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REVIEW ARTICLE

Management Considerations and Challenges in Older Individuals with Diffuse Large B-cell Lymphoma

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ABSTRACT

Diffuse Large B-cell Lymphoma (DLBCL) is classically a disease of older individuals. However, varying definitions of "older" age, underrepresentation in clinical trials, and significant patient heterogeneity requires a highly personalized treatment approach. Older patients often have comorbidities leading to decreased tolerance with standard of care therapies; however, predictive tools such as the simplified Comprehensive Geriatric Assessment may help tailor treatments accordingly. Several approaches have been introduced to augment therapeutic tolerance in the front-line setting, including prephase therapies, attenuation of current standard of care chemoimmunotherapy dosing, or alternative chemotherapeutic agents when prohibitive comorbidities such as cardiovascular disease are present. In the relapsed and refractory disease setting antibody-based therapies have improved outcomes and demonstrated therapeutic tolerance in older patients. Cellular therapies and bone marrow transplantation remain options for fit patients who are eligible and should be considered. The aim of this review is to focus on patient assessment and treatment recommendations in older patients with DLBCL.

Introduction

Diffuse Large B-cell Lymphoma (DLBCL) is a disease primarily affecting older individuals. The incidence ranges from 5.5 to 7.2 per 100,000 persons, which is projected to increase over the next 5 years[1–3]. While aggressive and fatal if left untreated, it is a highly curable disease with chemoimmunotherapy, with the current standard of care being rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). While 30-40% of patients over the age of 60 years with DLBCL may relapse, a growing number of promising therapies including chimeric antigen receptor T-cells (CAR-T), bispecific T-cell engagers (BiTe), autologous stem cell transplantation (ASCT), and targeted therapies are available[4]. However, these therapies are associated with unique and often significant toxicities, and there is limited data on the utilization of these agents in older individuals.

The number of individuals over the age of 65 years in the United States is rising and will be approximately 20% by the year 2030[5]. While the number of older patients is increasing, they are frequently excluded from clinical trials due to comorbidities and limited performance status; hence, conclusions are frequently derived from post hoc analyses, retrospective real-world studies, and meta-analyses. The most utilized cutoff to describe the older population is an age of greater than 65 years, but a homogenous definition is lacking. While there are recent trials to tailor therapies in this patient population, new treatment strategies have limited insight into tolerance and outcomes in older individuals. Therefore, a better understanding is needed on how to optimally adapt and tailor frontline therapies and treatments in the relapsed/refractory (r/r) disease setting. Therefore, the aim of this review is to provide a better understanding of treatment selection and provide a summary of therapeutic options in older patients with DLBCL.

Epidemiology

DLBCL is the most common subtype of non-Hodgkin lymphoma (NHL), comprising 30% of new diagnoses[6]. While it can occur at any age, it is most commonly diagnosed between 65-74 years, with a median age of 66 years[1,2,6–9]. The 5-year relative survival based on Surveillance, Epidemiology, and End Results (SEER) is 64.7%[1]. Over the past three decades, the overall death rate for DLBCL has decreased from 2.8 to 1.7 per 100,000 per year[1,10]. There is a distinct survival difference based on age in patients with DLBCL; median overall survival (OS) in patients 65-79 years is 43 months, and 25 months for those ≥80 years[11,12]. Based on 1,169 patients from Sweden, those older than 60 years with an event free survival (EFS) over 24 months, there is a higher incidence of adverse events (AE) in the subsequent 5 years compared to those younger than 60 years[13]. There is clearly a difference in overall survival (OS) by different age cohorts with older age correlating with poorer outcomes.

Based on 2,941 patients (median age 67) with DLBCL in the Swedish registry, the rate of relapse is 18%[14]. Of that group 72% will relapse in 2-years. For those between 70-79 years and older than 80 years, 30% and 17% have relapsed disease, respectively. The response rate to relapsed disease is 20% (11-34%) based on the SCHOLAR-1 study, a pool of 4 clinical trials. For those >65 years OS was

6.9mo (95% confidence interval (CI); 4.9-9.5mo), with response rate of 30% (95% CI; 20-40%)[15].

Disease Biology

DLBCL can be identified by its heterogenous morphology and its genetic profile. The 3 gene expression profiles of DLBCL are activated B-cell (ABC), germinal B-cell (GBC), and unclassified[16,17]. ABC and GBC can be further subdivided based on their genetic mutations, for example ABC can have variable expression and mutations in NF-kB, *PRDM1*, *BCR*, *MYD88*, *TNFAIP3*, and *NOTCH1*[16]. Germinal center B-cell type can have mutations in *BCL2*, *MYC*, or *TP53*. Based on 131 patients aged 50-91, there is a higher prevalence of ABC subtype with older age; 67% patients over the age of >80 compared to 28% aged 50-60 years had ABC (P=0.01)[18]. Typical work up for DLBCL includes florescent in situ hybridization (FISH) to analyze for *MYC*, *BCL2*, and *BCL6* in DLBCL. Those with translocations with one, two, or all three genes are labeled as single hit, double hit, or triple hit disease, respectively. Double and triple hit disease are often poorly differentiated or undifferentiated and are associated with poorer prognosis[19].

Frailty and Fitness Assessment

Older adults are a highly heterogeneous population with a diverse array of medical complexities. When assessing older patients with DLBCL, a comprehensive geriatric assessment (GA) is recommended to accurately assess functional reserves and qualitatively divide patients into fit, unfit, or frail cohorts. However, real-world settings have several barriers that limit widespread application of this practice, including lack of time and experience utilizing these tools. There are several GA tools available. The Practical Geriatric Assessment was developed by the Cancer and Aging Research Group (CARG); it is a 19-step questionnaire that informs oncological decision making and assesses a patient's impairments. Components of this questionnaire can be used in the CARG Chemo-Toxicity calculator to predict the risk of chemotherapy toxicity[20].

The American Society of Clinical Oncology (ASCO) 2018 guidelines recommend that all older adults receiving systemic therapy should have specific geriatric assessment[21]. Two recent studies investigated the outcomes of GA, namely GAIN-S and GAP70+ in 2021. Li et al. demonstrated that using a GA tools in 613 patients aged 65-91 treated for various malignancies reduced grade 3 chemotoxicity from 60.6% to 50.5%[22]. Mohile et al. showed that in adults >70 years with lymphoma or solid tumors, 51% of patients had a grade 3-5 toxicities effect compared to 71% of patients that did not undergo a pre-treatment GA (relative risk (RR) 0.74; 95% CI 0.64-0.86; P=0·0001)[23]. As a result, 2023 ASCO guidelines were updated to recommend completing a GA on all adults over the age of 65 years that require systemic therapies[24].

Another tool called the simplified comprehensive geriatric assessment (sCGA) classifies patients as "fit", "unfit", and "frail" based on their age, activities of daily living (ADL), instrumental activities of daily living (IADL), and comorbidities[25]. Patients who achieve a "fit" classification are typically <80 years, have 8/8 score in IADL, and 6/6 score in Katz index of ADL[25]. Those that are >80 years without comorbidities, or elderly with

comorbidities such as creatine clearance (CrCl) < 70 mL/min and/or Cumulative Illness Rating Scale-Geriatric (CIRS-G) > 6 are considered "unfit"[14]. Patients that are >80 years old are labeled "frail". The sCGA was studied in 1,207 patients and concluded that fit and unfit patients <80 years old had a 3-year OS of 75%, while frail patients >80 years had 3-year OS of 43%[25]. Specifically in DLBCL, the sCGA found that 2-year OS was 84% in fit patients and 47% in non-fit patients (P<0.0001)[26]. The CARG Practical Geriatric Assessment and the sCGA are validated tools that should be employed in patients >65 with DLBCL. In general, fit patients benefit from a full dose/curative approach chemoimmunotherapy, whereas unfit patients may need reduced intensity options with an emphasis on palliation rather than curative therapy. Older patients that are considered frail need to be managed with extreme caution and treatment highly personalized given the lack of evidence-based treatment approaches. Geriatric services should be utilized when available.

Pre-Treatment Considerations

PREPHASE

Older patients with DLBCL are prone to developing treatment-related toxicities with standard of care chemoimmunotherapy regimens. Moreover, performance status (PS) at diagnosis may be negatively impacted by proinflammatory effects arising from disease burden. In such cases, a "prephase" therapy with corticosteroids prior to chemotherapy may improve performance status prior to initiating therapy and hence avoid undertreatment[27]. A small prospective pilot study has suggested a beneficial role of prephase rituximab and prednisone therapy prior to R-CHOP in older patients over 70 years or between 60 to 70 years with a Karnofsky performance scale score of <80[19]. A recent prospective study of 188 newly diagnosed DLBCL patients (median age of 56 years, range 18-83 years) concluded that a prephase treatment with vincristine 1mg on day 1 and prednisolone 100mg on days 1-7 prior to first cycle of multiagent chemotherapy improved performance status and reduced incidence of both neutropenia and neutropenic fever. Oral prednisone therapy is given over 5 to 7 days in combination with allopurinol and hydration to mitigate tumor-lysis. However, corticosteroids should be used cautiously in this population given risks of mental status changes, insomnia, and hyperglycemia, and use should be individualized based on comorbidities and performance status.

CARDIOTOXICITY

Doxorubicin, an anthracycline chemotherapy, is an important backbone in chemoimmunotherapy regimens for DLBCL. There is a well-known risk for cardiotoxicity, which is further augmented by older age (>65 years), cumulative dose received, preexisting structural heart disease, coronary artery disease, hypertension, and mediastinal radiation therapy[29]. For patients with cardiac risk factors, it is recommended to undergo risk stratification and consideration of R-CEOP (cyclophosphamide, etoposide, vincristine, and prednisone ± rituximab) which uses etoposide 50mg/m^2 IV followed by 2 days of oral 100mg/m^2 instead of doxorubicin[29,30]. When using doxorubicin, total cumulative dose should be limited to 360mg/m^2 [30]. In adults with pre-existing cardiomyopathy where it is felt that anthracycline therapy must be utilized in an otherwise fit patient, the addition of dexrazoxane has shown to be

cardioprotective and prevent worsening of cardiomyopathy[31]. Further studies are needed in the DLBCL landscape to expand on alternative regimens to anthracyclines that do not sacrifice survival and outcomes[31].

NEUTROPENIC FEVER

The risk of febrile neutropenia is elevated with standard R-CHOP regimens in older patients. Current guidelines suggest prophylaxis with granulocyte- colony stimulating factor (G-CSF) in patients who have >20% risk of developing febrile neutropenia. These risk factors include advanced age, Ann Arbor stage III/IV, poorer Eastern Cooperative Oncology Group (ECOG) PS, anemia, bone marrow involvement, and malnutrition. IMPACT NHL reported an underutilization of G-CSF administration in older patients even if they were considered high-risk. A subsequent multivariate analysis revealed a strong association between febrile neutropenia and lack of G-CSF[32]. Morita et al. conducted a retrospective analysis to compare outcomes in the treatment of DLBCL prior to approval of pegfilgrastim[33]. Overall there was a difference in relative dose index (RDI) for those who received pegfilgrastim (85.2% vs 92.0%, P=0.039), however when stratified by age (≤69 years, 70-79 years, ≥80 years), there was no improvement in RDI. However, they found reduced incidence of neutropenic fever with pegfilgrastim compared to no G-CSF (RR 0.51, 95% CI: 0.41 to 0.62) or filgrastim (RR 0.66, 95% CI: 0.44 to 0.98[33,34]. These studies highlight the important role for G-CSF administration in older patients receiving chemoimmunotherapy for DLBCL.

CENTRAL NERVOUS SYSTEM PROPHYLAXIS

Approximately 5% of patients with DLBCL will have central nervous system (CNS) involvement, but this can range from 1%-15%[35,36]. For those at high risk (>4 points) identified by the CNS-international prognostic index (IPI) (age > 60 years, lactate dehydrogenase above upper limit normal, ECOG performance status >1, Ann Arbor stage 3/4, more than 1 site of extra-nodal disease, and renal or adrenal involvement), there are conflicting recommendations for IT prophylaxis[4,27,34,35]. CNS chemoprophylaxis can be given as an intrathecal administration, commonly methotrexate or cytarabine, or as systemic high dose methotrexate (HD-MTX). Based on 690 patients treated with intrathecal methotrexate and R-CHOP over the age of 70, the average 2-year relapse rate varied from 3% for those with a CNS-IPI score of 1-3, to 21.8% for those with a CNS-IPI of 6[37]. There was increased risk of infection related admissions in this patient population and those with renal and adrenal involvement, and there was no change in either adjusted or unadjusted CNS relapse for intrathecal prophylaxis when measuring outcomes by the CNS-IPI[37]. There is ongoing debate surrounding the clinical application of CNS prophylaxis, and more data is needed to make firm recommendations in this population.

Table 1. Selected studies depicting front line treatments for DLBCL

Trial	Age (years)	Treatment	n	ORR (%)	CR (%)	PFS (%) (HR, 95% CI, p-value)	OS (%) (HR, 95% CI, p-value)	TRM (%)
LNH98-5, phase 3[4,38,39]	60-80	CHOP	197	69	63	30 (5 y); 20.1 (10y)	45 (5 y); 27.6 (10y)	6 (infections, cachexia, cardiovascular)
		R-CHOP	202	83	75	54 (5y); 36.5 (10y)	58 (5y); 43.5 (10y)	6 (as above)
RICOVER-60, phase 3[40]	60-80	6xCHOP14 + Rx2 vs 8xCHOP14	306 304	-	76 78 (6xR-CHOP vs 8xR-CHOP)	73 (3 y) 69	78.1 (3 y) 72.5	8 vs 7 (in 8 vs 6 cycles)
Cunningham et al, phase 3[41]	19-88	R-CHOP14x6 + Rx2 R-CHOP21x8	540 540	91 88 (P=0.12)	41 49	75.4 (2y) 74.8 (0.94, 0.76–1.17, P=0.5)	82.7 (2y) 80.8 (0.90, 0.70-1.15, P=0.3)	2 vs 1 (+ 2 vs 1 cardiac related deaths > 3 months after rx)
LNH03-6B, phase 3[42]	60-80	R-CHOP14x8 R-CHOP21x8	304 298	87 86 (P=0.6)	71 74	60 (3y) 62 (0.99, 0.78-1.26, P=0.8)	69 (3y) 72 (0.96, 0.73-1.26, P=0.7)	5 vs 5
Zhang et al, phase 2[43]	75-86	DA-EPOCH-R	31	87	71	60 (3y)	63 (3y)	None
CALGB 50303 Phase 3[44]	18-86 19-84	R-CHOP DA-EPOCH-R	250 241	88 87	60 59	66 (5y) 68 (5y) HR 0.93 (0.68-1.27; P=0.65)	79 (5y) 78 (5y) HR 1.09 (0.75-1.59, P= 0.64)	2 vs 2 (primarily infections)
POLARIX Phase 3[45]	19-80	R-CHOP Pola-R-CHP	439 (68% > 60 yrs) 440 (70% > 60 yrs)	84 86	74 78	70 (2y) 77 (2y)	89 (2y) 89 (2y)	3 vs 2 (primarily infection)
Peyrade et al, phase 2[46]	80-95	R-miniCHOP	149	73	62	47 (2y)	59 (2y)	8

Trial	Age (years)	Treatment	n		ORR (%)	CR (%)	PFS (%) (HR, 95% CI, p-value)	OS (%) (HR, 95% CI, p-value)	TRM (%)
Shin et al, phase 2[47]	61-85	RD-RCHOP	85		90	67	72 (3y)	83 (3y)	6
Nowakowski et al., phase 2[48]	24-92	R^2CHOP R-CHOP	145 135 (efficacy population)	166 171 (safety population)	97	73	61 (3y)	75 (3y)	1 vs 4
Moccia et al (Retrospective)[49]	21-92 34-93	R-CHOP R-CEOP	140 70		-	-	62 (10y) 53 (10y) (Time to progression)	49 (10y) 30 (10y)	4 vs 4
ANZINTER3 trial Phase 3[50]	71 (65–86); 39% > 72 73 (64–84); 51% > 72	R-CHOP R-miniCEOP	110 114		87 81	73 68	EFS 48 (37–58) 46 (36–55) P=0.53	62 (51–71) 63 (52–72) P=0.70	9 vs 6

n number of patients, ORR Overall response rate, CR complete remission, PFS pathologic free survival, HR hazard ration, CI confidence interval, OS overall survival, TRM Treatment-related mortality

Frontline Therapy

FIT PATIENTS

Rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone

Rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP) is the standard of care first-line therapy for DLBCL in patients of all age groups, including older, fit patients, who do not have double/triple hit disease, HIV, or primary mediastinal large B-cell lymphoma[51,52]. First, Feugier et al. compared CHOP to R-CHOP in 399 untreated patients age 60-80 years in 2005, and found that R-CHOP had favorable EFS (p=0.00002), DFS (p<0.00031), and OS (p<0.0073), compared to CHOP. The 2-year and 5-year OS for R-CHOP is 70% (95%CI 63%-77%) and 58% (95% CI, 50.8%-64.5%) respectively[4,53]. Relapse and progression in R-CHOP among 60-80 years old was 38% with EFS of 3.8 years[53].

Since R-CHOP became standard first line therapy, it has been well-tolerated in fit, older patients[54]. The accepted regimen is 6-8 cycles of rituximab cyclophosphamide, doxorubicin, vincristine, and prednisolone every 21 days (R-CHOP21)[41]. For patients >80 years compared to those 70-79 years, there is no difference in the 2-year relapse incidence rate for R-CHOP (univariable subhazard ratio (SHR) 1.20; 95%CI 0.87–1.67; P = 0.27), which suggests non-relapse mortality (NRM) drives inferior survival in the aging population[55]. Other considerations such as increasing the frequency of R-CHOP to every 14 days for those >65 years has been studied, but did not improve OS (HR 0.84, 95% 0.60-1.16)[41,61]. While there is no data with prospective comparisons of 6 vs 8 cycles of R-CHOP-21, two population-based studies and an analysis of the GOYA trial support similar efficacy in those >70 and ≤70 years (NCT01287741)[56,57]. Given shorter treatment duration and chemotherapy exposure, we typically favor 6 cycles.

Polatuzumab vedotin, cyclophosphamide, doxorubicin, and prednisone

Polatuzumab vedotin (Pola) is an anti-CD79b targeting antibody-drug conjugate with monomethyl auristatin E (MMAE) coupled via a peptide linker, which is a microtubule inhibitor. Pola demonstrated encouraging activity as monotherapy and when combined with anti-CD20 monoclonal antibody (mAB) therapy in the r/r setting with manageable toxicity profile[94]. Polatuzumab vedotin, cyclophosphamide, doxorubicin, and prednisone (Pola-R-CHP) replaces vincristine in standard R-CHOP and has been studied in the POLARIX trial as first line therapy, due to outstanding efficacy in phase Ib/2 trial (ORR 89%, CR 77%)[58]. POLARIX trial included about 70% patients >60 years, however patients >80 years were excluded (PFS improved to 76.7% compared to 70.2% treated with RCHOP alone however no difference in OS was observed)[59]. The PFS benefit was only observed in patients >60 years, IPI of 3-5, and ABC subtype DLBCL. This demonstrates that for older patients, especially with intermediate to high-risk disease, Pola-R-CHP is an alternative that offers 6.5% PFS benefit in specific subsets. In a recent subgroup analysis focusing on patients ≥ 70 years, Pola-R-CHP had a lower risk of progression, relapse or death compared to R-CHOP (HR 0.64; 95% CI: 0.41–0.99), but no significant difference in 2-year OS or DFS. Safety and rate of grade 3-5 adverse events were similar[60].

Rituximab, lenalidomide, cyclophosphamide, doxorubicin, vincristine, and prednisone

The addition of lenalidomide to R-CHOP is R^{2}CHOP. In 145 patients with median age of 66 years (range 24-92) given R^{2}CHOP, there was a 34% reduction in risk of progression or death compared to 135 patients in the R-CHOP arm[48]. Aggregate PFS at 3-years was 73% compared to 61% (P=0.03), and OS was 83% compared to 75% (HR 0.67, P=0.05). When stratified by age (≥60 years vs <60 years), 105 in the R^{2}CHOP ≥60 years had improved OS with HR of 0.74 when compared to R-CHOP (80%CI 0.52, 1.06). However, there were significantly more toxicities, with 81% over 60 years compared to 63% under 60 experiencing a grade 3/4 AE with neutropenia, anemia, and thrombocytopenia composing of the most frequent complications[48].

While several phase II studies suggested that that R^{2}CHOP improved therapeutic efficacy in ABC-DLBCL, the phase III ROBUST trial comparing R^{2}CHOP to R-CHOP did not demonstrate a significant difference in PFS or OS. In this analysis, 52% were above the age of 65 years, 30% above age 70 years, and 3% above 80 years. There was no difference in outcomes when controlling for age. Safety profiles were similar, although a greater of proportion in the R^{2}CHOP had grade 3 of higher hematologic toxicities[61].

HOVON 130 examined R^{2}CHOP in 82 patients with DLBCL with MYC+ mutation[62]. Out of that group, 39 participants (47%) were 65-84 years old. Two-year OS was 73% (95% CI: 62-82)[62]. There were 71 serious adverse events in 36 patients, mainly infections and GI toxicities[72]. De Jonge et al. also recruited 77 patients from HOVON 130 with median age of 63 into the R^{2}CHOP group, which was younger than the median age of 70 for the 56 patients in the R-CHOP group (P=0.018)[63]. After treatment there was no difference in response rate: 69.8% in R-CHOP and 80.5% in R^{2}CHOP. Subgroup analysis for single hit (*MYC*) and double hit/triple hit (*MYC* with *BCL2* and/or *BCL6* demonstrated improved OS, with HR of 0.34 and 0.57 for R^{2}CHOP and R-CHOP, respectively. Therefore, while R^{2}CHOP may benefit small subsets of patients, it is associated with significant toxicities with limited benefit in OS.

Rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin

Rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (R-EPOCH) is a continuous infusion regimen administered over 96-hours and with addition of etoposide to standard R-CHOP agents. It can be used for fit patients with aggressive histological subtypes, particularly those with double/triple hit DLBCL. For older patients over the age of 80 years, the dose can be adjusted based on absolute neutrophil count nadir at the end of the previous cycle (DA-EPOCH-R). In 207 patients with median age of 83 years (range 80-96) with DLBCL, 3-year failure free survival (FFS) was 74% (95% CI, 39%-91%) and OS was 73% (95% CI, 37%-91%)[64]. A retrospective study of 42 patients with DLBCL, who had a median age of 72 years, were given EPOCH[65]. Of those median PFS was 69% and OS was 78% at 18-months. In the pooled group of 42 patients with DLBCL, 8 with T-cell lymphoma, and 4 with Burkitt lymphoma, there were cardiac events in 22% with 2 having doxorubicin-induced cardiomyopathy, and 52% with neutropenic fever and infection[65]. Overall, both R-EPOCH or DA-EPOCH-R are appropriate treatments for older fit patients, but caution is advised

with hematologic toxicities and cumulative doxorubicin dosing.

UNFIT OR 80 YEARS AND OLDER

Attenuated rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone

Patients with an unfit classification including age > 80 years, depressed creatine clearance, or CIRS-G greater than 6, have historically developed more frequent toxicities with standard R-CHOP[66]. Rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-mini-CHOP) uses attenuated R-CHOP dosing with cyclophosphamide 400 mg/m^2, doxorubicin 25 mg/m^2, and vincristine 1 mg capped-dose[12]. This was first studied prospectively in a phase II trial which included 149 patients older than 80 years (range: 80-95 years); 2-year PFS was 47% and OS was 59%[67]. However, this study did not have a control arm and the patients selected were mostly fit with a good performance status. Hounsome et al. compared R-CHOP and R-mini-CHOP and found that patients over 80 years had an OS of 57% compared to 54% with R-CHOP[12]. For those aged 65-79, 3-year OS was 59%, compared to 57% for R-CHOP. According to Juul et al., OS for those > 85 years was not negatively impacted by an attenuated dosage, suggesting R-mini-CHOP remains an acceptable treatment in this population[12,68]. The ongoing POLAR BEAR trial is currently comparing R-mini-CHOP to R-pola-mini-CHP in unfit patients over 75 or >80 years, which will offer additional insight into unfit patients (NCT04332822)[69].

UNFIT OR CONTRAINDICATIONS TO ANTHRACYCLINES

Rituximab, cyclophosphamide, etoposide, vincristine, and prednisone

The regimen of rituximab, cyclophosphamide, etoposide, vincristine, and prednisone (R-CEOP) utilizes etoposide instead of doxorubicin, and is reserved for patients who are not candidates for anthracyclines[70]. Moccia et al studied R-CEOP in 70 patients with DLBCL with median age of 73 years compared to R-CHOP[49]. There was no difference between R-CEOP and R-CHOP; 10-year time to progression was 53% vs 62% (P = 0.089) and disease-specific survival was 58% vs 67% (P = 0.251), respectively. OS at 10 years was lower in R-CEOP group at 5 and 10 years (47% and 30%, compared to R-CHOP which had 65% and 49% survival respectively.[49] The authors attributed lower survival to frailty in the study population, but recommend the regimen for those with contraindications to anthracyclines. This suggests that BR is a valid palliative therapeutic option for frail patients.

Bendamustine and rituximab

Bendamustine and rituximab (BR) is used at 90mg/m^2 for 2 days with and 375mg/m^2 on day 1, respectively, every 28 days. Based on 45 patients with median age of 81 years with DLBCL, 53% achieved CR after 6 months, and ORR was 62%[71]. There were 35 grade 3 and 4 AE in 23 patients with 37% incidence of neutropenia despite 58% use of G-CSF. Two year PFS was 38% with a median PFS of 10 months. There was no significant difference in OS or PFS between >80 years and ≤80 years. There was also no difference in outcome for activities of daily living, or IPI.[71] In the B-R-ENDA trial, 2-year PFS and OS in patients >80 years was 45% (95% CI: 28%-61%) and 46% (95% CI: 28-63%) respectively.[72] In patients ≤80 years, PFS and OS was 32% (95% CI: 13%-51%) and 37% (95% CI: 17%-57%) respectively. This suggests that BR can be

used for frail population despite a lack of intent to cure[72].

Rituximab and Lenalidomide

In frail patients, a chemotherapy-free regimen can be considered such as rituximab and lenalidomide (R^2)[73]. In the phase 3 REMARC study, lenalidomide maintenance therapy for 2 years in patients with median age of 69 years (range 58-80) who achieved complete or partial response to R-CHOP were studied. The HR for PFS for lenalidomide was 0.795 (95% CI 0.531–1.190; P = 0.2632), and those with dose reductions had a HR of 0.788 (95% CI 0.515–1.205; P = 0.2694)[74]. The most common grade 3 and 4 adverse events were neutropenia in 56% compared to 22% in the placebo group which led to 61% and 41% dose reductions respectively. In addition, the FIL_ReRi clinical trial studied R^2 as frontline therapy in 65 patients with DLBCL over the age of 70 years. Results demonstrated an ORR of 50.8%, and 2-year PFS and OS of 40.5% and 48.2%, respectively. However, 52.3% of patients had at least grade 3 toxicities[41]. Ibrutinib with R2 was also studied (iR2) in 30 patients with de novo DLBCL aged 75 years or older. Results showed an ORR of 66.7% and CR of 56.7%[75]. This combination has paved the way for chemotherapy-free regimens in older patients with de novo DLBCL, and ongoing studies such as Zanubrutinib, rituximab and lenalidomide (ZR2) are underway (NCT04460248).

Frail

RADIATION THERAPY

Radiation therapy for DLBCL has been examined for palliative treatment for patients who cannot tolerate chemotherapy[76]. Based on Wong et al., 217 patients with DLBCL were given palliative radiotherapy, which showed local control in 66.7% of cases[77]. In this group the median age was 76 years, however the range was 25-103 years so many patients were included that were not elderly. Expectedly, those that received palliative radiotherapy had increased risk of progression. However, there was no association with refractory or relapsed disease, which suggests that treating r/r DLBCL with radiotherapy can be an appropriate penultimate treatment[77].

SUPPORTIVE CARE

Supportive care including palliative support/ hospice should always be actively discussed as a treatment option in older patients, particularly those who are frail and when the provider feels chemotherapy, radiation, or immunotherapy will not prolong survival or enhance toxicities, morbidity, or mortality. Analgesia, symptomatic control of dyspepsia, diarrhea, nausea, vomiting, and generalized pain should be promptly addressed safely.

Novel Therapies for Relapsed and Refractory Disease

Relapsed disease is defined as a new lesion found on imaging that increases in size by 50% after achieving disease remission. Refractory disease is when there is an increase in node size during or at the end of therapy. Chemoresistance is often synonymous with progressive disease (PD), especially when there is PD in less than <12 months[78].

ANTIBODY-BASED THERAPIES

Three antibody-based therapies are available for patients with r/r DLBCL: Tafasitamab, loncastuximab tesirine, and polatuzumab vedotin.

TAFASITAMAB

Tafasitamab is a humanized, anti-CD19 mAB.

Single agent efficacy is modest (with 26% ORR), but combination with lenalidomide has led to improved outcomes[79]. In the multicenter, open-label, phase II study (L-MIND), 81 patients with a median age of 72 years (62-76) with r/r DLBCL who failed or were not candidates for autologous stem cell transplantation (ASCT) were studied[80]. The ORR was 61% and 43% had CR. The median duration of response (DOR) was 21.7 months, and 72% had response lasting more than one year. Neutropenia was the most common grade 3 adverse event, affecting nearly 50%. There were four treatment-emergent adverse events leading to death, however, none of them were related to the study treatment.

Real-world experiences with Tafasitamab/ Lenalidomide (Tafa-len) have been reported, showing lower responses and less favorable outcomes. In a multicenter study performed in the US,178 patients, most of which would not have met inclusion for L-MIND, were assessed[81]. ORR was 31% with CR of 19%. Median PFS was 1.9 months and OS was 6.5 months[81]. Interestingly, patients older than 70 years had a longer PFS, perhaps owing to the biological differences in disease or an enhanced sensitivity to Tafa-Len based therapy.

LONCASTUXIMAB TESIRINE

Loncastuximab tesirine is an anti-CD19 antibody drug conjugate with pyrrolobenzodiazepine (PBD) dimer payload tesirine which causes DNA crosslinking, possibly leading to evasion of DNA repair[82]. LOTIS-2 was a phase 2 study aimed to evaluate the efficacy and safety of single-agent Loncastuximab tesirine in patients with r/r DLBCL who had failed at least two prior lines of therapy[83]. Of 145 enrolled patients, 55% were older than 65 years, and 8% patients had HGBCL histology (10% with DHL/THL). Median lines of prior therapy were three, and patients with prior CAR-T cell therapy were included if they had CD-19 expression. ORR was 48.3%, CR was 24.1%, and the DOR was 10.3 months (13.4 in patients with CR and 5.7 in patients with PR). The most common grade 3 or higher adverse events were neutropenia (26%), thrombocytopenia (18%), and elevated gamma-glutamyl transferase (17%). Five patients did have fatal adverse events which included sepsis, septic shock, pneumonia, intestinal obstruction, and acute kidney injury. There were 47% that went on to receive subsequent therapy due to progression of disease, with 10% of patients receiving CAR-T cell therapy indicating CD-19 expression may still be persistent after treatment with Loncastuximab tesirine[84,85]. Loncastuximab tesirine appears to have a good tolerable profile in older patients with r/r DLBCL.

POLATUZUMAB VEDOTIN

Prior to frontline use, Pola was assessed in combination with BR, in comparison with BR alone in r/r setting. In this phase II randomized trial[86], about 57% of patients were ≥ 65 years, in whom Pola-BR showed benefit in PFS compared to BR alone (HR 0.33; 95% CI 0.17-0.65) on subgroup analysis, along with patients with higher IPI and ABC subtype. Over 75% of patients were refractory to prior therapy in each subgroup. The ORR rate was 45% vs 17.5% favoring Pola-BR, with mDOR of 12.6 vs 7.7 months[86]. Most common adverse events were hematologic, including grade 3-4 neutropenia (46.2%), thrombocytopenia (41%), and anemia (28.2%), noted higher in the pola-BR cohort[86]. The most common fatal adverse event was infection in 9 pola-BR patients vs 11

in BR patients[86]. Other combinations currently being evaluated include Mosunetuzumab and Pola in second line in an ongoing phase 1b/2 trial with primary analysis showing high activity, durable responses, and manageable toxicities[87]. The ongoing SUNMO phase III trial will assess the efficacy of this combination compared to R-GemOx in R/R DLBCL (NCT05171647)[88].

BISPECIFIC ANTIBODIES

BiTe are molecules which target two different antigens, one present on tumor cells and another on T cells, engaging and redirecting immune-effector cells for cytotoxic activity against malignant B-cells. Current BiTes include mosunetuzumab-axgb, epcoritamab-bysp, glofitamab, and all of which are CD3/CD20 targeting antibodies with good response rates in r/r DLBCL.

MOSUNETUZUMAB

Mosunetuzumab is a CD20/CD3 IgG BiTe which has been developed for B-cell malignancies. It was assessed for patients with r/r DLBCL who had received 2 or more lines of therapy in a dose-expansion cohort (including transformed follicular lymphoma patients) with fixed therapy (8 treatments if in CR otherwise total 17 treatments)[87,89]. Eighty-eight patients were enrolled, and most patients had advanced disease (83% with stage III/IV disease) with median of 3 prior lines of prior therapy. The ORR was 37% with CR in 21%. CR rates in 65 years and older were comparable (29%) to the overall population. Median DOR was 7 months. mPFS was 3.2 months and mOS was 11.5 months. Most common adverse events were hematologic, including neutropenia in which 21.6% were grade 3 or higher. Cytokine release syndrome (CRS) (26.1%) was mostly low grade (grade 1, 20.5% or 2, 3.4%). Tolerability was excellent, as noted by 84% patients in the study receiving >90% dose intensity with low rates of treatment discontinuation due to AEs (4.5%). It is currently being evaluated in combination with other therapies such as polatuzumab or chemotherapy[87,90].

EPCORITAMAB

Epcoritamab is a CD3/CD20 targeting BiTe which is available as a subcutaneous injection. The phase I/II study included 157 patients, with approximately 50% of patients ≥ 65 years. The ORR was 63.1%, with 38.9% in CR, and mDOR of 12 months. In this study, mPFS was 4.4 months and mOS was not reached. These patients had at least two prior lines of therapy, and either failed or were ineligible for ASCT[91]. The median time to CR was 2.7 months, and an estimated 88.7% of complete responders had continued response at 6 and 9 months. Hematologic adverse events were the most common overall and 14.3% had grade 3 or worse neutropenia[91]. Grade 1-2 CRS was the most common overall adverse event, reported in ~ 50% patients, and neurologic toxicity (mostly grade 1-2) was noted in 6.4% patients, with one fatal outcome. Epcoritamab demonstrates promising results with manageable toxicity, although long-term management with treatment until progression creates a significant burden for heavily pre-treated older patients with r/r DLBCL. Strategies to stop treatment after a fixed duration or reduce the frequency of treatment by increasing spacing in later cycles for patients in CR should be further explored. Currently, epcoritamab is being investigated in combination with other chemotherapy in both untreated and r/r DLBCL patients.

GLOFITAMAB

Glofitamab (Glo) is a CD3/20 BiTe with 2:1 tumor to T-cell binding configuration conferring bivalency to CD20 malignant B-cells and monovalency to CD3 T-cells. A recent phase II study included a total of 155 patients, with 84 patients ≥65 years[92]. Pretreatment with obinutuzumab for 7 days is required prior to first dose of Glo to reduce disease burden and mitigate the risk of high-grade CRS. Results showed ORR of 52%, with 39% patients in CR. The median time to CR was 42 days, with few patients with progressive response from PR to CR between cycles 3 and 6. The mDOR was 18.4 months, mPFS was 4.9 months, and mOS has not yet been reached. There was no difference in treatment effects based on age or previous treatment with CAR-T therapy. At 12 months, 64% of responders and 78% of CR patients had ongoing responses. Overall, 62% patients had grade 3 or higher adverse events. Neutropenia was the most common grade 3 or higher adverse event, noted in 27% of patients, and CRS was the most common overall adverse event, noted in 63% patients (mostly grade1-2). Treatment with glofitamab for 12 months has a tolerable safety profile in older individuals. A number of combinations are being assessed including Glo-GemOx vs R-GemOx in r/r and Glo-Pola-R-CHP vs Pola-R-CHP in frontline setting for DLBCL.

Cellular Therapies in Older Patients with DLBCL

Advanced age is an independent risk factor for increased risk of relapse and death in patients with DLBCL[93,94]. Cellular therapies are important therapeutic strategies for r/r DLBCL. Historically, both autologous and allogenic stem cell transplantation were the mainstays of therapy, offering a second opportunity to potentially cure r/r DLBCL in medically fit patients. Moreover, efficacy and tolerance has been demonstrated in older patients[95]. While technically possible, risk for morbidity and mortality in older patients may preclude utilization of these therapies. Furthermore, CAR-T therapies may be tolerated by older fit patients who are not ideal candidates for autologous or allogeneic stem cell transplantation or who have chemoresistant disease[95,96].

CHIMERIC ANTIGEN RECEPTOR T-CELL THERAPY

Chimeric antigen receptors (CARs) are synthetically engineered immunoreceptors targeting a specific tumor antigen expressed on malignant cells[97]. Following autologous T-lymphocyte collection, engineered genetic sequences are introduced ex vivo via lentivirus or non-viral vectors followed by cellular expansion, and reintroduced to a patient that has received lymphodepleting chemotherapy (commonly fludarabine and cyclophosphamide)[98,99]. Once in circulation, CAR-T cells preferentially target tumor cells with aberrant expression of that specific antigen[97].

There are subsets of older patients who are not medically fit for stem cell transplantation but may still be able to tolerate and benefit from CAR-T therapy. Despite the common perception that age predicts frailty, reduced efficacy, or lack of tolerability, many of the pivotal CAR-T trials included patients in their 60s-80s[94,100–102]. While data on age can be extrapolated from these trial cohorts, much of the evidence currently available exploring efficacy and toxicities in older patients is based on post hoc analyses or retrospective data.

Importantly, univariate analysis in results reported by ZUMA-1 investigating Axicabtagene Ciloleucel (axi-cel) and from JULIET trial exploring tisagenlecleucel (tisa-cel) found that outcomes were similar in adults ≥65 years compared to younger patients[94,100]. A post hoc analysis of ZUMA-1 comparing outcomes in adults older and younger than 65 found similar or even better CAR-T expansion rates, ORR (92% vs 81%), CR (75% vs 53%), and PFS (13.2 vs 5.6 months) in the older cohort. Of the 27 patients ≥65 years, 42% had an ongoing response with minimum of 24-months of follow-up[94]. While rates of CRS were similar, the older cohort had a higher rate of immune effector cell-associated neurotoxicity syndrome (ICANS)[106]. In a retrospective analysis comparing outcomes of patients older than 70 years to younger patients receiving axi-cel and tisa-cel (80% received tisa-cel), there was no difference in the ORR and no statistical difference in the median PFS (54% in younger patients compared to 32% in older patients at 12 months). Although older patients did have worsening disability, there was no difference in rates or grades of toxicities, or duration of hospitalization[103]. The US Lymphoma CAR-T Consortium also studied safety and efficacy of axi-cel in older patients ≥65 years compared to younger patients, and reported similar rates of CRS, ICU admission, and length of hospitalization. Similar to the ZUMA-1 post hoc analysis, there was a higher rate of neurotoxicity seen in older patients (78% vs. 65%)[104]. Importantly, it has been suggested that age itself may not be a risk factor for ICANS development in so much as tumor burden and resultant T-cell expansion[105].

Advancing age does not appear to be a negative prognostic predictor of outcomes in CAR-T. In an analysis of the German Stem Cell Transplant Registry, it was noted that age did not negatively impact PFS in patients receiving commercially available CAR-T. In fact, the HR of 0.904 (95% CI 0.825–0.990) improved with advancing decades of life suggesting outcomes improved with increasing age[106]. Older adults (>65 years) had a numerically higher risk of ICANS in both axi-cel and tisa-cel. Of note, NRM was higher in the older population (9% vs 3%) and was significantly lower in the tisa-cel group. ORR was 69 and 43%, CR was 58% and 31%, and PFS at 12 months was 36% and 26% for the older and younger cohorts, respectively. When comparing older age cohorts (65-69, 70-74, ≥75 years), there was no difference in survival[106,107]. In another study in which 37% (n=484) were ≥65 years, older patients had favorable ORR (odds ratio [OR],1.39; 95% CI, 1.05-1.83), yet had a higher rate of CRS (OR, 1.41; 95% CI, 1.02 to 1.94) and ICANS (OR, 1.77; 95% CI, 1.39-2.26)[102]. In a recent study of adults over the age of 65 years or with ECOG performance status of 2 or higher receiving axi-cel or chemoimmunotherapy after two or more lines of therapy, 12 month OS rates were 62% vs 28% (HR 0.30, 95% CI 0.24-0.37), and ORR was 76% (CR 58%) vs 28% (CR 16%) favoring axi-cel. This suggests tolerability and efficacy of CAR-T even in later lines for both older and frail patients[108]. Furthermore, in a phase 2 trial assessing Lisocabtagene maraleucel (liso-cel) (PILOT study, second line setting) for patients ineligible for ASCT, the ORR was 80% (95% CI 68-89), with most common grade 3 events being neutropenia (48%), CRS (21%), and neurologic events (31%), hence demonstrating good efficacy and comparable toxicity profile[109].

Most of these results consistently demonstrate similar outcomes in older patients receiving CAR-T. Differences in reports of CRS, ICANS, and outcomes are likely inherent limitations of retrospective data, lack of patient control, comorbidities, and disease burden. Ultimately, CAR-T appears to be a well-tolerated and efficacious treatment modality compared to age-matched controls and should be individualized to each patient.

AUTOLOGOUS STEM CELL TRANSPLANTATION

Since 1995, ASCT has been approved for r/r DLBCL for consolidative purposes in chemo-sensitive disease based on the results of the PARMA trial[110]. While previously the standard of care for chemo-sensitive r/r DLBCL, the role and place of ASCT in the CAR-T era is evolving. Moreover, with the development of novel effective salvage regimens, the benefit and utility of ASCT particularly in the older patient population needs to be more clearly delineated[80,108,111]. Many older patients may not be offered ASCT because of physician bias or concern for the ability to tolerate myeloablative conditioning regimens. Historically, studies suggested that older patients suffered from high treatment related mortality (TRM), potentially due to the use of high-dose total body irradiation[112]. However, advances in conditioning regimens and management of toxicities over the past two decades has made it apparent that individualized patient factors and treatment strategies, rather than age, should be factors contributing to decisions regarding ASCT in older patients[96]. That said, older patients may be more susceptible to significant toxicities compared to younger patients, which may increase TRM and impact clinician decision to proceed with ASCT for consolidative purposes[113–115]. In general, studies suggest that ASCT is feasible in adults over the age of 70 years, with a modest increase in toxicities and TRM[96,113,116–120]. In an analysis in which patients who received carmustine, etoposide, cytarabine, and melphalan (BEAM) conditioning and ASCT, patients aged 60-69 years and ≥70 years were compared. While the majority developed febrile neutropenia, gastrointestinal and cardiovascular toxicities, and infections, older patients were found to have higher risk for grade ≥3 cardiovascular toxicities (HR: 3.36; 95%CI: 2.25-5.00; P < 0.001) and skin toxicities (HR, 2.45; 95% CI, 1.08-5.54, P = 0.032). When adjusting for the number of grade ≥3 toxicities within the first 100 days, older patients had a 1.71-fold (95% CI, 1.08-2.71) increased risk for progression or death relative to younger patients[113]. In a study of the CIBMTR database, outcomes of ASCT with BEAM conditioning in DLBCL patients aged 60-69 years (n=363) versus ≥70 years (n=103) between 2008 and 2019 were compared[115]. Multivariate analysis did not demonstrate a significant difference in non-relapse mortality (NRM); HR 1.43, 95% CI 0.85-2.39), relapse, (HR 1.11, 95% CI 0.79-1.56), or PFS (HR 1.23, 95% CI 0.92-1.63). Patients ≥70 years had a higher mortality (HR 1.39, 95% CI 1.05-1.85, P=0.02), which was attributed to a poorer post-relapse OS (HR 1.82, 95% CI 1.27-2.61, P=0.001)[115]. In a study of the European Blood and Marrow Transplantation registry comparing 463 patients with r/r DLBCL over the age of 60 years to younger patients, older patients were more heavily pretreated, less likely to have a first CR at the time of transplantation and received

transplant later after diagnosis compared to younger patients. NRM was higher in elderly patients at 100 days (4.4 % vs. 2.8 %), at 1 year (8.7% vs. 4.7%) and at 3 years (10.8% vs. 6.5%) (P=0.002). In addition, the risk of relapse was higher in older patients (38% vs 32%, P=0.006). The PFS and OS in older and younger patients was 51% vs 62% (P<0.001) and 60% vs. 70% (P<0.001), respectively[117]. In the older population, there is increased risk of treatment toxicity, NRM, and R/R disease, however if toxicities are well managed ASCT can be tolerated and improve survival.

ALLOGENIC STEM CELL TRANSPLANT

While allogenic stem cell transplant (allo-SCT) remains an option in r/r setting, it is not often used due to comparable PFS (49% vs 46%) and higher non-relapse/procedure related mortality (24% vs 10%) when compared to ASCT[121]. Moreover, with availability of CAR-T cell therapy and other novel, more well-tolerated therapies described above, allo-SCT is reserved for salvage or consolidation for fit patients who have failed previous therapies including CAR-T. The evidence for allo-SCT in patients older than 65 years is scarce, with data limited to retrospective studies. Shah et al. pooled 727 patients with NHL that were >65 years who underwent allo-SCT from 2000 to 2015, out of which 30% were DLBCL[122]. While there is an improvement in overall survival over 15 years, NRM at 1 year was 24% and >50% patients died primarily due to relapsed disease at the end of follow up. Additionally, 180-day and 2-year cumulative incidences of acute and chronic graft vs host disease (GVHD) were 13% and 39%, respectively[122]. Hence, allo-SCT remains an option as salvage or consolidation therapy, but is rarely used in older patients given toxicities and risk for TRM.

Conclusion

As the population of adults over the age of 65 years grows, so will cancer burden. While DLBCL is a highly curable disease, special considerations must be factored into personalized treatment decisions for older patients. Level of fitness, comorbidities, and GA evaluations are all important in determining the ideal treatment regimen and should be applied in clinical practice to balance successful treatment with potentially life-threatening toxicities. There are a wide variety of front line and salvage therapies that may off cure or prolong life. A uniform definition of a chronological age for older patients, inclusion in clinical trials, and application of standard risk assessment tools will benefit the future of management of geriatric oncology patients.

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NG, SA, SRP: Conceptualization, methodology, literature review, writing original draft, review and editing, visualization, creation of tables, final approval. H.H.: Writing original draft, literature review, review and editing, final approval. MK: Writing original draft, literature review, review and editing, final approval; JR: Writing original draft, literature review, review and editing, final approval. EAB: Conceptualization, methodology, literature review, writing original draft, review and editing, visualization, creation of tables, final approval, supervision.

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References:

1. National Cancer Institute. SEER Cancer Stat Facts: Diffuse Large B-Cell Lymphoma. Published 2023. Accessed March 20, 2024. https://seer.cancer.gov/statfacts/html/dlbcl.html

2. Kanas G, Ge W, Quek RGW, Keeven K, Nersesyan K, Jon E. Arnason. Epidemiology of diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL) in the United States and Western Europe: population-level projections for 2020–2025. *Leuk Lymphoma*. 2022;63(1):54-63. doi:10.1080/10428194.2021.1975188

3. Wang Y, Ren X, Huang K, et al. Comparison of first-line treatments for elderly patients with diffuse large B-cell lymphoma: A systematic review and network meta-analysis. *Front Immunol*. 2023;13. doi:10.3389/fimmu.2022.1082293

4. Coiffier B, Lepage E, Brière J, et al. CHOP Chemotherapy plus Rituximab Compared with CHOP Alone in Elderly Patients with Diffuse Large-B-Cell Lymphoma. *New England Journal of Medicine*. 2002;346(4):235-242. doi:10.1056/NEJMoa011795

5. U.S. Census Bureau. 2020 Census Demographic and Housing Characteristics File (DHC). https://www.census.gov/data/tables/2023/dec/2020-census-dhc.html

6. Leukemia and Lymphoma Society. NHL SUBTYPES. https://www.lls.org/lymphoma/non-hodgkin-lymphoma/nhl-subtypes

7. Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2017. Published online April 2020.

8. Wang SS. Epidemiology and etiology of diffuse large B-cell lymphoma. *Semin Hematol*. Published online November 2023. doi:10.1053/j.seminhematol.2023.11.004

9. Arcari A, Cavallo F, Puccini B, Vallisa D. New treatment options in elderly patients with Diffuse Large B-cell Lymphoma. *Front Oncol*. 2023;13. doi:10.3389/fonc.2023.1214026

10. Al Armashi AR, Al Zubaidi A, Mahmood O, Thierheimer M, Alkrekshi A, Abdulhaq H. Trends in Diffuse Large B-Cell Lymphoma Mortality in the United States: A Comprehensive Review from 2000 to 2020. *Blood*. 2023;142(Supplement 1):1765-1765. doi:10.1182/blood-2023-180270

11. Ulu BU, Yiğenoğlu TN, Başcı S, et al. Factors affecting survival in elderly patients with diffuse large B-Cell lymphoma. *Leuk Res*. 2021;110:106700. doi:10.1016/j.leukres.2021.106700

12. Hounsome L, Eyre TA, Ireland R, et al. Diffuse large B cell lymphoma (DLBCL) in patients older than 65 years: analysis of 3 year Real World data of practice patterns and outcomes in England. *Br J Cancer*. 2022;126(1):134-143. doi:10.1038/s41416-021-01525-4

13. Abu Sabaa A, Mörth C, Hasselblom S, et al. Age is the most important predictor of survival in diffuse large B-cell lymphoma patients achieving event-free survival at 24 months: a Swedish population-based study. *Br J Haematol*. 2021;193(5):906-914. doi:10.1111/bjh.17206

14. Ekberg S, Crowther M, Harrysson S, Jerkeman M, E. Smedby K, Eloranta S. Patient trajectories after diagnosis of diffuse large B-cell lymphoma—a multistate modelling approach to estimate the chance of lasting

remission. *Br J Cancer*. 2022;127(9):1642-1649. doi:10.1038/s41416-022-01931-2

15. Crump M, Neelapu SS, Farooq U, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. *Blood*. 2017;130(16):1800-1808. doi:10.1182/blood-2017-03-769620

16. Shimkus G, Nonaka T. Molecular classification and therapeutics in diffuse large B-cell lymphoma. *Front Mol Biosci*. 2023;10. doi:10.3389/fmolb.2023.1124360

17. Roschewski M, Phelan JD, Wilson WH. Molecular Classification and Treatment of Diffuse Large B-Cell Lymphoma and Primary Mediastinal B-Cell Lymphoma. *The Cancer Journal*. 2020;26(3):195-205. doi:10.1097/PPO.0000000000000450

18. Mareschal S, Lanic H, Ruminy P, Bastard C, Tilly H, Jardin F. The proportion of activated B-cell like subtype among de novo diffuse large B-cell lymphoma increases with age. *Haematologica*. 2011;96(12):1888-1890. doi:10.3324/haematol.2011.050617

19. Rosenwald A, Bens S, Advani R, et al. Prognostic Significance of *MYC* Rearrangement and Translocation Partner in Diffuse Large B-Cell Lymphoma: A Study by the Lunenburg Lymphoma Biomarker Consortium. *Journal of Clinical Oncology*. 2019;37(35):3359-3368. doi:10.1200/JCO.19.00743

20. Hurria A, Togawa K, Mohile SG, et al. Predicting Chemotherapy Toxicity in Older Adults With Cancer: A Prospective Multicenter Study. *Journal of Clinical Oncology*. 2011;29(25):3457-3465. doi:10.1200/JCO.2011.34.7625

21. Mohile SG, Dale W, Somerfield MR, et al. Practical Assessment and Management of Vulnerabilities in Older Patients Receiving Chemotherapy: ASCO Guideline for Geriatric Oncology. *Journal of Clinical Oncology*. 2018;36(22):2326-2347. doi:10.1200/JCO.2018.78.8687

22. Li D, Sun CL, Kim H, et al. Geriatric Assessment–Driven Intervention (GAIN) on Chemotherapy-Related Toxic Effects in Older Adults With Cancer. *JAMA Oncol*. 2021;7(11):e214158. doi:10.1001/jamaoncol.2021.4158

23. Mohile SG, Mohamed MR, Xu H, et al. Evaluation of geriatric assessment and management on the toxic effects of cancer treatment (GAP70+): a cluster-randomised study. *The Lancet*. 2021;398(10314):1894-1904. doi:10.1016/S0140-6736(21)01789-X

24. Williams GR, Hopkins JO, Klepin HD, et al. Practical Assessment and Management of Vulnerabilities in Older Patients Receiving Systemic Cancer Therapy: ASCO Guideline Questions and Answers. *JCO Oncol Pract*. 2023;19(9):718-723. doi:10.1200/OP.23.00263

25. Merli F, Luminari S, Tucci A, et al. Simplified Geriatric Assessment in Older Patients With Diffuse Large B-Cell Lymphoma: The Prospective Elderly Project of the Fondazione Italiana Linfomi. *Journal of Clinical Oncology*. 2021;39(11):1214-1222. doi:10.1200/JCO.20.02465

26. Tucci A, Martelli M, Rigacci L, et al. Comprehensive geriatric assessment is an essential tool to support treatment decisions in elderly patients with diffuse large B-cell lymphoma: a prospective multicenter evaluation in 173 patients by the Lymphoma Italian Foundation (FIL). *Leuk Lymphoma*. 2015;56(4):921-926. doi:10.3109/10428194.2014.953142

27. Lugtenburg PJ, Mutsaers PGNJ. How I treat Elderly Patients with DLBCL in the frontline setting. *Blood*. Published online November 22, 2022. doi:10.1182/blood.2020008239

28. Rudresha AH, Hassan SA, Sreevalli A, et al. Pre-phase strategy to mitigate first cycle effect in diffuse large B cell lymphoma. *J Egypt Natl Canc Inst*. 2022;34(1):20. doi:10.1186/s43046-022-00116-5

29. Lugtenburg PJ, Mutsaers PGNJ. How I treat Elderly Patients with DLBCL in the frontline setting. *Blood*. Published online November 22, 2022. doi:10.1182/blood.2020008239

30. Zamorano JL, Lancellotti P, Rodriguez Muñoz D, et al. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines. *Eur Heart J*. 2016;37(36):2768-2801. doi:10.1093/eurheartj/ehw211

31. Ganatra S, Nohria A, Shah S, et al. Upfront dexrazoxane for the reduction of anthracycline-induced cardiotoxicity in adults with preexisting cardiomyopathy and cancer: a consecutive case series. *Cardio-Oncology*. 2019;5(1):1. doi:10.1186/s40959-019-0036-7

32. Smith TJ, Bohlke K, Lyman GH, et al. Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update. *Journal of Clinical Oncology*. 2015;33(28):3199-3212. doi:10.1200/JCO.2015.62.3488

33. Morita Y, Kanemasa Y, Sasaki Y, et al. Impact of pegfilgrastim approval on relative dose intensity and outcomes of R-CHOP for diffuse large B-cell lymphoma. *Medicine*. 2022;101(10):e29028. doi:10.1097/MD.0000000000029028

34. Schmitz N, Zeynalova S, Nickelsen M, et al. CNS International Prognostic Index: A Risk Model for CNS Relapse in Patients With Diffuse Large B-Cell Lymphoma Treated With R-CHOP. *Journal of Clinical Oncology*. 2016;34(26):3150-3156. doi:10.1200/JCO.2015.65.6520

35. Schmitz N, Frontzek F. CNS prophylaxis in DLBCL: time to say goodbye? *Blood*. 2022;139(3):315-317. doi:10.1182/blood.2021014043

36. Burns EA, Wilson JJ, Mathur S, et al. Long-term outcomes in patients with Burkitt lymphoma older than 65 years: an analysis of the Texas Cancer Registry. *Ann Hematol*. 2023;102(10):2753-2763. doi:10.1007/s00277-023-05328-w

37. Eyre TA, Kirkwood AA, Wolf J, et al. Stand-alone intrathecal central nervous system (CNS) prophylaxis provide unclear benefit in reducing CNS relapse risk in elderly DLBCL patients treated with R-CHOP and is associated increased infection-related toxicity. *Br J Haematol*. 2019;187(2):185-194. doi:10.1111/bjh.16070

38. Feugier P, Van Hoof A, Sebban C, et al. Long-Term Results of the R-CHOP Study in the Treatment of Elderly Patients With Diffuse Large B-Cell Lymphoma: A Study by the Groupe d'Etude des Lymphomes de l'Adulte. *Journal of Clinical Oncology*. 2005;23(18):4117-4126. doi:10.1200/JCO.2005.09.131

39. Coiffier B, Thieblemont C, Van Den Neste E, et al. Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: a

study by the Groupe d'Etudes des Lymphomes de l'Adulte. *Blood*. 2010;116(12): 2040-2045. doi:10.1182/blood-2010-03-276246

40. Pfreundschuh M, Schubert J, Ziepert M, et al. Six versus eight cycles of bi-weekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas: a randomised controlled trial (RICOVER-60). *Lancet Oncol*. 2008;9(2):105-116. doi:10.1016/S1470-2045(08)70002-0

41. Cunningham D, Hawkes EA, Jack A, et al. Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone in patients with newly diagnosed diffuse large B-cell non-Hodgkin lymphoma: a phase 3 comparison of dose intensification with 14-day versus 21-day cycles. *The Lancet*. 2013;381(9880):1817-1826. doi:10.1016/S0140-6736(13)60313-X

42. Delarue R, Tilly H, Mounier N, et al. Dose-dense rituximab-CHOP compared with standard rituximab-CHOP in elderly patients with diffuse large B-cell lymphoma (the LNH03-6B study): a randomised phase 3 trial. *Lancet Oncol*. 2013;14(6):525-533. doi:10.1016/S1470-2045(13)70122-0

43. Zhang WH, Li GY, Ma YJ, et al. Reduced-dose EPOCH-R chemotherapy for elderly patients with advanced stage diffuse large B cell lymphoma. *Ann Hematol*. 2018;97(10):1809-1816. doi:10.1007/s00277-018-3369-7

44. Bartlett NL, Wilson WH, Jung SH, et al. Dose-Adjusted EPOCH-R Compared With R-CHOP as Frontline Therapy for Diffuse Large B-Cell Lymphoma: Clinical Outcomes of the Phase III Intergroup Trial Alliance/CALGB 50303. *Journal of Clinical Oncology*. 2019;37(21):1790-1799. doi:10.1200/JCO.18.01994

45. Tilly H, Morschhauser F, Sehn LH, et al. Polatuzumab Vedotin in Previously Untreated Diffuse Large B-Cell Lymphoma. *New England Journal of Medicine*. 2022;386(4):351-363. doi:10.1056/NEJMoa2115304

46. Peyrade F, Jardin F, Thieblemont C, et al. Attenuated immunochemotherapy regimen (R-miniCHOP) in elderly patients older than 80 years with diffuse large B-cell lymphoma: a multicentre, single-arm, phase 2 trial. *Lancet Oncol*. 2011;12(5):460-468. doi:10.1016/S1470-2045(11)70069-9

47. Shin HJ, Chung JS, Song MK, Kim SK, Choe S, Cho GJ. Addition of rituximab to reduced-dose CHOP chemotherapy is feasible for elderly patients with diffuse large B-cell lymphoma. *Cancer Chemother Pharmacol*. 2012;69(5):1165-1172. doi:10.1007/s00280-011-1814-6

48. Nowakowski GS, Hong F, Scott DW, et al. Addition of Lenalidomide to R-CHOP Improves Outcomes in Newly Diagnosed Diffuse Large B-Cell Lymphoma in a Randomized Phase II US Intergroup Study ECOG-ACRIN E1412. *Journal of Clinical Oncology*. 2021;39(12):1329-1338. doi:10.1200/JCO.20.01375

49. Moccia AA, Schaff K, Freeman C, et al. Long-term outcomes of R-CEOP show curative potential in patients with DLBCL and a contraindication to anthracyclines. *Blood Adv*. 2021;5(5):1483-1489. doi:10.1182/bloodadvances.2020002982

50. Merli F, Luminari S, Rossi G, et al. Cyclophosphamide, doxorubicin, vincristine, prednisone and rituximab versus epirubicin, cyclophosphamide, vinblastine, prednisone and rituximab for the initial treatment of elderly "fit" patients with diffuse large B-cell

lymphoma: results from the ANZINTER3 trial of the Intergruppo Italiano Linfomi. *Leuk Lymphoma*. 2012;53(4):581-588. doi:10.3109/10428194.2011.621565

51. Chan JY, Somasundaram N, Grigoropoulos N, et al. Evolving therapeutic landscape of diffuse large B-cell lymphoma: challenges and aspirations. *Discover Oncology*. 2023;14(1):132. doi:10.1007/s12672-023-00754-8

52. Di M, Huntington SF, Olszewski AJ. Challenges and Opportunities in the Management of Diffuse Large B-Cell Lymphoma in Older Patients. *Oncologist*. 2021;26(2):120-132. doi:10.1002/onco.13610

53. Feugier P, Van Hoof A, Sebban C, et al. Long-Term Results of the R-CHOP Study in the Treatment of Elderly Patients With Diffuse Large B-Cell Lymphoma: A Study by the Groupe d'Etude des Lymphomes de l'Adulte. *Journal of Clinical Oncology*. 2005;23(18):4117-4126. doi:10.1200/JCO.2005.09.131

54. Habermann TM, Weller EA, Morrison VA, et al. Rituximab-CHOP Versus CHOP Alone or With Maintenance Rituximab in Older Patients With Diffuse Large B-Cell Lymphoma. *Journal of Clinical Oncology*. 2006;24(19):3121-3127. doi:10.1200/JCO.2005.05.1003

55. Eyre TA, Martinez-Calle N, Hildyard C, et al. Impact of intended and relative dose intensity of R-CHOP in a large, consecutive cohort of elderly diffuse large B-cell lymphoma patients treated with curative intent: no difference in cumulative incidence of relapse comparing patients by age. *J Intern Med*. 2019;285(6):681-692. doi:10.1111/joim.12889

56. Sehn LH, Congiu AG, Culligan DJ, et al. No Added Benefit of Eight Versus Six Cycles of CHOP When Combined with Rituximab in Previously Untreated Diffuse Large B-Cell Lymphoma Patients: Results from the International Phase III GOYA Study. *Blood*. 2018;132(Supplement 1):783-783. doi:10.1182/blood-2018-99-116845

57. Wästerlid T, Biccler JL, Brown PN, et al. Six cycles of R-CHOP-21 are not inferior to eight cycles for treatment of diffuse large B-cell lymphoma: a Nordic Lymphoma Group Population-based Study. *Annals of Oncology*. 2018;29(8):1882-1883. doi:10.1093/annonc/mdy184

58. Tilly H, Morschhauser F, Bartlett NL, et al. Polatuzumab vedotin in combination with immunochemotherapy in patients with previously untreated diffuse large B-cell lymphoma: an open-label, non-randomised, phase 1b–2 study. *Lancet Oncol*. 2019;20(7):998-1010. doi:10.1016/S1470-2045(19)30091-9

59. Tilly H, Gomes da Silva M, Vitolo U, et al. Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*. 2015;26:v116-v125. doi:10.1093/annonc/mdv304

60. Hu B, Reagan PM, Sehn LH, et al. Subgroup analysis of elderly patients (pts) with diffuse large B-cell lymphoma (DLBCL) in the Phase 3 POLARIX study. *Hematol Oncol*. 2023;41(S2):416-418. doi:10.1002/hon.3164_306

61. Nowakowski GS, Chiappella A, Gascoyne RD, et al. ROBUST: A Phase III Study of Lenalidomide Plus R-CHOP Versus Placebo Plus R-CHOP in Previously Untreated Patients With ABC-Type Diffuse Large B-Cell Lymphoma. *Journal of Clinical Oncology*.

2021;39(12):1317-1328. doi:10.1200/JCO.20.01366

62. Martine E.D. Chamuleau, Coreline N. Burggraaff, Marcel Nijland, et al. Treatment of patients with MYC rearrangement positive large B-cell lymphoma with R-CHOP plus lenalidomide: results of a multicenter HOVON phase II trial. *Haematologica*. 2019;105(12):2805-2812. doi:10.3324/haematol.2019.238162

63. de Jonge AV, van Werkhoven ED, Dinmohamed AG, et al. A Propensity Score-Adjusted Comparison of Lenalidomide + R-CHOP Versus R-CHOP for *MYC* -Rearranged DLBCL Patients. *Blood*. 2022;140(Supplement 1):2059-2060. doi:10.1182/blood-2022-163204

64. Chihara D, Westin JR, Oki Y, et al. Management strategies and outcomes for very elderly patients with diffuse large B-cell lymphoma. *Cancer*. 2016;122(20):3145-3151. doi:10.1002/cncr.30173

65. Owens CN, Migliacci JC, Horwitz SM, et al. Dose-Adjusted EPOCH +/- Rituximab in Older Patients with High Grade Diffuse Large B-Cell Lymphoma, Burkitt and T-Cell Lymphoma: An Effective Regimen with Acceptable Toxicity Profile. *Blood*. 2014;124(21):4450-4450. doi:10.1182/blood.V124.21.4450.4450

66. Hershman DL, McBride RB, Eisenberger A, Tsai WY, Grann VR, Jacobson JS. Doxorubicin, Cardiac Risk Factors, and Cardiac Toxicity in Elderly Patients With Diffuse B-Cell Non-Hodgkin's Lymphoma. *Journal of Clinical Oncology*. 2008;26(19):3159-3165. doi:10.1200/JCO.2007.14.1242

67. Peyrade F, Jardin F, Thieblemont C, et al. Attenuated immunochemotherapy regimen (R-miniCHOP) in elderly patients older than 80 years with diffuse large B-cell lymphoma: a multicentre, single-arm, phase 2 trial. *Lancet Oncol*. 2011;12(5):460-468. doi:10.1016/S1470-2045(11)70069-9

68. Juul MB, Jensen PH, Engberg H, et al. Treatment strategies and outcomes in diffuse large B-cell lymphoma among 1011 patients aged 75 years or older: A Danish population-based cohort study. *Eur J Cancer*. 2018;99:86-96. doi:10.1016/j.ejca.2018.05.006

69. Mats Jerkeman. A Randomized, Multicenter, Phase III Trial Comparing Treatment With R-mini-CHOP With R-mini-CHP + Polatuzumab Vedotin in Patients With Diffuse Large Cell B Cell Lymphoma (POLAR BEAR). https://clinicaltrials.gov/study/NCT04332822

70. Di M, Huntington SF, Olszewski AJ. Challenges and Opportunities in the Management of Diffuse Large B-Cell Lymphoma in Older Patients. *Oncologist*. 2021;26(2):120-132. doi:10.1002/onco.13610

71. Storti S, Spina M, Pesce EA, et al. Rituximab plus bendamustine as front-line treatment in frail elderly (>70 years) patients with diffuse large B-cell non-Hodgkin lymphoma: a phase II multicenter study of the *Fondazione Italiana Linfomi*. *Haematologica*. 2018;103(8):1345-1350. doi:10.3324/haematol.2017.186569

72. Braulke F, Zettl F, Ziepert M, et al. First-line Treatment With Bendamustine and Rituximab for Old and Frail Patients With Aggressive Lymphoma: Results of the B-R-ENDA Trial. *Hemasphere*. 2022;6(12):e808. doi:10.1097/HS9.0000000000000808

73. Wang M, Fowler N, Wagner-Bartak N, et al. Oral lenalidomide with rituximab in relapsed or refractory diffuse large cell, follicular and transformed lymphoma: a phase

II clinical trial. *Leukemia*. 2013;27(9):1902-1909. doi:10.1038/leu.2013.95

74. Thieblemont C, Howlett S, Casasnovas R, et al. Lenalidomide maintenance for diffuse large B-cell lymphoma patients responding to R-CHOP: quality of life, dosing, and safety results from the randomised controlled REMARC study. *Br J Haematol*. 2020;189(1):84-96. doi:10.1111/bjh.16300

75. Xu PP, Shi ZY, Qian Y, et al. Ibrutinib, rituximab, and lenalidomide in unfit or frail patients aged 75 years or older with de novo diffuse large B-cell lymphoma: a phase 2, single-arm study. *Lancet Healthy Longev*. 2022;3(7):e481-e490. doi:10.1016/S2666-7568(22)00123-4

76. Jones G, Plastaras J, Ng A, Kelsey C. The Evolving Role of Radiation Therapy in DLBCL: From Early-Stage to Refractory Disease. *Oncology*. 2022;(3612):718-727. doi:10.46883/2022.25920980

77. Wong J, Pickles T, Connors J, et al. Efficacy of Palliative Radiation Therapy (RT) for Chemotherapy Relapsed or Refractory Diffuse Large B-Cell Lymphoma: A Population-Based Retrospective Review. *Pract Radiat Oncol*. 2021;11(2):e203-e209. doi:10.1016/j.prro.2020.11.003

78. Kuczynski EA, Sargent DJ, Grothey A, Kerbel RS. Drug rechallenge and treatment beyond progression—implications for drug resistance. *Nat Rev Clin Oncol*. 2013;10(10):571-587. doi:10.1038/nrclinonc.2013.158

79. Jurczak W, Zinzani PL, Gaidano G, et al. Phase IIa study of the CD19 antibody MOR208 in patients with relapsed or refractory B-cell non-Hodgkin's lymphoma. *Annals of Oncology*. 2018;29(5):1266-1272. doi:10.1093/annonc/mdy056

80. Salles G, Duell J, González Barca E, et al. Tafasitamab plus lenalidomide in relapsed or refractory diffuse large B-cell lymphoma (L-MIND): a multicentre, prospective, single-arm, phase 2 study. *Lancet Oncol*. 2020;21(7):978-988. doi:10.1016/S1470-2045(20)30225-4

81. Qualls DA, Lambert N, Caimi PF, et al. Tafasitamab and lenalidomide in large B-cell lymphoma: real-world outcomes in a multicenter retrospective study. *Blood*. 2023;142(26):2327-2331. doi:10.1182/blood.2023021274

82. Zammarchi F, Corbett S, Adams L, et al. ADCT-402, a PBD dimer–containing antibody drug conjugate targeting CD19-expressing malignancies. *Blood*. 2018;131(10):1094-1105. doi:10.1182/blood-2017-10-813493

83. Caimi PF, Ai W, Alderuccio JP, et al. Loncastuximab tesirine in relapsed or refractory diffuse large B-cell lymphoma (LOTIS-2): a multicentre, open-label, single-arm, phase 2 trial. *Lancet Oncol*. 2021;22(6):790-800. doi:10.1016/S1470-2045(21)00139-X

84. Caimi PF, Ardeshna KM, Reid E, et al. The AntiCD19 Antibody Drug Immunoconjugate Loncastuximab Achieves Responses in DLBCL Relapsing After AntiCD19 CAR-T Cell Therapy. *Clin Lymphoma Myeloma Leuk*. 2022;22(5):e335-e339. doi:10.1016/j.clml.2021.11.005

85. Alderuccio JP, Ai WZ, Radford J, et al. Loncastuximab tesirine in relapsed/refractory high-grade B-cell lymphoma: a subgroup analysis from the LOTIS-2 study. *Blood Adv*. 2022;6(16):4736-4739. doi:10.1182/bloodadvances.2022007782

86. Sehn LH, Herrera AF, Flowers CR, et al. Polatuzumab Vedotin in Relapsed or Refractory Diffuse Large B-Cell Lymphoma.

Journal of Clinical Oncology. 2020;38(2):155-165. doi:10.1200/JCO.19.00172

87. Budde LE, Olszewski AJ, Assouline S, et al. Mosunetuzumab with polatuzumab vedotin in relapsed or refractory aggressive large B cell lymphoma: a phase 1b/2 trial. *Nat Med*. 2024;30(1):229-239. doi:10.1038/s41591-023-02726-5

88. Westin J, Olszewski AJ, Fogliatto L, et al. SUNMO: A phase III trial evaluating the efficacy and safety of mosunetuzumab in combination with polatuzumab vedotin vs rituximab plus gemcitabine and oxaliplatin in patients with relapsed/refractory aggressive B-cell non-Hodgkin lymphoma. *Journal of Clinical Oncology*. 2023;41(16_suppl):TPS7586-TPS7586. doi:10.1200/JCO.2023.41.16_suppl.TPS7586

89. Bartlett NL, Assouline S, Giri P, et al. Mosunetuzumab monotherapy is active and tolerable in patients with relapsed/refractory diffuse large B-cell lymphoma. *Blood Adv*. 2023;7(17):4926-4935. doi:10.1182/bloodadvances.2022009260

90. Olszewski AJ, Phillips TJ, Hoffmann MS, et al. Mosunetuzumab in combination with CHOP in previously untreated DLBCL: safety and efficacy results from a phase 2 study. *Blood Adv*. 2023;7(20):6055-6065. doi:10.1182/bloodadvances.2023010840

91. Thieblemont C, Phillips T, Ghesquieres H, et al. Epcoritamab, a Novel, Subcutaneous CD3xCD20 Bispecific T-Cell–Engaging Antibody, in Relapsed or Refractory Large B-Cell Lymphoma: Dose Expansion in a Phase I/II Trial. *Journal of Clinical Oncology*. 2023;41(12):2238-2247. doi:10.1200/JCO.22.01725

92. Dickinson MJ, Carlo-Stella C, Morschhauser F, et al. Glofitamab for Relapsed or Refractory Diffuse Large B-Cell Lymphoma. *New England Journal of Medicine*. 2022;387(24):2220-2231. doi:10.1056/NEJMoa2206913

93. Shipp M, Harrington D, Anderson J, Armitage J. A Predictive Model for Aggressive Non-Hodgkin's Lymphoma. *New England Journal of Medicine*. 1993;329(14):987-994. doi:10.1056/NEJM199309303291402

94. Neelapu SS, Jacobson CA, Oluwole OO, et al. Outcomes of older patients in ZUMA-1, a pivotal study of axicabtagene ciloleucel in refractory large B-cell lymphoma. *Blood*. 2020;135(23):2106-2109. doi:10.1182/blood.2019004162

95. Muffly L, Pasquini MC, Martens M, et al. Increasing use of allogeneic hematopoietic cell transplantation in patients aged 70 years and older in the United States. *Blood*. 2017;130(9):1156-1164. doi:10.1182/blood-2017-03-772368

96. Greenwell IB, Dahi PB. Transplant and chimeric antigen receptor T-cell therapies in elderly patients with lymphoma, a narrative review. *Ann Lymphoma*. 2022;6:8-8. doi:10.21037/aol-22-7

97. Burns EA, Gentille C, Trachtenberg B, Pingali SR, Anand K. Cardiotoxicity Associated with Anti-CD19 Chimeric Antigen Receptor T-Cell (CAR-T) Therapy: Recognition, Risk Factors, and Management. *Diseases*. 2021;9(1):20. doi:10.3390/diseases9010020

98. Roberts ZJ, Better M, Bot A, Roberts MR, Ribas A. Axicabtagene ciloleucel, a first-in-class CAR T cell therapy for aggressive NHL. *Leuk Lymphoma*. 2018;59(8):1785-1796. doi:10.1080/10428194.2017.1387905

99. Ghosh AK, Chen DH, Guha A, Mackenzie S, Walker JM, Roddie C. CAR T Cell Therapy–

Related Cardiovascular Outcomes and Management. *JACC CardioOncol*. 2020;2(1): 97-109. doi:10.1016/j.jaccao.2020.02.011

100.Schuster SJ, Bishop MR, Tam CS, et al. Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma. *New England Journal of Medicine*. 2019;380(1):45-56. doi:10.1056/NEJMoa1804980

101.Abramson JS, Palomba ML, Gordon LI, et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. *The Lancet*. 2020;396(10254):839-852. doi:10.1016/S0140-6736(20) 31366-0

102.Jacobson CA, Chavez JC, Sehgal AR, et al. Axicabtagene ciloleucel in relapsed or refractory indolent non-Hodgkin lymphoma (ZUMA-5): a single-arm, multicentre, phase 2 trial. *Lancet Oncol*. 2022;23(1):91-103. doi:10. 1016/S1470-2045(21)00591-X

103.Ram R, Grisariu S, Shargian-Alon L, et al. Toxicity and efficacy of chimeric antigen receptor T-cell therapy in patients with diffuse large B-cell lymphoma above the age of 70 years compared to younger patients – a matched control multicenter cohort study. *Haematologica*. 2021;107(5):1111-1118. doi: 10.3324/haematol.2021.278288

104.Sano D, Lekakis L, Feng L, et al. SAFETY AND EFFICACY OF AXICABTAGENE CILOLEUCEL (AXI-CEL) IN OLDER PATIENTS: RESULTS FROM THE US LYMPHOMA CAR-T CONSORTIUM. *Hematol Oncol*. 2019;37(S2): 304-305. doi:10.1002/hon.113_2630

105.Nastoupil LJ, Jain MD, Feng L, et al. Standard-of-Care Axicabtagene Ciloleucel for Relapsed or Refractory Large B-Cell Lymphoma: Results From the US Lymphoma CAR T Consortium. *Journal of Clinical Oncology*. 2020;38(27):3119-3128. doi:10.12 00/JCO.19.02104

106.Dreger P, Holtick U, Subklewe M, et al. Impact of age on outcome of CAR-T cell therapies for large B-cell lymphoma: the GLA/DRST experience. *Bone Marrow Transplant*. 2023;58(2):229-232. doi:10.1038/ s41409-022-01867-4

107.Chihara D, Liao L, Tkacz J, et al. Real-world experience of CAR T-cell therapy in older patients with relapsed/refractory diffuse large B-cell lymphoma. *Blood*. 2023;142(12):1 047-1055. doi:10.1182/blood.2023020197

108.Bishop MR. The benefit of CAR T cells in older patients. *Blood*. 2020;135(23):2020-2021. doi:10.1182/blood.2020005592

109.Sehgal A, Hoda D, Riedell PA, et al. Lisocabtagene maraleucel as second-line therapy in adults with relapsed or refractory large B-cell lymphoma who were not intended for haematopoietic stem cell transplantation (PILOT): an open-label, phase 2 study. *Lancet Oncol*. 2022;23(8):1066-1077. doi:10.1016/S1 470-2045(22)00339-4

110.Philip T, Guglielmi C, Hagenbeek A, et al. Autologous Bone Marrow Transplantation as Compared with Salvage Chemotherapy in Relapses of Chemotherapy-Sensitive Non-Hodgkin's Lymphoma. *New England Journal of Medicine*. 1995;333(23):1540-1545. doi:10. 1056/NEJM199512073332305

111.Sehn LH, Herrera AF, Flowers CR, et al. Polatuzumab Vedotin in Relapsed or Refractory Diffuse Large B-Cell Lymphoma. *Journal of Clinical Oncology*. 2020;38(2):155-165. doi:10.1200/JCO.19.00172

112.Sweetenham JW, Pearce R, Philip T, et al. High-dose therapy and autologous bone

marrow transplantation for intermediate and high grade non-Hodgkin's lymphoma in patients aged 55 years and over: results from the European Group for Bone Marrow Transplantation. The EBMT Lymphoma Working Party. *Bone Marrow Transplant*. 1994;14(6):981-987.

113.Dahi PB, Lee J, Devlin SM, et al. Toxicities of high-dose chemotherapy and autologous hematopoietic cell transplantation in older patients with lymphoma. *Blood Adv*. 2021;5(12):2608-2618. doi:10.1182/bloodadvances.2020004167

114.Andorsky DJ, Cohen M, Naeim A, Pinter-Brown L. Outcomes of auto-SCT for lymphoma in subjects aged 70 years and over. *Bone Marrow Transplant*. 2011; 46(9):1219-1225. doi:10.1038/bmt.2010.289

115.Munshi PN, Chen Y, Ahn KW, et al. Outcomes of Autologous Hematopoietic Cell Transplantation in Older Patients with Diffuse Large B-Cell Lymphoma. *Transplant Cell Ther*. 2022;28(8):487.e1-487.e7. doi:10.1016/j.jtct.2022.05.029

116.Sun L, Li S, El-Jawahri A, et al. Autologous Stem Cell Transplantation in Elderly Lymphoma Patients in Their 70s: Outcomes and Analysis. *Oncologist*. 2018;23(5):624-630. doi:10.1634/theoncologist.2017-0499

117.Jantunen E, Canals C, Rambaldi A, et al. Autologous stem cell transplantation in elderly patients (>=60 years) with diffuse large B-cell lymphoma: an analysis based on data in the European Blood and Marrow Transplantation registry. *Haematologica*. 2008;93(12):1837-1842. doi:10.3324/haematol.13273

118.Hermet E, Cabrespine A, Guièze R, et al. Autologous hematopoietic stem cell transplantation in elderly patients (≥70years) with non-Hodgkin's lymphoma: A French Society of Bone Marrow Transplantation and Cellular Therapy retrospective study. *J Geriatr Oncol*. 2015;6(5):346-352. doi:10.1016/j.jgo.2015.04.005

119.Davison K, Chen BE, Kukreti V, et al. Treatment outcomes for older patients with relapsed/refractory aggressive lymphoma receiving salvage chemotherapy and autologous stem cell transplantation are similar to younger patients: a subgroup analysis from the phase III CCTG LY.12 trial. *Annals of Oncology*. 2017;28(3):622-627. doi:10.1093/annonc/mdw653

120.Chihara D, Izutsu K, Kondo E, et al. High-Dose Chemotherapy with Autologous Stem Cell Transplantation for Elderly Patients with Relapsed/Refractory Diffuse Large B Cell Lymphoma: A Nationwide Retrospective Study. *Biology of Blood and Marrow Transplantation*. 2014;20(5):684-689. doi:10.1016/j.bbmt.2014.01.025

121.Chopra R, Goldstone AH, Pearce R, et al. Autologous versus allogeneic bone marrow transplantation for non-Hodgkin's lymphoma: a case-controlled analysis of the European Bone Marrow Transplant Group Registry data. *Journal of Clinical Oncology*. 1992;10(11):1690-1695. doi:10.1200/JCO.1992.10.11.1690

122.Shah NN, Ahn KW, Litovich C, et al. Allogeneic transplantation in elderly patients ≥65 years with non-Hodgkin lymphoma: a time-trend analysis. *Blood Cancer J*. 2019;9(12):97. doi:10.1038/s41408-019-0261-1