual-level socioeconomic status (SES) data are not available, the SEER-Medicare file includes information on the socioeconomic characteristics of each patient's census tract. These data are derived from the 2000 U.S. Census and include the percentage of residents living in poverty and the percentage with only a high school

education, the two parameters used in previous SEER-Medicare studies (20-22). Other demographic variables included in this study were sex, marital status (single, married, widowed, or unknown), and type of geographical area (non-urban/rural, urban, or metropolitan).

Each DLBCL case was also classified with regard to Ann Arbor stage (I/II, III/IV, or unknown), primary site of disease (nodal or extranodal), performance status (poor or not poor), NCI Comorbidity Index score (0, 1, or ≥2), and year of diagnosis. Performance status was classified as poor if a patient had claims for any of the following: hospice, home health agency, skilled nursing facility, oxygen, or wheelchair/related supplies. Similar claims-based measures of performance status have been used in other studies (23-26). NCI Comorbidity Index scores were calculated using the Deyo adaptation of the Charlson Comorbidity Index (CCI) to identify from Medicare claims the 15 non-cancer comorbidities included in the CCI (27, 28).

Treatment and Mortality Classification

Initial DLBCL therapy was ascertained from Medicare claims within 6 months of diagnosis; observation was defined as no treatment within this time frame. Because information regarding the receipt of oral medications without an intravenous equivalent is not available in SEER-Medicare, patients were assumed to have received prednisone when their claims data included the other components of CHOP or CVP.

Date and cause of death were obtained from SEER to ascertain vital status. Since SEER only reports month and year of diagnosis, date of diagnosis for survival analyses was assigned as the 15th day of the reported month of diagnosis. Patients were followed until

death, enrollment in an HMO, or last date of available Medicare claims. Patients diagnosed in 2009 were excluded from the survival analysis to allow a minimum follow-up of one year.

Statistical Analysis

Characteristics of persons >80 years old were compared to those in individuals 80 years of age or younger using chi-squared tests. Multivariable logistic regression models were employed to investigate the relationships between patient characteristics and initial R-CHOP therapy, with results expressed as adjusted odds ratios (OR) with 95% confidence intervals (CI). The logistic regression models adjusted for sex, race, marital status, percent in census tract living in poverty, percent in census tract with only a high school education, stage, primary site of disease, NCI comorbidity index score, and performance status.

Cox proportional hazards models assessed the effect of treatments on OS, and were adjusted for the same variables described above, as well as age at diagnosis. All variables were tested for the proportional hazards assumption. Race was the only variable that violated this assumption, and thus the final Cox model was stratified on race. For all analyses, a two sided α-error was set equal to 0.05. Data were analyzed using SAS 9.4 (Cary, NC).

RESULTS

Patient Characteristics

A cohort of 3,513 DLBCL patients was identified, including 922 patients (26%) >80 years old at diagnosis. The mean and median ages at diagnosis in the sub-cohort of patients >80 years old were 85 and 84 years, respectively. The corresponding mean and median estimate for those ≤80 years of age was 73 years. Characteristics of patients in each age category are displayed in Table 1. Compared to patients ≤80 years old, those >80 years old were more likely to be female, widowed, live in a metropolitan area, have extranodal disease, and have poor performance status; patients >80 years old were less likely to have late stage disease and to live in a census tract with >25% of residents completing high school only (all $p<0.05$).

Treatment Selection

Compared to patients ≤80 years old, those >80 years of age were more likely to undergo observation and less likely to receive R-CHOP or CHOP ($p<0.0001$) [Table 2]. Patients over the age of 80 years were also more likely to receive CVP or R-CVP ($p<0.0001$).

As shown in Table 3, among patients >80 years old, the initial receipt of R-CHOP was more commonly associated with being married (reference single; OR 1.65, 95% CI 1.23-2.21). The initial receipt of R-CHOP was less common in patients with extranodal disease (reference nodal disease; OR 0.62, 95% CI 0.46-0.82) and in those with poor performance status (reference not poor; OR 0.59, 95% CI 0.43-0.79).

Survival Analyses

In the multivariable Cox proportional hazards model with observation as the reference category (Table 4), R-CHOP for >4 cycles was associated with the most favorable OS (HR 0.39, 95% CI 0.28-0.54). Other treatment regimens associated with significantly

better OS were R-CHOP for ≤4 cycles (HR 0.53, 95% CI 0.41-0.68) and CVP with or without rituximab (HR 0.55, 95% CI 0.41-0.75).

DISCUSSION

In this study, we examined treatment patterns and outcomes in very elderly DLBCL patients using data from a national cohort treated with modern chemoimmunotherapy. Somewhat unexpectedly, we found that standard-of-care R-CHOP was the most common initial management strategy in this age group (53% of patients). These data indicate a rather widespread application of the best available evidence for DLBCL to the very elderly population following the 2002 publication of a randomized controlled trial demonstrating the superiority of R-CHOP over CHOP in patients >60 years of age (29). It is also worth noting that approximately one-quarter of patients over the age of 80 years had no initial therapy recorded in the 6 months following diagnosis.

R-CHOP use in the very elderly varied with marital status, disease site, and performance status. Married patients were more likely to receive R-CHOP than those who were single, an observation most likely explained by differences in social and family support. Our findings are in agreement with several previous studies indicating that married patients had lower mortality from various cancers, including DLBCL (30-33).

The observation of survival benefit in patients initially treated with CVP with or without rituximab relative to those who underwent observation is supported by previous studies describing improved survival in elderly DLBCL patients treated with non-anthracycline-based chemoimmunotherapy. Prior SEER-Medicare studies found that among DLBCL patients >65 years old, those who received non-anthracycline-based

chemoimmunotherapy had similar 3-year OS as those who received anthracycline-based chemotherapy without rituximab (34, 35). The present study confirms these findings using more recent SEER-Medicare data that controls for performance status.

Although DLBCL treatment patterns and outcomes in very elderly patients previously have not been well-characterized, there is some prior evidence that this group may benefit from standard treatment. A 1999 study found no difference in 5-year OS between DLBCL patients who were ≥80 years old and their younger counterparts (6). A phase II clinical trial found that among very elderly DLBCL patients with an Eastern Cooperative Oncology Group performance status of 0-2, low-dose R-CHOP conferred a survival benefit and was well-tolerated (7). Another previous study showed that DLBCL patients aged 80 years and older experienced marked improvement in survival with the advent of rituximab, indicating that the benefits of chemoimmunotherapy may apply across all age groups (8).

In a more recent population-based but relatively small study, Varga and colleagues reported that DLBCL patients ≥80 years of age (n=40) were significantly less likely to be treated with standard therapy and had significantly lower 1-year OS and event-free survival than similar 20-79 year old DLBCL patients (9). Another finding of that study was significantly better OS in those who received standard therapy relative to those who received no treatment, an observation confirmed in another study of DLBCL patients aged 75 years and older (10). Additionally, studies examining outcomes in very elderly patients with NHL have emphasized that standard treatments should be considered in this population to improve survival (11-13).

A notable feature of the present study is the use of data on a large national cohort of DLBCL patients with validated SEER demographic and clinical information. Importantly, using claims data only may overestimate the proportion of patients who undergo observation, since some of these patients may have instead received oral chemotherapy or other regimens not captured by their Medicare claims. Thus, using observation as a reference category in the survival analyses provides a conservative estimate of the relative benefits of the treatment regimens. In contrast to a prior National Cancer Data Base study on the diffusion of chemoimmunotherapy over time (14), the current study contained more detailed information on the type of chemoimmunotherapy given and provided more complete capture of rituximab use.

This study also has some limitations. First, claims data were used to indirectly assess comorbidity, performance status, and treatment, and information on treatment dose was lacking. We partially addressed this limitation by evaluating survival according to the number of R-CHOP treatment cycles. These analyses revealed that R-CHOP for >4 cycles was associated with a particularly high OS in very elderly DLBCL patients. Additionally, since patients who died within 6 months of diagnosis were excluded, the results of the present study may not be generalizable to elderly patients with the most advanced disease or the most severe comorbidity profile.

In conclusion, DLBCL patients over 80 years old were less likely than younger patients to receive R-CHOP and were more likely to undergo observation or receive R-CVP. In keeping with the previously reported findings among younger patients, the benefits of R-CHOP were also evident in very elderly individuals newly diagnosed with DLBCL. CVP with or without rituximab also appeared to be an effective treatment in DLBCL patients

>80 years old, and may serve as a viable treatment alternative in this population. Further studies are needed to characterize the impact of DLBCL treatment on quality of life in very elderly patients, and treatment algorithms should be developed to help guide therapy in this population.

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TABLES

Table 1. Characteristics of patients aged >80 years old (n=922) versus those aged 66-80 years (n=2,591).

Variable	**Age ≤80 years N (%)**	**Age >80 years N (%)**	**χ^2 p-value[1]**
Sex			
Male	1,286 (49.6)	391 (42.4)	0.0002
Female	1,305 (50.4)	531 (57.6)	
Race			
Caucasian	2,301 (88.8)	832 (90.2)	0.2295
Non-Caucasian	290 (11.2)	90 (9.8)	
Stage			
I/II	1,366 (52.7)	503 (54.6)	0.0041
III/IV	1,069 (41.3)	339 (36.8)	
Unknown	156 (6.0)	80 (8.7)	
Primary site of disease			
Nodal	1,705 (65.8)	572 (62.0)	0.0398
Extranodal	886 (34.2)	350 (38.0)	
Performance status			
Poor	420 (16.2)	249 (27.0)	<0.0001
Not poor	2,171 (83.8)	673 (73.0)	
Comorbidity index score			
0	1,571 (60.6)	544 (59.0)	0.6066

1	654 (25.2)	237 (25.7)	
≥2	366 (14.1)	141 (15.3)	
Marital status			
Married	1,621 (62.6)	394 (42.7)	<0.0001
Single	357 (13.8)	78 (8.5)	
Widowed	481 (18.6)	394 (42.7)	
Unknown	132 (5.1)	56 (6.1)	
% in census tract who completed high school only[2]			
≤25%	1,126 (43.6)	439 (48.0)	0.0224
>25%	1,456 (56.4)	476 (52.0)	
% in census tract living in poverty[2]			
<20%	2,255 (87.3)	805 (88.0)	0.6134
≥20%	327 (12.7)	110 (12.0)	
Type of geographical area			
Non-urban/rural	309 (11.9)	97 (10.5)	0.0324
Urban	158 (6.1)	38 (4.1)	
Metropolitan	2,124 (82.0)	787 (85.4)	
Year of diagnosis			
2004	456 (17.6)	147 (15.9)	0.4622
2005	418 (16.1)	173 (18.8)	
2006	448 (17.3)	152 (16.5)	
2007	428 (16.5)	158 (17.1)	

2008	422 (16.3)	142 (15.4)	
2009	419 (16.2)	150 (16.3)	

1. Chi-squared tests were performed to compare patient characteristics of those older than 80 years versus those aged 66-80 years.

2. 16 patients were excluded due to low cell counts.

Note: percentages may not add up to 100.0% due to rounding.

Table 2. First-line management strategies of patients aged >80 years old (n=922) versus those aged 66-80 years (n=2,591).

First-line management strategy	**Age ≤80 years N (%)**	**Age >80 years N (%)**	**χ^2 p-value[1]**
Observation	286 (11.0)	244 (26.5)	<0.0001
CVP	17 (0.7)	15 (1.6)	
R-CVP	137 (5.3)	143 (15.5)	
CHOP	121 (4.7)	35 (3.8)	
R-CHOP	2,030 (78.4)	485 (52.6)	

1. Chi-squared tests were performed to compare management strategies of those older than 80 years versus those aged 66-80 years.

Note: CVP=cyclophosphamide, vincristine, and prednisone; R-CVP=rituximab, cyclophosphamide, vincristine, and prednisone; CHOP=cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CHOP=rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone

Table 3. Multivariable logistic regression results for R-CHOP vs. others as first-line management in patients greater than 80 years old (n=922).

Variable	**OR (95% CI)**	**p-value**
Sex		
Male	Reference	
Female	1.17 (0.87-1.57)	0.3054
Race		
Caucasian	Reference	
Non-Caucasian	0.78 (0.49-1.23)	0.2767
Stage		
I/II	Reference	
III/IV	1.18 (0.88-1.57)	0.2641
Primary site of disease		
Nodal	Reference	
Extranodal	0.62 (0.46-0.82)	0.0008
Performance status		
Not poor	Reference	
Poor	0.59 (0.43-0.79)	0.0005
Comorbidity index score		
0	Reference	
≥2	0.92 (0.63-1.34)	0.6686
Marital status		

Single	Reference	
Married	1.65 (1.23-2.21)	0.0009
% in census tract who completed high school only		
≤25%	Reference	
>25%	0.78 (0.60-1.03)	0.0764
% in census tract living in poverty		
<20%	Reference	
≥20%	0.74 (0.49-1.13)	0.1655

Note: R-CHOP=rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; OR=odds ratio; CI=confidence interval

Table 4. Treatment-associated survival analysis in patients greater than 80 years old, with adjusted Cox proportional hazard ratios (n=772).

Initial treatment regimen	**OS HR (95% CI)**
Observation	Reference
CVP +/- R*	0.55 (0.41-0.75)
CHOP	0.74 (0.45-1.22)
R-CHOP (≤4 cycles)*	0.53 (0.41-0.68)
R-CHOP (>4 cycles)*	0.39 (0.28-0.54)

Note: OS=overall survival, HR=hazard ratio; CI=confidence interval; CVP=cyclophosphamide, vincristine, and prednisone; R=rituximab; CHOP=cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CHOP=rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone

Note: * denotes statistical significance.

Note: Patients diagnosed in 2009 were excluded from this analysis in order to allow at least 1 year of follow-up.