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Clinical Outcomes, Treatment Toxicity, and Health Care Utilization in Older Adults with Aggressive Non-Hodgkin Lymphoma

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Disclosures of potential conflicts of interest may be found at the end of this article.

Abstract

Background. Although balancing treatment efficacy with risks of complications is critical for older adults with aggressive non-Hodgkin lymphoma (NHL), few studies have described these patients' clinical outcomes, rates of toxicities, and health care utilization.

Methods. We conducted a retrospective analysis of adults ≥65 years diagnosed with aggressive NHL and receiving systemic therapy at Massachusetts General Hospital from April 2000 to July 2020. We abstracted patient characteristics, clinical outcomes, treatment toxicity, unplanned hospitalizations, and intensive care unit (ICU) admissions within 6 months of treatment initiation from the medical record. Using multivariable logistic regression, we examined factors associated with rates of grade 3 + nonhematologic toxicity and unplanned hospitalization.

Results. Among 295 patients (median age, 73 years; 39.0% female), 5-year overall survival (OS) was 74.2%. Five-year OS by age group (65–69, 70–74, 75–79, and 80+ years) was

82.2%, 72.0%, 73.6%, and 66.4%, respectively. Overall, 42.4% experienced grade 3+ toxicity, with 8.1% experiencing grades 4–5. The rates of unplanned hospitalization and ICU admission were 41.0% and 6.1%, respectively. In multivariable analysis, hypoalbuminemia (odds ratio [OR], 4.29; $p < .001$) and high comorbidity score (OR, 4.22; $p < .001$) were associated with likelihood of grade 3+ toxicity. Hypoalbuminemia (OR, 2.83; $p = .003$), high comorbidity score (OR, 3.93; $p = .001$), and receipt of EPOCH (etoposide, prednisone, vincristine, cyclo-phosphamide, doxorubicin; OR, 5.45; $p = .012$) were associated with likelihood of unplanned hospitalization.

Conclusions. The majority of older adults receiving upfront therapy for aggressive NHL survive beyond 5 years, yet nearly half experience substantial treatment toxicities and unplanned hospitalizations. Our findings underscore the need for supportive care interventions to enhance the care experience of this population. *The Oncologist* 2021;26:965–973

Implications for Practice: The results of this study highlight the potential benefits of intensive chemoimmunotherapy for the majority of older adults with aggressive non-Hodgkin lymphoma, even at advanced ages. Nearly half of older adults experienced substantial treatment toxicities and unplanned hospitalizations, emphasizing the unmet need for supportive care interventions in this population. The present study also identified hypoalbuminemia and patient comorbidity score as factors associated with grade 3+ nonhematologic toxicity and unplanned hospitalization. These findings may guide the development and implementation of targeted supportive care interventions in high-risk older adults with aggressive non-Hodgkin lymphoma.

Introduction

Aggressive non-Hodgkin lymphoma (NHL) represents the most common lymphoid malignancy and frequently affects older adults [1]. In 2019, aggressive NHL in patients aged 65 years and above accounted for approximately a quarter

of all the estimated 74,000 new NHL cases in the U.S. [2, 3]. Treatment of aggressive NHL often requires intensive chemotherapy or chemoimmunotherapy, which is potentially curative but can result in substantial toxicities [4, 5]. Thus, aggressive NHL represents a malignancy that is prevalent and highly problematic for the geriatric oncology population.

Older adults with aggressive NHL have unique care needs that can impact their tolerance of intensive treatment [6, 7]. Older adults often have multiple comorbid conditions, altered physical function and nutritional status, and impaired metabolism of chemotherapeutic agents [7, 8]. However, older adults with lymphoma are often undertreated [9, 10]. Importantly, the relative dose intensity to maximize survival for older patients with diffuse large B-cell lymphoma (DLBCL), the most common subtype of aggressive NHL, is unclear, as some studies have demonstrated an association between augmented relative dose intensity and prolonged survival, whereas others have shown similar survival with less intensive treatment approaches for frail patients [11, 12]. Therefore, oncologists must balance the curative potential of therapy with the risks of toxicities and intensive health care use when discussing risks and benefits of treatment decisions in older adults. Yet, older adults are underrepresented in clinical trials of lymphoma therapies, resulting in a lack of data to guide discussions regarding specifics for this unique geriatric oncology population [13]. Moreover, age alone is often used to aid treatment decision-making in older adults [10], and we lack information identifying the factors beyond age alone that may predict for treatment toxicity, which is necessary for informed decision-making and treatment selection. Thus, a critical need exists for evidence describing the complications of older adults receiving treatment for aggressive NHL and identifying factors associated with the ability to tolerate treatment.

In this study, we sought to describe the clinical outcomes, treatment toxicity, and health care utilization of older adults treated for aggressive NHL and to identify factors associated with augmented treatment toxicity and health care utilization. By developing a greater understanding of which older patients with aggressive NHL may be at higher risk for experiencing adverse treatment effects, this study will provide important new data to guide informed decision-making and ultimately improve the outcomes and care delivery for this unique geriatric oncology population.

MATERIALS AND METHODS

Study Design

We conducted a retrospective analysis of consecutive adult patients aged ≥65 years with a new diagnosis of aggressive NHL receiving initial systemic treatment with chemotherapy or chemoimmunotherapy at the Massachusetts General Hospital (MGH) between April 2000 and July 2020. Consolidative radiation was permitted. We excluded patients with an indolent histology and those not receiving systemic therapy. We identified the eligible cohort through the MGH Research Patient Data Registry database, which stores clinical data for 6.5 million individuals who receive their care from Mass General Brigham providers in Massachusetts. We used aggressive NHL diagnoses codes to identify

patients treated for aggressive NHL, which we confirmed by manual chart review. We received approval for this study from the Dana-Farber/Harvard Cancer Center Institutional Review Board.

Clinical Information

We abstracted information from the electronic health record through a comprehensive chart review conducted by a trained research coordinator under the supervision of an oncologist (P.C.J.) who confirmed outcomes requiring clinical interpretation. We collected patients' demographics, Eastern Cooperative Oncology Group (ECOG) performance status (date nearest to the date of treatment initiation), comorbidity score (Charlson comorbidity index excluding the patients' lymphoma diagnosis) [14], lymphoma diagnosis, date of diagnosis, date of treatment initiation, stage, baseline serum lactic acid dehydrogenase (LDH) and albumin (closest to date of diagnosis), systemic therapy received, whether or not central nervous system (CNS) prophylaxis was given with intravenous or intrathecal methotrexate, and duration of follow-up.

Clinical Outcomes and Health Care Utilization

We obtained information regarding presence and grade of nonhematologic toxicities (given that treatment regimens are sometimes intentionally dosed to induce grade 4 neutropenia in this population) and organ system involved, presence of dose reduction following initiation of therapy, frequency and dates of treatment interruption, response to treatment, and duration of follow-up. We calculated the rates of grade 3–5 nonhematologic toxicities, grade 4–5 nonhematologic toxicities, and rates of dose reduction and/or treatment interruption (defined as any delay in treatment of 1 week or more). Toxicities were graded by the Common Terminology Criteria for Adverse Events version 5.0. We included toxicities for all patients receiving first-line therapy, including those who receive an initial cycle but then switch to a different therapy based on clinical and molecular factors (e.g., starting with CHOP [cyclophosphamide, doxorubicin, vincristine, and prednisone] with rituximab and switching to EPOCH [etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin] with rituximab if high-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements were confirmed). However, we did not include toxicities related to second-line therapy for those who progress. We also collected survival data. For health care utilization, we obtained the frequency and dates of hospitalizations and intensive care unit (ICU) admissions within the first 6 months following treatment initiation. Hospitalizations for initial lymphoma presentation were not included. We reviewed the discharge summaries of hospital readmissions to determine the primary reason for each hospital readmission. We adapted a coding schema previously developed in patients with leukemia to determine reasons for hospital readmissions [15]. The reasons for hospital readmissions in the schema for our study included symptoms, fever without a source, febrile neutropenia, confirmed infection, dehydration/electrolyte abnormalities, planned hospitalization, hospitalization due to a noncancer medical condition, and cancer progression. We used symptoms as the reason for hospital admission when the admission was for symptom management, all other causes of admission were excluded, or no primary etiology of the admission was defined.

Statistical Analysis

We used descriptive statistics to summarize patients' sociodemographic and clinical characteristics, rates of toxicities, dose reductions, treatment interruptions and/or 1 week or longer treatment delay, and response. We calculated overall survival (OS) using the Kaplan-Meier method. We defined OS as the time from the date of diagnosis until the date of death from any cause. Data from patients who were alive were censored on the date of the last assessment. Estimates of OS at 5 years were obtained from Kaplan-Meier curves. We calculated median follow-up with the reverse Kaplan-Meier method. We used descriptive statistics to describe health care utilization (ICU admission and unplanned hospital admission within 6 months of treatment initiation) for all patients in this cohort and to characterize rates of toxicities, health care utilization, and survival by age bracket (grouped as 65–69, 70–74, 75–79, and 80+). Age brackets of 5 years have been used in other studies of older adults with lymphoma [16, 17].

We also assessed factors associated with the rates of (a) grade 3–5 nonhematologic toxicity (yes vs. no) and (b) unplanned hospitalization within 6 months of treatment initiation (yes vs. no) given the clinical importance of these outcomes. We used multivariable logistic regression to examine the association between patient demographics and clinical factors and these binary outcomes of interest [18, 19]. We first conducted univariate analyses to assess the association between patient demographic (age, sex, race, marital status) and clinical factors (ECOG performance status, comorbidity score; dichotomized to <2 versus ≥2 consistent with prior work) [11], advanced stage, hypoalbuminemia (defined as <3.5 g/dL consistent with prior work) [20], elevated LDH (≥250 U/L consistent with prior work) [21], diagnosis (DLBCL vs. all other histologies), treatment regimen (reduced-dose CHOP [mini-CHOP] with or without rituximab, CHOP with or without rituximab, EPOCH with or without rituximab, or other), and CNS prophylaxis (yes or no) with the binary outcomes of interest. We selected covariates a priori based on previous studies demonstrating that these covariates correlate with prognosis and/or rates of toxicities in aggressive NHL [22–27]. We then conducted multivariable logistic regression analyses including all covariates with a value of $p < .25$ in univariate analyses [28, 29]. We included treatment regimen in the multivariable model of grade 3–5 nonhematologic toxicity given the established association of treatment regimen with grade 3–4 adverse events [26]. All reported p values are two-sided with values of $p < .05$ considered statistically significant. We performed statistical analyses using Stata version 14.2 (StataCorp, College Station, TX).

RESULTS

Study Participants

Table 1 describes the sociodemographic and clinical characteristics of the patients ($n = 295$) in this study. The median age was 73 (range, 65–100 years; 96/295 or 32.5% were aged 65–69; 77/295 or 26.1% were aged 70–74; 59/295 or 20.0% were aged 75–79; 63/295 or 21.4% were aged 80+ years). The majority of patients were male (180/295, 61.0%), White (265/295, 89.8%), and married or with a life partner (195/295, 66.1%). Most patients (245/295, 83.1%) had an

ECOG performance status of 0 or 1. The most common lymphoma diagnosis was de novo DLBCL/grade 3B follicular lymphoma (204/295, 69.2%), followed by indolent lymphoma transformed to DLBCL (28/295, 9.5%) and high-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements (18/295, 6.1%). Overall, 59.5% of patients had advanced stage disease (175/295), and the median Charlson comorbidity index score was 0 (range, 0–6). Table 2 describes the treatment regimens received by the patients in this study. The majority received CHOP (194/295, 65.8%), followed by EPOCH (50/295, 17.0%) and mini-CHOP (27/295, 9.2%), all with or without rituximab. Approximately one-fifth (53/295, 18.0%) of patients received CNS prophylaxis. The majority of patients (201/295, 68.1%) received six cycles of systemic therapy over approximately 4.5 months of therapy, although the exact duration and whether or not radiation was included varied by patient.

Clinical Outcomes and Health Care Utilization

Table 2 describes the clinical outcomes and health care utilization of the patients in our cohort. The overall response rate was 86.9% (253/291), and the complete response rate was 84.2% (245/291). With a median follow-up of 5.9 years (interquartile range, 3.8–8.4), the rate of 5-year OS was 74.2% (95% confidence interval [CI], 68.4–79.1).

The rate of grade 3–5 nonhematologic toxicities with therapy was 42.4% (125/295), and the rate of grade 4–5 nonhematologic toxicities was 8.1% (24/295). Among those with grade 3–5 nonhematologic toxicities, the most common included febrile neutropenia (40.0%) and infections (33.6%). Death from treatment toxicity occurred in 3.9% (10/295) of patients, and the most common cause of death was infection. Overall, 41.0% (121/295) had an unplanned hospital admission within the first 6 months following initiation of therapy, and 6.1% (18/295) of patients had an ICU admission in the first 6 months after initiation of therapy. Of patients with an evaluable first unplanned hospitalization ($n = 121$), the most common reasons for hospitalization were febrile neutropenia (41.3%), followed by infections (28.1%), other noncancer medication conditions (13.2%), and symptoms (9.1%). Among all patients, 14.9% (44/295) had a therapy dose reduction and/or a dose delay.

Clinical Outcomes by Age Bracket

Among patients aged 65–69, 70–74, 75–79, and 80+ years, rates of 5-year OS were 82.2% (95% CI, 72.4–88.7), 72.0% (95% CI, 59.7–81.1), 73.6% (95% CI, 59.2–83.6), and 66.4% (95% CI, 52.5–77.0), respectively. Grade 3–5 nonhematologic toxicity occurred in 35.4% (34/96), 46.8% (36/77), 50.9% (30/59), and 39.7% (25/63) of patients, respectively, and grade 4–5 nonhematologic toxicity occurred in 3.1% (3/96), 9.1% (7/77), 8.5% (5/59), and 14.3% (9/63) of patients, respectively. Among patients aged 65–69, 70–74, 75–79, and 80+ years, the rates of unplanned hospitalization within 6 months of therapy initiation were 34.4% (33/96), 45.5% (35/77), 47.5% (28/59), and 39.7% (25/63), respectively, and the rates of ICU admission within 6 months of therapy initiation were 3.1% (3/96), 5.2% (4/77), 6.8% (4/59), and 11.1% (7/63), respectively. The rates of dose reduction and/or dose delay were 12.5% (12/96), 16.9% (13/77), 13.6% (8/59), and 17.5% (11/63), respectively.

Table 1. Patient characteristics ($n = 295$)

Characteristic	n (%)
Age, median (range), years	73 (65–100)
Female sex	115 (39.0)
White race[a]	265 (89.8)
Relationship status	
Married/life partner	195 (66.1)
Single	22 (7.5)
Divorced/legally separated	20 (6.8)
Widowed	54 (18.3)
Other/unknown	4 (1.4)
Lymphoma subtype	
DLBCL, GCB subtype	73 (24.8)
DLBCL, non-GCB subtype	61 (20.7)
DLBCL, other/follicular lymphoma grade 3B	70 (23.7)
Indolent lymphoma transformed to DLBCL[b]	28 (9.5)
HGBCL with *MYC* and *BCL2* and/or *BCL6* rearrangement	18 (6.1)
T-cell lymphoma	13 (4.4)
Other	32 (10.9)
ECOG performance status	
0–1	245 (83.1)
2–4	45 (15.3)
Unknown	5 (1.7)
Stage	
Limited	119 (40.5)
Advanced	175 (59.5)
Pretreatment albumin, median (range), g/dL	4 (1.7–5.1)
LDH, median (range), U/L	236 (57–10,850)
CCI score, median (range)	0 (0–6)
Comorbid conditions according to CCI	
Myocardial infarction	9 (3.1)
Congestive heart failure	8 (2.7)
Peripheral vascular disease	4 (1.4)
Cerebrovascular disease (without hemiplegia)	8 (2.7)
Dementia	2 (0.7)
Chronic pulmonary disease	16 (5.4)
Rheumatic disease	10 (3.4)
Peptic ulcer disease	8 (2.7)
Mild liver disease	3 (1.0)
Moderate-severe liver disease	0 (0.0)
Diabetes without complications	30 (10.2)
Diabetes with chronic complications	2 (0.7)
Moderate-severe renal disease	6 (2.0)
Solid tumor malignancy without metastatic disease	18 (6.1)
Solid tumor malignancy with metastatic disease	2 (0.7)
Hematologic malignancy (not including main cancer diagnosis)	2 (0.7)
Acquired immunodeficiency syndrome	0 (0.0)

[a]The race of four patients was not recorded.
[b]Richter's transformation was classified under other.
Abbreviations: CCI, Charlson comorbidity index; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; GCB, germinal center B-cell–like; HGBCL, high-grade B-cell lymphoma, LDH, lactic acid dehydrogenase.

Table 2. Clinical outcomes and treatment

Outcome	All ages (*n* = 295)	65–69 years (*n* = 96)	70–74 years (*n* = 77)	75–79 years (*n* = 59)	80+ years (*n* = 63)
Overall response rate	86.9	85.4	90.9	88.1	83.1[a]
Complete response rate	84.2	84.4	85.7	86.4	80.0[a]
5-year overall survival (95% CI)	74.2 (68.4–79.1)	82.2 (72.4–88.7)	72.0 (59.7–81.1)	73.6 (59.2–83.6)	66.4 (52.5–77.0)
Grade 3 or higher non-hematologic toxicity	42.4	35.4	46.8	50.9	40.0
Grade 4 or 5 non-hematologic toxicity	8.1	3.1	9.1	8.5	14.3
Unplanned hospital admission	41.0	34.4	45.5	47.5	39.7
ICU admission	6.1	3.1	5.2	6.8	11.1
One week or more treatment delay and/or dose reduction	14.9	12.5	16.9	13.6	17.5
Treatment regimen					
Mini-CHOP (±R)	9.2	0	0	3.4	39.7
CHOP (±R)	65.8	69.8	68.8	76.3	46.0
EPOCH (±R)	17.0	17.7	24.7	15.3	7.9
Other	8.1	12.5	6.5	5.1	6.4
CNS prophylaxis	18.0	17.7	19.5	22.0	12.7

[a]Four patients had missing data.

Abbreviations: CI, confidence interval; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CNS, central nervous system; EPOCH, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin; ICU, intensive care unit; mini-CHOP, reduced-dose CHOP; R, rituximab.

Table 3. Multivariable analysis of factors associated with grade 3–5 organ toxicity (*n* = 286)

Variable	Odds ratio (95% CI)	SE	*p* value
Albumin <3.5 g/dL	4.29 (2.12–8.68)	1.54	<.001
Advanced stage	1.73 (0.93–3.22)	0.55	.082
Charlson comorbidity index score ≥ 2	4.22 (1.90–9.36)	1.72	<.001
ECOG performance status	1.35 (0.94–1.94)	0.25	.104
LDH ≥250 U/L	1.14 (0.61–2.13)	0.36	.680
CNS prophylaxis	2.03 (0.99–4.17)	0.74	.054
Female sex	0.70 (0.38–1.30)	0.22	.256
Married	1.60 (0.83–3.07)	0.53	.160
White race	0.57 (0.22–1.49)	0.28	.160
Age category			
65–69 years	Ref	Ref	Ref
70–74 years	1.63 (0.76–3.46)	0.63	.207
75–79 years	2.08 (0.96–4.54)	0.83	.065
80+ years	1.10 (0.43–2.84)	0.53	.532
Diagnosis of DLBCL (de novo or transformed)	0.91 (0.40–2.09)	0.39	.826
Treatment			
Mini-CHOP (±R) (reference)	Ref	Ref	Ref
CHOP (±R)	1.17 (0.36–3.82)	0.71	.795
EPOCH (±R)	2.26 (0.60–8.54)	1.53	.227
Other	1.77 (0.40–7.87)	1.35	.452

Abbreviations: CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CI, confidence interval; CNS, central nervous system; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; EPOCH, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin; LDH, lactic acid dehydrogenase; mini-CHOP, reduced-dose CHOP; R, rituximab.

Factors Associated with Grade 3–5 Toxicity

In univariate logistic regression, ECOG performance status (odds ratio [OR], 1.93; 95% CI, 1.45–2.59; *p* < .001), high comorbidity score (OR, 3.83; 95% CI, 1.95–7.56; *p* < .001), hypoalbuminemia (OR, 5.46; 95% CI, 3.03–9.86; *p* < .001), advanced stage (OR, 2.48; 95% CI, 1.52–4.07; *p* < .001), elevated LDH

Table 4. Multivariable analysis of factors associated with hospitalization

Variable	Odds ratio (95% CI)	SE	p value
Albumin <3.5 g/dL	2.83 (1.43–5.58)	0.98	.003
Advanced stage	1.72 (0.93–3.16)	0.53	.082
Charlson comorbidity index score ≥ 2	3.93 (1.82–8.49)	1.55	.001
ECOG performance status	1.28 (0.90–1.81)	0.23	.168
LDH ≥250 U/L	1.18 (0.64–2.18)	0.37	.586
CNS prophylaxis	1.64 (0.81–3.32)	0.59	.167
Female sex	0.61 (0.33–1.12)	0.19	.110
Married	1.38 (0.73–2.60)	0.45	.319
White race	0.52 (0.21–1.33)	0.25	.171
Age category			
65–69 years	Ref	Ref	Ref
70–74 years	1.47 (0.70–3.08)	0.56	.305
75–79 years	2.00 (0.93–4.31)	0.78	.075
80+ years	1.53 (0.61–3.80)	0.71	.362
Diagnosis of DLBCL (de novo or transformed)	1.37 (0.60–3.11)	0.57	.451
Treatment			
Mini-CHOP (±R) (reference)	Ref	Ref	Ref
CHOP (±R)	1.84 (0.57–5.93)	1.10	.309
EPOCH (±R)	5.45 (1.45–20.5)	3.68	.012
Other	3.77 (0.86–16.5)	2.83	.078

Abbreviations: CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CI, confidence interval; CNS, central nervous system; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; EPOCH, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin; LDH, lactic acid dehydrogenase; mini-CHOP, reduced-dose CHOP; R, rituximab.

(OR, 2.20; 95% CI, 1.37–3.56; $p = .001$), and CNS prophylaxis (OR, 2.22; 95% CI, 1.21–4.06; $p = .010$) were associated with a greater likelihood of grade 3–5 nonhematologic toxicity. In contrast, female sex (OR, 0.60; 95% CI, 0.37–0.97; $p = .036$) and lymphoma subtype of DLBCL (OR, 0.51; 95% CI, 0.29–0.89; $p = .018$) were associated with a lower risk of grade 3–5 nonhematologic toxicity. Age bracket, treatment regimen, marital status, and race were not associated with likelihood of grade 3–5 nonhematologic toxicity.

In multivariable models ($n = 286$), hypoalbuminemia (OR, 4.29; 95% CI, 2.12–8.68; $p < .001$) and high comorbidity score (OR, 4.22; 95% CI, 1.90–9.36; $p < .001$) were both associated with a greater likelihood of grade 3–5 nonhematologic toxicity (Table 3).

Factors Associated with Unplanned Hospitalization

In univariate logistic regression analyses, ECOG performance status (OR, 1.75; 95% CI, 1.33–2.32; $p < .001$), high comorbidity score (OR, 3.65; 95% CI, 1.87–7.12; $p < .001$), hypoalbuminemia (OR, 3.79; 95% CI, 2.16–6.65; $p < .001$), advanced stage (OR, 2.27; 95% CI, 1.38–3.71; $p = .001$), elevated LDH (OR, 2.13; 95% CI, 1.33–3.45; $p = .002$), and CNS prophylaxis (OR, 1.97; 95% CI, 1.08–3.59; $p = .027$) were associated with a greater likelihood of unplanned hospitalization in the first 6 months after initiation of therapy. In contrast, female sex (OR, 0.58; 95% CI, 0.35–0.94; $p = .027$) was associated with a lower risk of unplanned hospitalization in the first 6 months after initiation of therapy. Age bracket, treatment regimen, lymphoma diagnosis, marital status, and race were not associated with likelihood

of unplanned hospitalization in the first 6 months after initiation of therapy.

In multivariable models ($n = 286$), hypoalbuminemia (OR, 2.83; 95% CI, 1.43–5.58; $p = .003$), high comorbidity score (OR, 3.93, 95% CI, 1.82–8.49; $p = .001$), and treatment regimen of EPOCH with or without rituximab (OR, 5.45; 95% CI, 1.45–20.5; $p = .012$) were associated with a greater likelihood of unplanned hospitalization in the first 6 months after initiation of therapy (Table 4).

DISCUSSION

In this study, we found that older adults receiving therapy for newly diagnosed aggressive NHL often experience good survival outcomes, but these patients often experience substantial toxicities and frequent hospitalizations. We demonstrated favorable survival across multiple age brackets and also identified factors associated with greater risk of experiencing toxicities and health care utilization. Our findings underscore the survival benefits of aggressive NHL treatment in older adults, the limitations of using age alone to guide the selection of personalized therapy, and the unmet medical need for interventions to reduce toxicity in this population.

Our results support that a significant majority of older adults with NHL experience durable OS with intensive therapy. Nearly three-quarters of patients in our cohort were alive at 5 years after diagnosis. Furthermore, rates of 5-year survival exceeded 65% in all age brackets, further highlighting the potential benefit of these intensive therapies in older adults

even at advanced ages. Prior studies of adults aged 80 years and older with DLBCL have demonstrated a 2-year survival rate of 59%–63% when treated with chemoimmunotherapy [5, 30]. Our work adds to prior research by including a sample encompassing multiple age brackets across a broad set of aggressive NHL subtypes. Despite these promising survival outcomes in older adults, data suggest that older adults with lymphoma are often undertreated and that age alone is commonly used for treatment decision-making [9, 10]. This is especially important in aggressive NHL, where intensive chemoimmunotherapy is potentially curative in a significant proportion of patients [5]. Our work highlights the potential benefits of intensive chemoimmunotherapy in older adults with aggressive NHL, irrespective of age, and emphasizes the limitations of using age alone as a factor for selecting risk-adapted therapy.

Despite the encouraging survival results in our study, a substantial percentage of patients experienced treatment toxicities, treatment interruptions and delays, and unplanned hospitalizations. Nearly half of the patients in our cohort had grade 3–5 nonhematologic toxicity, and more than 40% experienced an unplanned hospital admission. Moreover, about 15% had a therapy dose reduction and/or treatment interruption. In a randomized study of adults aged 80 years and older with DLBCL, those receiving mini-CHOP with rituximab had a grade 3–5 toxicity rate (including hematologic toxicities) of 66.7% [31]. Furthermore, prior data in older patients with DLBCL over age 80 demonstrated a hospitalization rate of 41% due to adverse events [30]. Our results add to this literature by describing rates of toxicities and health care utilization among older adults with a wide range of aggressive NHL histologies treated outside of a clinical trial setting. By describing clinical outcomes, rates of treatment toxicity, and health care utilization, these findings may aid clinicians in communicating important information about the ramifications of treatment and provide patients with critical information to plan for the future. Our work demonstrates that the burden of treatment toxicity and health care use in this population is significant, underscoring the need for interventions to support patients during their illness course to potentially reduce toxicities. Notably, prior studies in patients with solid tumors have shown that geriatric impairments in functional status and social activities correlate with increased risk of treatment toxicity and chemotherapy interruptions [32]. Thus, incorporating geriatric assessment–guided efforts could help to further identify older adults with aggressive NHL at the highest risk of experiencing adverse clinical outcomes during treatment.

We found that less than 10% of older adults experienced severe complications such as grade 4–5 nonhematologic toxicity or ICU admission within 6 months of treatment initiation. However, as expected, the rates of severe complications were more frequent in those aged 80 years and older. Compared with patients aged 65–69 years, those aged 80 or older had nearly a fivefold higher rate of grade 4–5 nonhematologic toxicity and more than threefold higher rate of ICU admission. These findings are highly relevant, as data on the prevalence of severe complications in older adults with aggressive NHL receiving routine clinical care are sparse. Although severe complications are uncommon even among adults aged 80 years and older, this work highlights the need for novel tools to identify those at the highest risk for poor outcomes

and treatment-related mortality. Future studies in larger cohorts should examine patient-, disease-, treatment-, and geriatric-specific factors that are associated with grade 4–5 toxicities and ICU admissions in this population.

We also identified several clinical factors associated with the risk of grade 3–5 nonhematologic toxicities and unplanned hospitalization. Hypoalbuminemia, patients' comorbidity score, and the use of EPOCH were all significantly associated with a greater likelihood of unplanned hospitalization. Interestingly, hypoalbuminemia and the comorbidity score identified patients at risk of complications beyond traditionally used disease risk factors such as age, performance status, LDH, and stage. Although patients' comorbidities have been shown to increase the risk of morbidity and mortality in patients receiving cancer therapy [33], the mechanisms by which hypoalbuminemia affects clinical outcomes remains unclear. Hypoalbuminemia may relate to nutritional status or disease biology as albumin is a prognostic factor for survival in DLBCL and is affected by proinflammatory mediators including interleukein-6, interleukin-1, and tumor necrosis factor [20, 22, 31, 34–36]. Future work should investigate the potential mechanisms underlying this relationship to identify novel biomarkers to identify those at the highest risk for treatment toxicity. Importantly, hypoalbuminemia and patient comorbidities are clinical factors that could be easily used as triggers to identify patients with aggressive NHL who may benefit from additional supportive care interventions. For example, studies of prehabilitation and rehabilitation programs in patients with solid tumors and hospitalized older adults have shown promise in improving functional status, symptoms, and health care utilization [37–39]. Moreover, incorporating the geriatric assessment in the care of older adults with cancer has been shown to help reduce rates of grade 3–5 toxicities [40]; therefore, the incorporation of geriatric assessments and geriatric interventions for older adults with aggressive lymphomas who have hypoalbuminemia or multiple comorbid conditions may mitigate toxicity and health care utilization and facilitate selection of treatment regimens. Thus, our findings may guide the development and implementation of targeted supportive care interventions in high-risk older adults with aggressive NHL.

Our study has several limitations worth considering. First, this is a retrospective study of patients at a large academic site who were extremely fit with a low number of comorbidities and predominately White, and thus our findings likely underestimate treatment toxicity and health care utilization outcomes and overestimate survival outcomes. Second, we were limited to information about patients' outcomes, toxicity rates, and health care utilization that were available in the medical record, and therefore our data may not have fully captured all clinical outcomes. Third, our sample size limited our ability to assess for factors associated with grade 4–5 treatment toxicity and likelihood of ICU admission. Finally, our data set lacked information from a formal geriatric assessment or patient-reported outcomes, such as quality of life, which are critical factors to understand in this population. Future efforts should prospectively evaluate longitudinal geriatric assessment tools and patient-reported outcomes to identify patients at high risk for treatment toxicities and further guide treatment selection and shared decision-making in older patients with aggressive NHL.

CONCLUSION

We demonstrated that older adults receiving therapy for newly diagnosed aggressive NHL often have favorable survival outcomes, yet these patients frequently experience substantial toxicities and health care utilization. We also identified salient factors associated with greater risk of experiencing grade 3–5 nonhematologic toxicity and unplanned hospitalization within 6 months of treatment initiation. Our findings underscore the need to prospectively identify older adults with aggressive NHL at highest risk for poor clinical outcomes and develop targeted supportive care interventions to improve the care for this unique geriatric oncology population.

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DISCLOSURES

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For Further Reading:
Guru Subramanian Guru Murthy, Aniko Szabo, Mehdi Hamadan. Contemporary Outcomes for Advanced-Stage Classical Hodgkin Lymphoma in the U.S.: Analysis of Surveillance, Epidemiology, and End Results Database. **The Oncologist** 2019;24:1488–1495.

Implications for Practice:
This article evaluates contemporary outcomes for advanced-stage Hodgkin lymphoma (HL) in the U.S. using the Surveillance, Epidemiology, and End Results database. Although overall survival (OS) has improved in each 5-year period since 2000, the 3-year OS from 2010 to 2014 remains inadequate at 81.8% and is limited by patient demographics. New therapies are indicated to improve clinical outcomes in advanced-stage HL.