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B-CELL NHL, T-CELL NHL, AND HODGKIN LYMPHOMA (J AMENGUAL, SECTION EDITOR)

Considerations for the Treatment of Diffuse Large B Cell Lymphoma in the Elderly

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Abstract

Purpose of Review Diffuse large B cell lymphoma (DLBCL) is a curable and common malignancy in elderly population. Elderly patients, especially those 80 and older, have poor outcomes compared with those < 60. This may be due to the disease biology, comorbidities, and/or functional limitations.

Recent Findings Prospective data, and especially randomized data, are limited. The FIL tool objectively categorizes patients as fit, unfit, or frail. Fit and unfit patients can benefit from chemoimmunotherapy with curative intent. Evidence guiding treatment of frail patients is limited, but it appears that frail patients have similar survival regardless of treatment with curative or palliative intent.

Summary For fit and unfit patients, treatment options include rituximab with dose-attenuated CHOP or regimens with adriamycin alternatives if there is concern for cardiovascular adverse effects (AEs). Frail patients are extremely sensitive to toxicity from therapies. Frail patients and those 80 and older could greatly benefit from trials incorporating novel agents.

Keywords Lymphoma · DLBCL · Elderly · Frailty

Introduction

Diffuse large B cell lymphoma (DLBCL) is the most common subtype of Non-Hodgkin's Lymphoma (NHL) and if untreated has a median survival of < 1 year [1, 2]. The median age at diagnosis of DLBCL is 67, and approximately 30% of cases are diagnosed in patients > 70 [3]. Per 2014 Medicare-SEER data, 33% of patients 80 or older with DLBCL do not receive treatment for a potentially curable malignancy [2, 4]. Patients 75 or older are vastly underrepresented in clinical trials, accounting for < 10% of patients enrolled in NCI cooperative group trials [4]. As life expectancy improves, the incidence of NHL has been increasing 8–10% yearly. The population > 75 is expected to triple by 2030, and therefore, elderly patients with DLBCL will quickly comprise a substantial number of oncology patients [1, 3–5].

Gene expression profiling (GEP) has identified 2 groups of DLBCL with different prognoses based on cell of origin: the germinal center (GCB) and the activated B cell (ABC). Increased age is associated with higher genomic complexity, increased expression of the anti-apoptotic protein BCL2, and increased prevalence of the ABC subtype of DLBCL, which is associated with poorer responses to therapy and decreased survival [6]. However, disease biology is likely not the sole explanation for poorer survival in geriatric patients. A recent retrospective analysis of 542 patients with DLBCL showed that when chemoimmunotherapy with curative intent is feasible, relapse rates are independent of age. Cumulative incidences of relapse for chemoimmunotherapy-treated patients at 1 and 4 years were found to be 10% and 20% for patients > 80 and 20% and 29% for younger patients ($p = 0.12$). Additionally, disease-related mortality rates were similar between older and younger patients, 53% vs. 61% ($p = 0.5$) [7].

With increasing age often come multiple comorbidities, reduced functional reserve, and decreased social support [8],

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elderly patients are at increased risk of chemotherapy toxicity with regard to weight loss, nutritional status, and fatigue. It has been demonstrated that large changes in body weight (> 9.3%) after the first cycle of therapy are associated with shorter median and overall survivals [9]. Elderly patients may receive fewer cycles of therapy due to toxicity. A recent retrospective analysis of 100 patients treated with reduced-dose R-CHOP (50–80%) found that relative dose intensity did not affect survival, but number of cycles (less than 6) and Charlson Comorbidity Index (summation of comorbidities that categorizes patients into low-intermediate for scores 0–3 and high risk for score ≥ 4) score ≥ 3 were associated with poorer outcomes [10].

Thus, while DLBCL is a potentially curable malignancy, clinicians are cautious to balance toxicity vs. efficacy in elderly patients, particularly those with multiple comorbidities and/or age 80+. This review aims to (1) discuss the role of comprehensive geriatric assessments in guiding decision making for individual patients and (2) summarize evidence guiding current treatment regimens.

Comprehensive Geriatric Assessments

In the older patient, the goal of maintaining quality of life may exceed the goal of cure or extending life, and assessment of "frailty" often drives therapeutic decision-making. Comprehensive geriatric assessments (CGAs) can include evaluation of functional status, comorbid medical conditions, cognition, psychological state, social support, nutritional status, and concurrent medications [11]. However, many of these assessments are quite time-consuming, and some have components for both patients/caregivers and providers. Thus, CGAs have not been widely adopted into typical clinical practice [12]. As a result, judgment of frailty of the individual patient is typically subjective based on age, comorbidities, and performance status (PS).

The Italian Lymphoma Foundation (FIL) has created a CGA that can be done easily in a busy provider's office. The FIL tool (Table 1) incorporates the Chronic Illness Rating Scale–Geriatric (CIRS-G), Instrumental Activities of Daily Living (IADL), and Activities of Daily Living (ADL) to categorize patients into fit, unfit, or frail [13]. The CIRS-G evaluates function of all organs systems (except for hematological comorbidity) by assigning a comorbidity score between 0 and 4 for each system. Next, patient's independence in ADLs (bathing, dressing, toileting, transferring, feeding, and continence) and IADLs (ability to use telephone, shopping, food preparation, housekeeping, laundry, mode of transportation, responsibility for own medications, ability to handle finances) are assessed, and 1 point is assigned for independence in each activity.

Table 1 FIL tool [13, 14]

	FIT	Unfit	Frail
Age		≥ 80 fit	≥ 80 unfit
ADL	6	5	≤ 4
IADL	8	6–7	≤ 5
CIRS-G	•No organ/system with comorbidity score of 3–4 • AND < 5 comorbidities score 2	• No organ/system with comorbidity score of 3–4 • AND 5–8 comorbidities score 2	• Any organ/system with comorbidity score 3–4 • OR > 8 comorbidities score 2

ADL: 1 point is assigned for independence in each ADL activity (bathing, dressing, toileting, transferring, feeding, and continence) and then points are added; maximum score of 6 and minimum score of 0

IADL: 1 point is assigned for independence in each IADL activity (ability to use telephone, shopping, food preparation, housekeeping, laundry, mode of transportation, responsibility for own medications, ability to hand finances) and then points are added; maximum score of 8 and minimum score of 0

CIRS-G: Each organ/system is evaluated using CIRS-G scale except for hematological and a comorbidity score between 0 and 4 is assigned for each organ/system

(From Tucci et al. [14••], reprinted by permission of Taylor & Francis Ltd.)

A patient is classified as "fit" if age < 80 has a score of 6 for ADLs and a score of 8 for IADLs (1 point assigned for independence in each activity for IADL), and on CIRS-G scale, there are fewer than 5 organ systems with grade 2 comorbidities (and no organ systems with grade 3–4 comorbidities). The patient is classified as "unfit" if he/she is "fit" but age ≥ 80 or if age < 80 with an ADL score of 5, and/or IADL score of 6–7, and/or CIRS-G with no grade 3–4 comorbidities and 5–8 grade 2 comorbidities. All other patients who do not meet the criteria for "fit" or "unfit" are classified as frail [13] (Table 1). This tool can be administered in under 10 min and could be done by a nurse or another trained member of the clinical team.

A prospective study evaluating the FIL tool enrolled elderly patients ages 69 or older [14••]. The FIL tool was applied at the time of enrollment but the treatment regimen was at the investigator's discretion. Among the fit and unfit elderly patients treated with curative intent (R-CHOP like regimen with at least 70% dose intensity), two-year overall survival (OS) was significantly better in fit than in non-fit patients (84% vs. 47%, $p < 0.0001$). Frail patients had inferior OS irrespective of treatment intent (i.e., curative vs. palliative; 2-year OS 44% vs. 39%, $p = 0.75$) [14••]. This suggests that the FIL tool could help select fit and unfit patients for therapy with curative intent and guide clinicians to discuss palliative approaches with frail

patients. Future studies in newly diagnosed elderly patients with DLBCL could be strengthened by prospective, objective assessment of frailty using the FIL tool.

R-CHOP like Regimens with Curative Intent (Table 2)

Regimens with Reduced-Intensity CHOP

The landmark randomized phase III trial by the Groupe d'Etude des Lymphomes del'Adulte (GELA) comparing CHOP to R-CHOP in patients ages 60–80 with newly diagnosed DLBCL showed significant improvement in rates of compete response (CR), progression-free survival (PFS), and OS with addition of rituximab [15]. This lead to R-CHOP becoming the standard of care for the majority of cases of DLBCL [16, 17]. In 2010, GELA published the results of 10-year follow-up with continued improved survival with R-CHOP vs. CHOP (10-year PFS 36.5% vs. 20%; 10-year OS 43.5% vs. 27.6%) [18••]. To date, there has been no widely accepted standard of care for those 80+ or with multiple comorbidities. The majority of regimens studied in these populations have been variations of R-CHOP, either attenuation of chemotherapy doses and/or substituting alternative drugs for adriamycin due to concern for cardiotoxicity.

Rituximab + 70%CHOP

A study published in 2011 looked at rituximab + 70%CHOP (R-70%CHOP) in elderly patients 70 and older compared with a cohort of patients 50–69 receiving full-dose R-CHOP. The rates of CR (R-70%CHOP-79% and standard R-CHOP-78%, $p = 0.7$) and 3-year PFS (R-70%CHOP-64%, R-CHOP-72%, $p = 0.43$) were similar between the two cohorts; however, both the 3-year OS (R-70%CHOP-58%, R-CHOP-78%, $p < 0.05$) and 3-year EFS (R-70%CHOP-45%, R-CHOP-70%, $p < 0.05$) were inferior in the R-70%CHOP cohort. The patients in the R-70%CHOP cohort had comparable rates of thrombocytopenia (grade 4, 8.2% vs. 4.3%) and anemia (grade 4, 4.9% vs. 5.8%), but a higher incidence of paralytic ileus (grade 3+, 13.1% vs. 2.9%). Patients receiving full-dose R-CHOP had a higher frequency of leukopenia (grade 4, 76.8% vs. 60.7%). The rates of fever and infection were comparable in both groups [19]. The authors concluded that R-70%CHOP is a reasonable option for elderly patients as it provides similar CR and PFS with an acceptable toxicity profile.

R-miniCHOP

R-miniCHOP has been a widely accepted approach in very elderly patients with DLBCL based on a single-arm phase II

Table 2 R-CHOP and modified R-CHOP regimens

	Age (median)	Regimen	*n*	Completed cycles	Treatment-related deaths	CR	2-year EFS (%)	2-year OS	5-year PFS	5-year OS	10-year-PFS	10-year-OS
R-CHOP												
Randomized phase III	60–80 (69)	R-CHOP × 8	202	80%	4%	76%	57%	70%	54%	58%	36.50%	43.50%
Coiffier et al. [15, 18••]		CHOP × 8	197	72%	1%	63%	38%	57%	30%	455%	20%	27.60%
R-70%CHOP	Age	Regimen	*n*	Completed cycles	Death during treatment	CR	3-year PFS (%)	3-year OS				
Retrospective, non-matched controls	≥ 70	R-70%CHOP × 6	61	85%	4.90%	79%	64%	58%				
Meguro et al. [19]	50–69	R-CHOP × 6	69	97%	1.40%	78%	72%	78%				
R-miniCHOP	Age	Regimen	*n*	Completed cycles	Treatment-related deaths	CR	median OS	2-year OS				
Singe-arm phase II	80–95	R-miniCHOP × 6	149	72%	8%	62%	29 months	59%				
Peyrade et al. [20••]												

study [20••]. One hundred fifty patients over 80 years old (80–95) with ECOG of 0–2 and without any moderate impairment in organ function were treated with an anticipated 6 cycles of R-miniCHOP (rituximab 375 mg/m^2 IV, cyclophosphamide 400 mg/m^2 IV, adriamycin 25 mg/m^2 IV, vincristine 1 mg/m^2 IV on day 1; prednisone 40 mg/m^2 days 1–5). After a median follow-up of 20 months, the CR rate was 62%, median OS was 29 months, and 2-year OS was 59%. Treatment-related mortality was 8% with the greatest number of deaths in the first 2 cycles. The rate of febrile neutropenia was 8% with only 2% grade 4–5. Authors also calculated OS based on risk factors: albumin, aaIPI (age-adjusted international prognostic index), and IADLs score. Though lower aaIPI and IADLs of 4 were associated with longer survival, higher albumin was the only variable statistically significant for improvement in OS. R-miniCHOP is felt by many to offer a compromise between toxicity and efficacy in patients 80 and older.

Regimens with Adriamycin Alternatives (Table 3)

Patients with history of ischemic heart disease, hypertension, and diabetes mellitus are at increased risk of developing congestive heart failure with anthracyclines, and many elderly patients have one or more of these comorbidities. Of note, the GELA phase III trial of CHOP vs. R-CHOP had a treatment-related mortality of 4%, an 8% rate of grade 3–4 cardiotoxicity, and 14% of deaths secondary to cardiovascular etiology in the R-CHOP arm. Thus, the goal of several trials has been to decrease both treatment-related mortality and cardiotoxicity by incorporating agents other than standard adriamycin into a R-CHOP-like regimen [15, 16, 18••].

R-miniCEOP (Epirubicin)

In 2003, Intergruppo Italiano Linfomi conducted a randomized phase III trial comparing full dose R-CHOP with R-miniCEOP (cyclophosphamide 750 mg/m^2, epirubicin 50 mg/m^2, vinblastine 5 mg/m^2, prednisone 50 mg/m^2 days 1–5) in "fit" elderly patients age > 65 with ECOG PS 0–3 [18••]. "Fit" was defined as ADL score of 6, less than three grade 3 CIRS-G comorbidities, and no grade 4 co-comorbidities (excluding hematologic comorbidities). Overall, results were similar in two groups after median follow-up of 42 months in terms of CR (73%-R-CHOP, 68%-R-miniCEOP, $p = 0.466$), mEFS (48%-R-CHOP, 46%-R-miniCEOP, $p = 0.54$), and 5-year OS (62%-R-CHOP, 63% R-miniCEOP, $p = 0.71$). The toxicity profile was also similar between arms, but there was a higher number of deaths from lymphoma relapse/progression in the R-miniCEOP group (47% vs. 66%, $p = 0.165$). Treatment-related mortality was higher in R-CHOP arm (9.1% vs. 6.1%). Of note, two patients had to discontinue treatment in the R-CHOP arm secondary to cardiac dysfunction, and one patient in the R-miniCEOP arm developed grade 4 arrhythmia [21].

R-COMP

R-COMP (rituximab 375 mg/m^2, cyclophosphamide 750 mg/m^2, non-pegylated liposomal doxorubicin 50 mg/m^2, vincristine 1.4 mg/m^2, and prednisone 100 mg/day, days 1–5) was evaluated in a single-arm, phase II trial of 75 patients, median age of 72 (range 61–83) with left ventricular ejection fraction (LVEF) ≥ 50% [22]. After a median follow-up of 33 months, the CR rate

Table 3 Regimens with adriamycin alternatives

R-miniCEOP	Age (median)	Regimen	*n*	Completed cycles	Treatment-related deaths	CR	5-year EFS	5-year OS	
Randomized phase III	65–86 (72)	R-CHOP × 6	110	85%	9.10%	73%	48%	62%	
Merli et al. [21]		R-miniCEOP × 6	114	84%	6.10%	68%	46%	63%	
R-COMP	Age (median)	Regimen	*n*	Completed cycles	Treatment-related deaths	CR	3-year PFS	3-year EFS	3-year OS
Single arm phase II	61–83 (72)	R-COMP × 8	72	58%	7%	57%	69%	39%	72%
Luminari et al. [22]									
R-CEOP	Age (median)	Regimen	*n*	Completed cycles	Treatment-related deaths	5-year TTP	5-year OS		
Retrospective, matched controls	34–93 (73)	R-CEOP	81	NA	9%	57%	49%		
Moccia et al. [23]		R-CHOP	162	NA		62	64%		
						$p = 0.21$	$p = 0.02$		
R-CGVP	Age (median)	Regimen	*n*	Completed cycles	Treatment-related deaths	CR	2-year-PFS	2-year OS	
Single arm phase II	52–90 (76.5)	R-CGVP × 6	61	51.60%	6.5%	39%	49.80%	55.80%	
Fields et al. [24]									

was 57%, 3-year OS was 72%, and 3-year PFS was 69%. The rate of cardiac toxicity was 21% (all grades) but only 4% ($n = 3$) were grades 3–4 (1 case of atrial fibrillation, 1case of congestive heart failure, and 1 case of cardiac ischemia). One patient's LVEF dropped more than 20%, and a total of 4 patients had to discontinue treatment because of a drop in LVEF.

Subsequently, a randomized phase III study was designed to compare the cardiotoxicity of R-CHOP with R-COMP. Authors measured LVEF before each cycle along with NT-proBNP to evaluate clinical and subclinical cardiotoxicity. The primary endpoint was an improvement of mean LVEF in the R-COMP arm compared with R-CHOP. Eighty-eight patients were randomized with 43 assigned to R-COMP and 45 to R-CHOP. The study did not reach its primary endpoint, but it did show that patients treated with R-COMP were less likely to have LVEF below 50% during treatment (4.6% vs. 15.8%). Additionally, NT-proBNP was normal in 90% of patients treated with R-COMP vs. only 66.7% of patients treated with R-CHOP [25].

R-CEOP (Etoposide)

R-CEOP (rituximab 375 mg/m2, cyclophosphamide 750 mg/m2, etoposide 50 mg/m2 IV on day 1 and then 100 mg/m2 PO on days 2 and 3, vincristine 1.4 mg/m2, and prednisone 50 mg/m2 days 1–5) has been evaluated retrospectively in patients with newly diagnosed DLBCL. Of note, patients who had begun treatment with R-CHOP but then switched to R-CEOP due to intolerance or because of a maximum threshold of anthracycline dosing was reached were also included in the analysis. Outcomes were compared 2:1 with a cohort that was treated with R-CHOP in the same time frame. The 5-year OS for R-CEOP was 49% vs. 64% for R-CHOP ($p = 0.02$), partly because of the comorbidities of patients in the R-CEOP group per the authors. Of note, the patients in the R-CEOP arm who had received partial treatment with anthracycline vs. no anthracycline at all had similar 5-year OS and 5-year TTP ($p = 0.77$)[23].

R-CGVP

In a single-arm phase II multicenter trial, 61 patients (age 52–90, median 76) with either LVEF $\leq$ 50% and cardiac comorbidity (diabetes, ischemic heart disease, or hypertension) or LVEF > 50% were treated with 6 cycles of R-CGVP (rituximab 375 mg/m^2, cyclophosphamide 750 mg/m^2, gemcitabine on days 1 and 8 (initial dose was 750 mg/m^2 and then escalated to 1000 mg/m^2 by cycle 3), vincristine 1.4 mg/m^2, and prednisone 100 mg/day, days 1–5). The CR rate was 39%, and the 2-year PFS and OS were 49.8% and 55.8%, respectively (median follow-up 24.9 months). Fifteen patients had cardiac adverse effects (AEs) of any grade (24.6%, grade 3–5, 16%). Twenty-seven patients died, but most of the deaths were due to lymphoma progression (56%). Six percent of deaths were secondary to treatment and 5% were cardiac-related [22]. The ORR and 2-year OS were higher in patients with LVEF $\leq$ 50% (70.4% and 65.7% vs. 54.3% and 46.1%) [24].

Palliative Regimens (Table 4)

Data guiding treatment options for frail and/or very elderly patients (i.e., > 80) are limited. A retrospective study looked at outcomes of patients > 80 years with both aggressive and indolent NHL who received a variety of therapies. 39.5% of the cases included were DLBCL. Treatments included corticosteroids alone or no treatment (15% for whole cohort, 8.8% for aggressive NHL), monotherapy (single-agent chemotherapy or rituximab; 35%, 22.5%), or polytherapy without anthracycline (18%, 21.6%) or with anthracycline (32%, 47.1%). Two-year OS for the whole cohort was approximately 55% but only 35% for aggressive NHL [31].

Rituximab Single Agent

Upon introduction of rituximab in clinical trials, a phase II study showed response rate of 37% for rituximab as monotherapy in relapsed/refractory (R/R) DLBCL [32]. There is no prospective trial has evaluated efficacy of single-agent rituximab in frontline setting for DLBCL.

Bendamustine + Rituximab

Bendamustine + rituximab (BR) (rituximab 375 mg/m^2 on day1 and bendamustine 120 mg/m^2 on days 2 and 3) has been studied in 2 phase II in frontline trials [26, 27]. Patients enrolled on these trials were deemed ineligible to receive R-CHOP by treating clinicians. Both studies were small (< 25 patients). CR rates were 52% and 54%. The median PFS and OS were both 7.7 months. In both trials, the major toxicity (grade $\geq$ 3) was hematologic (neutropenia, 17–23%). Common non-hematologic grade 3+ toxicities were fatigue (6–17%) and infection (10%). Though the CR rate is lower with BR than R-CHOP, BR is a potential treatment option in frail elderly patients given its toxicity profile.

RCVP

R-CVP (rituximab 375 mg/m^2, cyclophosphamide 750 mg/m^2, vincristine 1.4 mg/m^2, prednisone 40 mg/m^2 days 1–5) has been evaluated retrospectively in 43 patients 80 and older (median age 83, range 80–93) deemed unable to receive anthracyclines. Reasons for wanting to avoid anthracyclines were heterogeneous: ECOG PS 3 (42%), impaired renal function (53%), low LVEF (28%), and impaired hepatic function (16%). The CR rate was 37.2% with 2-year OS rate of 31.9%.

Table 4 Palliative regimens

Bendamustine + rituximab	Age (median)	Regimen	*n*	Completed cycles	Treatment-related deaths	CR	Median PFS	Median OS
Phase II	80–95 (85)	BR × 3 for Stage I/I	14	79%	Not reported	54%	7.7 months	7.7 months
Weidmann et al. [26]		BR × 6 for stage III/IV						
Bendamustine + rituximab	Age (median)	Regimen	*n*	Completed cycles	Treatment-related deaths	CR	Median PFS	Median OS
Phase II	> 65 (80)	Up to 8 cycles	23	47%	17%	52%	5.4 month	10.2 months
Park et al. [27]								
R-CVP	Age (median)	Regimen	*n*	Completed cycles	Treatment-related deaths	CR	Median OS	2-year OS
Retrospective	80–93 (83)	R-CVP × 8	43	58.10%	23%	37.20%	12.6 months	31.90%
Laribi et al. [28]								
R2; relapsed/refractory	Age (median)	Regimen	*n* (no.)	Lymphoma	Treatment-related deaths	CR	Median PFS	Median OS
Phase II	24–84 (66)	Lenalidomide + rituximab	45	DLBCL, FL, tFL	Not reported	22%	3.7 months	10.7 months
Wang et al. [29]			32	DLBCL		22%	2.8 months	10.2 months
R2; relapsed/refractory	Age (median)	Regimen	*n*	Lymphoma	CR	18-month OS rate		
Phase II	74.2(± 9.9)	Lenalidomide + rituximab	23	DLBCL	30%	55.10%		
Zinzani et al. [30]		Lenalidomide maintenance	10	SD or better response	10%	–		

Median PFS was 11.2 months, and median OS was 12.6 months [28]. Most of the adverse events were hematologic with 60.5% experiencing neutropenia (all grades). 32.5% of the patients had cardiac-related adverse events (11.6% grade 4). Eighteen patients were unable to complete the planned 8 cycles. Ten patients died early in the treatment: 6 from disease progression, 1 from cardiac failure, and 1 secondary to another malignancy. In this limited, retrospective cohort, R-CVP appears to have lower response rates and decreased survival compared with dose-attenuated R-CHOP or regimens with anthracycline alternatives.

Lenalidomide (Revlimid) + Rituximab

Thus far, there is only data on lenalidomide (Revlimid) + rituximab (R2) in the R/R setting. A single-arm phase II study evaluated the efficacy of oral lenalidomide (20 mg for 21 of 28-day cycle) with rituximab (375 mg/m^2 on day 1) in R/R patients with DLBCL. Thirty-two patients enrolled, ages 24–84 (median age 65). Seven patients (22%) achieved CR, and 2 patients achieved a partial response (PR). Median PFS was 2.8 months (1.8-NR), and median OS was 10.2 months (6.6-NR). The most common hematologic grade 3–4 toxicity was neutropenia (53%). Non-hematologic grade 3–4 toxicities included fatigue (7%), rash (4%), and electrolytes abnormalities (hypophosphatemia—9%). Of note, none of the patients in this trial discontinued lenalidomide because of toxicity [29].

Another single-arm phase II study evaluated R2 specifically in the elderly patients (age 65 or older) with R/R DLBCL. The regimen was slightly different, lenalidomide 20 mg daily on days 1–21 of 28-day cycle with rituximab 375 mg/m^2 on day 1 and day 21 for 4 cycles. At the end of 4 cycles, patients that had a CR, PR, or stable disease (SD) were started on lenalidomide maintenance (20 mg, days 1–21 of 28-day cycle). Twenty-three patients (median age 74.2) were treated. At the end of induction phase, 35% of patients had a response to therapy (CR and PR). Ten patients were started on maintenance (7 CR, 1 PR, and 2 SD) and 8 of these patients ultimately achieved CR (1 patient with PR converted to CR). The 18-month OS rate was 55.1%. The most common grade 3 toxicities were neutropenia (30%), thrombocytopenia (14%), and asthenia (5%). Nine patients had lenalidomide dose reductions due to toxicity [30].

Overall, these 2 studies show reasonable efficacy of lenalidomide with rituximab in the R/R setting. Currently, there is a phase II trial (NCT02955823) by the FIL group actively recruiting elderly frail patients (frailty defined by the FIL tool) to evaluate efficacy of this combination in frontline setting.

Steroids + Vincristine

In the NHL-B2 trial (which looked at both R-CHOP and R-CHOEP (addition of etoposide) on 14- and 21-day cycles in patients 61–75), the German High-Grade Non-Hodgkin's Lymphoma Study Group (DSHNHL) utilized the option of

"pre-phase" treatment with 7 days of prednisone and 1 mg of vincristine prior to starting R-CHOP. This pre-phase treatment reduced therapy-associated deaths form first cycle of R-CHOP to 2% from 5% without pre-phase treatment. Though this approach has not been validated in randomized trials, it can be considered in frail patients with high-tumor burden at diagnosis, low performance status, and high risk of iatrogenic complications prior to initiating systemic treatment [33].

Combinations with Novel Agents and Future Directions (Table 5)

Novel agents have been combined with R-CHOP in a number of settings with the hypothesis that the addition of these novel agents could increase CR and OS rates. Some of these studies have specifically focused on the elderly as either the target study population or a subgroup of interest.

Lenalidomide + R-CHOP

Lenalidomide (15 mg on days 1–14) was combined with R-CHOP for treatment of elderly patients with DLBCL in a single-arm phase II trial [34]. The study enrolled 49 patients age 60–80 categorized as "fit" and with LVEF > 45%. For this trial, patients were considered fit if they had no impairment in activity of daily living (ADL), no condition defining a geriatric syndrome, and no grade 4 comorbidity or of more than three grade 3 comorbidities according to CIRS-G scale. The rate of CR was 86%, and, after a median follow up of 28 months, 2-year OS, and PFS were 92% and 80%, respectively. Ninety percent of patients completed all 6 cycles. Three patients had progressive disease, and 2 stopped treatment because of AEs.

Lenalidomide Maintenance

The REMARC trial evaluated lenalidomide maintenance in elderly patients that responded to R-CHOP [35]. Elderly patients (58–80, median 69) with ECOG 0–2 that achieved either PR or CR were selected to either receive placebo or lenalidomide (25 mg on days 1–21 of 28-day cycle) for 24 months. Sixty-one percent of the patients on maintenance lenalidomide prematurely discontinued treatment. After a median follow-up of 39 months, 2-year PFS improved from 75 to 80% in the lenalidomide arm, and this PFS benefit disproportionately favored GCB DLBCL. In both arms, patients that had PR converted to CR (33% in lenalidomide arm and 29% in placebo arm, $p = 0.56$). The median OS was not reached in either arm, but the estimated 2-year OS was 87% for lenalidomide and 89% for placebo. There was no difference in OS with lenalidomide maintenance with regard to cell of origin. The main cause of death on study was lymphoma progression (59% in lenalidomide arm and 62% in placebo arm). The most common grade 3–4 adverse events were neutropenia (56%—lenalidomide, 22%—placebo), infection (8%, 6%), cutaneous reactions (5%, 1%), and cardiac disorders (6%, 3%). Of note, secondary malignancies were similar in both groups (10%, 13%).

Ibrutinib + R-CHOP (ibr + R-CHOP) in Non-GCB DLBCL

The results of a phase III study of R-CHOP vs. ibr + R-CHOP in adults with newly diagnosed non-GCB DLBCL were recently published [36]. Eight hundred thirty-eight adult patients were randomized 1:1 to standard R-CHOP vs. ibr + R-CHOP (ibr 560 mg daily). This study did not specifically focus on the elderly population, but median age was 62. In the ibr + R-CHOP group, 22.4% of the patients discontinued treatment because of AEs. Only 67.9% of the patients ≥ 60 completed 6 cycles of ibr + R-CHOP. Toxicity was higher in the ibr + R-CHOP with higher incidences of grade 3+ febrile neutropenia and pneumonia (53.1% vs. 34%) that lead to therapy discontinuation. Additionally, in patients ≥ 60, there were more serious adverse events in those randomized to ibr + R-CHOP (63.4% vs. 38.2%), and a higher number of patients received fewer than 6 cycles of ibr + R-CHOP (32.1% vs. 13.3%). The toxicity of the addition of ibrutinib was also higher than R-CHOP alone in patients younger than 60; however, in this younger population, a similar number of patients received fewer than 6 cycles (10.4% vs. 8.1% for ibr + R-CHOP vs. R-CHOP, respectively). The study did not reach its primary endpoint of improvement in EFS with ibr + R-CHOP overall or in the subgroup of patients greater than 60. Authors concluded that unexpected increased in toxicity associated with ibr + R-CHOP led to reduced total dosing of R-CHOP, thereby resulting in inferior outcomes in the 60 and older subgroup.

Our Approach (Fig. 1)

As demonstrated, studies focused on the elderly (i.e., 60 and older) and very elderly population (i.e., 80 and older) have been few, and randomized trials in these commonly encountered but vulnerable populations are even more rare. In addition, real-world patients are more heterogeneous and have more comorbidities than clinical trial patients [37]. Approximately 30% of patients have medical conditions that exclude them from the clinical trial participation [32]. Initial evaluation of the elderly patient should include assessment of all comorbidities and functional status with regard to ADLS and IADLS. While it should continue to be studied prospectively in trials specifically targeting the elderly population, we recommend consideration of using the FIL tool to asses elderly patients prior to selecting therapy given its ease of use and the available data thus far.

Table 5 Combinations with novel agents

Lenalidomide + R-CHOP	Age (years)	Regimen	*n*	Completed cycles	Treatment-related deaths	CR	2-years PFS	2-year OS
Single-arm phase II Vitolo et al. [34]	69 (64–71)	R-CHOP + Lenalidomide × 6	49	90%	0%	86%	80%	92%
Lenalidomide maintenance	Age (years)	Regimen	*n*	Completed cycles	Treatment-related deaths	Median PFS	2-year PFS	
Randomized phase III Thieblemont et al. [35]	69 (68–80)	Lenalidomide × 24 months	323	34%	0%	Not reached	80%	
	68 (59–80)	Placebo × 24 months	327	Not reported	Not reported	58.9 months	75%	
Ibrutinib + R-CHOP	Age (median)	Regimen	*n*	Completed cycles	Treatment-related deaths	3-year OS rate	Age < 60, 3-year OS	Age > 60, 3-year OS
Randomized Phase III Younes et al. [36]	19–88 (63)	Ibr + R-CHOP × 6	419	76.80%	2.6%	82.8	93.20%	76.6
	19–87 (61)	Placebo + R-CHOP × 6	419	86.80%	1.7%	81.4	80.9	81.7

In fit patients, we recommend using R-CHOP or similar therapy. In our experience, many patients less than the age of 80 are able to tolerate full-dose R-CHOP. In patients 80 or older, we typically empirically reduce the doses of adriamycin, cyclophosphamide, and vincristine by 20%, although the data above would also support the use of R-70%CHOP or R-miniCHOP.

In the unfit population, we recommend chemoimmunotherapy with curative intent. While the choice of regimen will be based upon the individual patient's comorbidities, options include R-70%CHOP, R-miniCHOP, R-COMP, R-CEOP, and R-CGVP. Between the dose-reduced regimens (R-70%CHOP and R-miniCHOP), R-miniCHOP was studied in a prospective phase II trial, while the evidence guiding R-70%CHOP is retrospective.

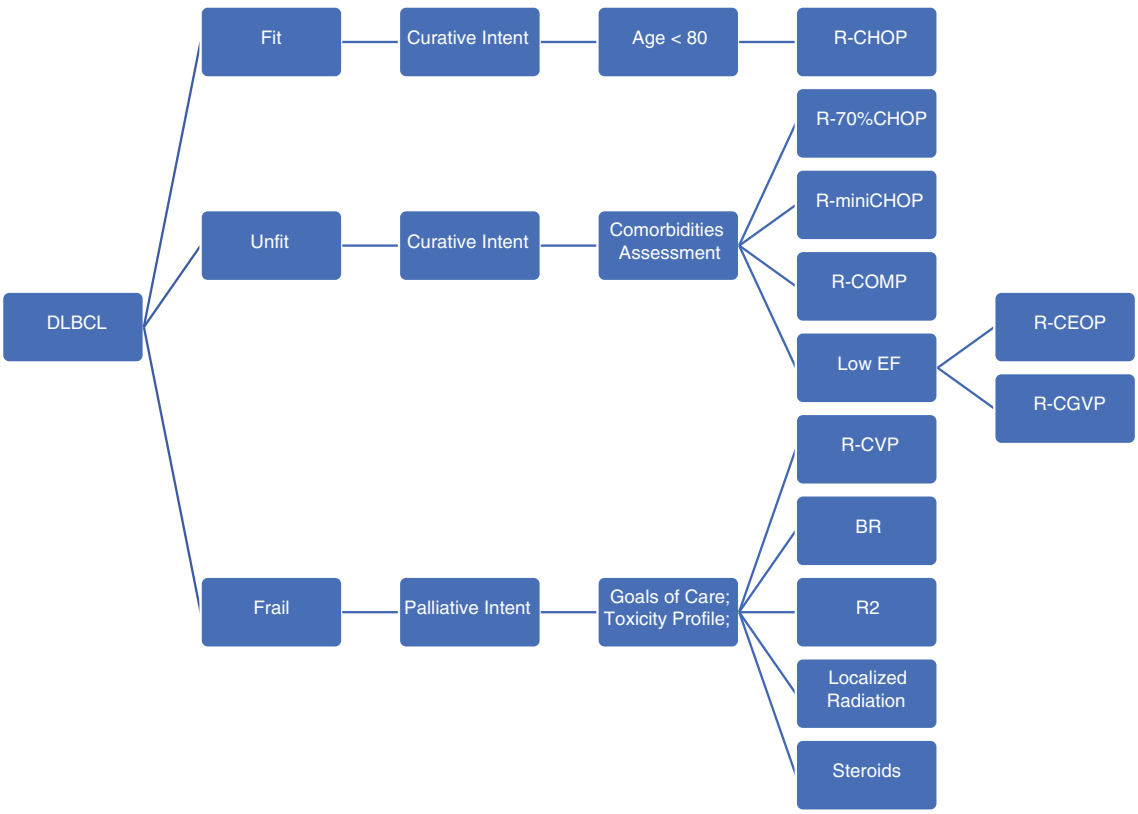

Fig. 1 Suggested treatment algorithm for elderly patients with newly diagnosed DLBCL

R-miniCHOP has a CR rate of 59% compared to 78% with R-70%CHOP. However, in the retrospective R-70%CHOP study, patients were included in the analysis if they had received only 1 cycle of R-70%CHOP. Thus, patients may have only received 1 cycle at the 70% dose and the rest of the cycles at a higher dose intensity. Sensitivity to vincristine may increase with age as patients 70 years old had a higher incidence of paralytic ileus. Based on comorbidities, one can choose between 50 and 70% doses of CHOP with rituximab. This may also be a population that could benefit from a pre-phase therapy of corticosteroids with or without vincristine.

In patients with a decreased EF at baseline or other significant cardiac impairment, clinicians may choose between R-CEOP and R-CGVP. Between these regimens, R-CGVP produced the lowest CR rates, but the trial evaluating R-CGVP specifically enrolled patients at high risk for poor cardiovascular outcomes (LVEF < 50%; more than 95% of patients with at least one cardiac risk factor, i.e., hypertensions, diabetes mellitus, or ischemic heart disease). Other trials have not selected such high-risk patients in a prospective setting. R-CEOP, though it produced higher CR rates, was evaluated in a retrospective trial, and any patient that had initially received R-CHOP but then was transitioned to R-CEOP was included in the survival analysis for R-CEOP. Ultimately, the choice lies with the patient and provider in terms of preference of schedule and/or AEs as these vary between the regimens.

In frail patients, the FIL group has shown that OS is not improved with R-CHOP-like regimens. In our limited, single-institution, retrospective experience, CR rate in frail patients treated with curative intent was 44% (data not published). In these patients, we recommend having frank discussions with patients and their caregivers. Depending on disease burden, disease location, and patient comorbidities, possible options for this group of patients include R-CVP, BR, R2, single agent rituximab, steroids, or localized radiation.

Conclusion

Geriatric assessment tools have potential to significantly aid decision-making when treating elderly patients with DLBCL. We recommend using FIL tool as it has been validated in a prospective trial of elderly patients with newly diagnosed DLBCL. Additionally, it can be applied in less than 10 min in outpatient setting. We recommend that elderly fit patients be treated with R-CHOP or similar regimen, and unfit patients should consider a R-CHOP-like regimen with dose and/or chemotherapy modifications. Currently, data to guide treatment decisions for frail elderly patients is exceedingly limited. Patients over 80, with multiple comorbidities, with poor functional status, and with impaired ADLs and/or IADLs are extremely sensitive to toxicity from therapy. Thus far, treatment with aggressive, R-CHOP-like regimens has not been shown to improve outcomes. While generally speaking, prospective, randomized trials are needed in the elderly and very elderly populations, perhaps it is the frail cohort that is most likely to benefit from future studies incorporating novel agents.

Compliance with Ethical Standards

Conflict of Interest Yasir Khan declares no conflict of interest. Elizabeth Brem reports personal fees from Pharmacyclics, Janssen, Bayer, Genetech, Celgene, and BMS/Pfizer.

Human and Animal Rights This article does not contain any studies with human or animal subjects performed by any of the authors.

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