Review Article

Initial treatment of elderly population with aggressive lymphoma: a narrative review of current evidence and future directions

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Background and Objective: Diffuse large B-cell lymphoma (DLBCL), a subtype of non-Hodgkin lymphomas (NHL), is commonly diagnosed in older individuals, and its mortality directly correlates with age. Despite recent advancements in treatment modalities for DLBCL, there is no universally accepted approach for elderly patients. R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) has remained the core therapy for decades but has higher toxicity and lower cure rates in the senior subgroup. This review article discusses the strategies for frailty assessment and subcategorization of the elderly population based on multidomain assessment tools. Further, it outlines potential regimens for the initial treatment of DLBCL based on different levels of frailty.

Methods: We conducted a thorough literature review via PubMed and Google Scholars databases to identify the most relevant articles on our subject. Publication dates or languages did not limit our search methodology.

Key Content and Findings: The older population is a heterogeneous group with different degrees of frailty and diminished functional reserve. Coexisting comorbidities in the elderly create additional management challenges. The lack of a global and comprehensive functionality assessment guideline is an area of unmet need. Despite these challenges, R-CHOP, or R-CHOP with modified components, and other chemoimmunotherapy regimens that were investigated as frontline therapies in elderly DLBCL have resulted in promising outcomes, particularly if the investigators carefully subcategorized the studied population using multidomain functionality assessment guidelines and consistently followed up with the patients.

Conclusions: R-CHOP is still considered the best initial treatment for the senior population 60–80 years old, but with careful genetic and functionality classifications. We recommend attenuated and modified versions of R-CHOP, such as R-miniCHOP, as an alternative option for the fit elderly over >80 years. For elderly patients with cardiac co-morbidities, R-CEOP (substituting doxorubicin with etoposide in R-CHOP) has proven to have curative potential. For fit, unfit, and frail, very elderly DLBCL patients (≥85 and mostly ≥90 years), initial treatment options remain challenging, and patients may be best served with a palliative approach.

Keywords: Aggressive lymphoma (AL); elderly population; diffuse large B-cell lymphoma (DLBCL); R-CHOP; initial treatment

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Introduction

As a result of an increase in life expectancy, the overall percentage of the elderly population with hematopoietic malignancies such as lymphoma is growing. Non-Hodgkin lymphoma (NHL) is the seventh most common malignancy in men and the sixth most common in women. Annually, more than 77,000 new NHL cases are diagnosed in the US, and more than 20,000 individuals die from this malignancy (1,2). Lymphomas can be broadly categorized as aggressive or indolent. The most common subtype of aggressive lymphoma (AL) is diffuse large B-cell lymphoma (DLBCL) (1-4).

DLBCL is potentially curable with combination immunochemotherapy but becomes distinctly more difficult to cure as patients get older and typically frailer. Frailty is a syndrome consisting of the physiological, psychological, functional, and social domains. Frailty in the elder population results in more vulnerability following a physiological stressor such as antineoplastic treatments, including chemotherapy, immunotherapy, and targeted agents. The coexistence of comorbidities such as heart failure and renal failure increases the risk of drug accumulation, toxicity, and organ damage. At the genomic level, the higher rate of DNA damage due to alteration in repair mechanisms and higher occurrence of hematopoietic malignancies with genetic complexity may result in malignancies more challenging to manage (1-5).

Hence, it is essential to consider the degree of frailty and the potential adverse effect (AE) of treatment on different organs' function while planning the initial therapy in the elderly population with DLBCL. Further, as the result of this decline in elderly physiological reserve, it is pertinent to dynamically evaluate and monitor their organ function at baseline, during, and after treatment. Regardless of recent advancements in therapeutic modalities, guidelines for dose adjustment, and geriatric assessment tools, the baseline evaluation, treatment, and follow-up remain a challenge for physicians and represent a burden for elderly patients with DLBCL (4-6). This review article discusses challenges inherent in treating elderly patients with DLBCL and outlines potential strategies for better treatment outcomes. We explore different promising regimens investigated in this population base on the level of their functionality. We present the following article in accordance with the Narrative Review reporting checklist. We present the following article in accordance with the Narrative Review reporting checklist (available at https://aol.amegroups.com/article/view/10.21037/aol-22-9/rc).

Methods

We identified relevant studies to our topic using PubMed and Google Scholar databases. No filtration was implemented for article selection while most relevant peer reviewed international literatures were included in our narrative review (see *Table 1*).

Preparatory measures in initiating treatment

The initial step for assessing comorbidities and choosing the best therapeutic strategies is to determine baseline organ functional status by conducting a thorough medical history (specifically drug history), physical exam, and

Table 1 The search strategy summary

Items	Specifications
Date of search	Literature search was conducted between January 12, 2022, and April 5, 2022
Databases and other sources searched	PubMed, Google Scholar
Search terms used	Aggressive, lymphoma, DLBCL, elderly, immunotherapy, chemotherapy, frail, fit, unfit,
Timeframe	Not specified
Inclusion and exclusion criteria	Included international peer-reviewed papers in the English language
Selection process	All the authors were involved in the selection and reviewing of the relevant publications

DLBCL, diffuse large B-cell lymphoma.

using clinical apparatus for estimating cardiac, renal, and pulmonary functions. The next step is to measure and score the concomitant risk factors using comorbidity scoring tools. Geriatric assessment tools have been developed to screen multiple geriatric-related domains and provide more accurate frailty assessment and functional reserve. Several geriatric assessment modalities have been devised and implemented in hematology and oncology clinical settings to identify subjects with a higher risk of morbidity or mortality after treatment (7,8).

Charlson *et al.* were among the first to develop comorbidity assessment tools. The Charlson Comorbidity Index (CCI) is a comprehensive tool that evaluates comorbidities that can alter clinical outcomes in longitudinal studies (9,10). CCI scores have shown to be independently associated with clinical outcomes in both oncologic and hematologic settings. A recent retrospective study by Johnson *et al.* investigated clinical outcomes and treatment toxicity in newly diagnosed NHL adults (from 2000 to 2020) aged ≥65 years who received systemic therapy. The authors found that 42.4% of the patients experienced grade 3+ toxicity, with 8.1% who experienced grades 4 or 5. Moreover, the study's results showed that the rates of unplanned hospitalization were 41.0% (6.1% of ICU admission). Among the investigated variables, patients with hypoalbuminemia and higher Charlson comorbidity score had significantly higher treatment-related toxicity and unplanned hospitalization (11). Another practical and comprehensive comorbidity scale is the Cumulative Illness Rating Scale-Geriatric (CIRS-G) which contains all organ functions, including psychiatric illnesses. Like CCI, CIRS-G has shown to be a valuable prognostic tool and independently correlates with outcomes in patients with NHL (12).

Besides organ function, specific attention must be paid to the physical status, psychological condition, cognitive function, and life expectancy of elderly patients with AL. The comprehensive geriatric assessment (CGA) is a multi-domain assessment tool implemented for the elderly and frail population. Besides organ function, it includes physical, psychological, mental health, cognitive function, nutritional status, socioeconomic status, and polypharmacy. Multiple studies have demonstrated the correlation of CGA score with mortality and morbidity in older patients with hematologic malignancies and further proof of the benefit of its usage in planning treatment strategies. However, the CGA requires clinician training and demands time and resources to administer (13,14).

Tucci *et al.* introduced a simplified version of CGA (SCGA) to further subcategorize frail elderly patients with DLBCL to adjust treatment intensity. Like CGA, SCGA has multi-domains, including the activity of daily living (ADL), Lawton-Brody Instrumental Activities of Daily Living (IADL), age, and CIRS-G, classifying patients into the fit, unfit, and frail categories. In their prospective multicenter observational study, Tucci and colleagues validated the SCGA as a predictive tool for outcome survival study in elderly populations with DLBCL. However, SCGA does not include patients' cognitive function, a vital prognostic factor. Some studies have demonstrated a lack of consistency in integrating SCGA-based approaches and improved patient outcomes (15).

Considering CGA and SCGA weaknesses, Di *et al.* implemented the Surveillance, Epidemiology, and End Results (SEER)-Medicare database combined with the Outcome and Assessment Information Set (OASIS). They proposed a novel global risk indicator that includes cognitive function as well as age, comorbidities, and functional status. Their results suggest that the global risk indicator tool is an independent predictor of treatment approach, adverse events in short intervals, and overall survival (OS) in the long term in the geriatric population with DLBCL and was superior to single domain assessment tools (16).

Nutritional status is another crucial factor that needs to be evaluated before initiating therapy. Malnutrition is a common disorder in subjects with hematologic malignancies and is directly correlated with higher mortality (17). Hence several nutritional assessment tools have been developed for better risk stratification. The geriatric nutrition risk index (GNRI) is a modified version of the prognostic nutritional index (PNI) developed for the octogenarian population. PNI is calculated from albumin and absolute lymphocyte count. Besides albumin, GNRI includes weight, ideal weight, and height. Controlling nutritional status (CONUT) is another nutritional index calculated from albumin, absolute lymphocyte count, and cholesterol level (18). Nagata *et al.*, in a recent retrospective study, investigated the effect of the CONUT score on OS in 472 DLBCL patients (median age of 68.5) who underwent initial treatment with either R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) or R-CHOP-like therapeutics. Study results showed that in patients >70 years old, high CONUT scores negatively affect OS (hazard ratio of 1.86 and $P<0.01$) (19).

DLBCL in elderly population

DLBCL is the most common AL in adults, specifically in the elderly. The median age of diagnosed cases of DLBCL is 66 years old, and almost one-third of them are 75 years old and above. Based on morphology, cytogenic and genomics, and molecular profiling, the 2017 World Health Organization (WHO) guideline updated DLBCL classifications into subtypes, including primary DLBCL of the CNS, primary cutaneous DLBCL leg-type, EBV positive DLBCL, T-cell/histiocyte-rich large B-cell lymphoma (LBLC), primary mediastinal or thymic LBCL, and intravascular LBCL (20). The rest of the DLBCL cases are categorized as DLBCL, not otherwise specified (NOS). Determining the cell of origin (COO) by implementing gene expression profiling, the NOS group is further divided into two subsets; germinal center B-cell-like (GCB) lymphomas that specifically express genes encoding CD10 and BCL6 and activated B-cell-like (ABC) group, that expresses IRF4 and BCL2 but not CD10 and BCL6. The prevalence of ABC increases with age, and it shares a high prevalence in primary DLBCL of the CNS and cutaneous leg-type; Studies have shown that ABC has a lower response rate to standard therapeutic regimens (20-22).

High-grade B-cell lymphoma (HGBL) is a DLBCL category introduced by WHO in the 2016 revision and replaced B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma. HGBL consists of two subgroups, HGBL with MYC and BCL2 or/and BCL6 rearrangements [double hits (DH) and triple-hit (TH) lymphoma] and HGBL NOS. Both categories can affect the geriatric population but with a higher median age in the HGBL NOS subgroup (21,22).

Initial treatment based on level of functionality and comorbidities

Fit category

Like other age groups, the standard treatment of choice for elderly DLBCL patients is R-CHOP. The standard protocol is 3 or 6 cycles (depending on stage) of CHOP combined with rituximab given every 21 days or R-CHOP-21 (rituximab 375 mg/m^2, vincristine 1.4 mg/m^2 (maximum dose, 2 mg), cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2 on day 1, and prednisone 100 mg days 1–5). Depending on the stage, the number of cycles may be decreased in lower-risk patients in the lower stages (I–II) (23,24). Although R-CHOP remains the standard frontline treatment for fit DLBCL patients, a significant proportion of patients are not cured by this modality (25). Multiple prospective trials have proposed and investigated similar protocols to R-CHOP, hoping to address its limitation in riskier subpopulations such as elderly patients with variable degrees of frailty. Modified and attenuated versions of the R-CHOP such as R-CHOP-14 (reducing R-CHOP-21 intervals to 14 days or two weeks), R-miniCHOP (around 50% dose reduction of CHOP portion), and CHOP-like regimens have been designed and investigated to alleviate potential side effects in the elderly with DLBCL (specifically in patients aged 80 and above) (24). When functionality and age were incorporated for further stratification, these regimens provided adequate disease control and represented rational alternative treatment options (25).

Delarue *et al.*, in a randomized trial, compared R-CHOP-14 and R-CHOP-21 treatments in 602 elderly (aged 60–80 years) subjects with untreated DLBCL. Three hundred and four patients were assigned to the R-CHOP-14 group and 298 patients to the R-CHOP-21. With a median follow-up of 56 months, the 3-year event-free survival did not differ between the two arms. Comparing the two groups, no significant differences were found comparing subjects who experienced at least one adverse event. The authors concluded that R-CHOP-14 and R-CHOP-21 had no differences in efficacy and resulted in a similar frequency of adverse events (26).

DA-EPOCH-R is similar to R-CHOP but also includes dose-adjusted etoposide. Compared to R-CHOP, it has shown significantly better progression-free survival (PFS) (82% in DA-EPOCH-R *vs.* 43% in R-CHOP) and OS (90% in DA-EPOCH-R *vs.* 62% in R-CHOP), but in younger patients (age <65 years) (27). Adjusted dosed EPOCH-R is another approach implemented by Zhang *et al.* in elderly patients with untreated CD20$^+$ DLBCL. They administered 70% standard EPOCH dose to patients aged 75 to 79 years and 50% to patients over 80 years with rituximab at a similar dosage to all patients. The complete response rate was 71%, and 3-year OS and PFS were 62.8% and 60.3%, respectively (28).

Phase III Intergroup Trial Alliance/CALGB 50303 study randomized 524 DLBCL patients in DA-EPOCH-R or R-CHOP arms (each received six cycles). Two-year PFS and OS were almost similar between the two cohorts (86.5% for DA-EPOCH-R *vs.* 85.7% for R-CHOP). On the other hand, grades 3 and 4 AE were significantly higher in the DA-EPOCH-R arm compared to the R-CHOP arm, including febrile neutropenia (35.0% in DA-EPOCH-R *vs.*

17.7% in R-CHOP), mucositis (8.4% in DA-EPOCH-R versus 2.1% in R-CHOP neuropathy (18.6% in DA-EPOCH-R *vs.* 3.3% in R-CHOP) and infection (16.9% in DA-EPOCH-R *vs.* 10.7% in R-CHOP). The Alliance study results showed that DA-EPOCH-R might be an alternative regimen limited to selected DLBCL subgroups (29). DA-EPOCH-R regimen has shown efficacy in treating DLBCL patients with high International Prognostic Index (IPI) and cytogenic features such as double-hit lymphoma. This treatment approach may be considered an alternative option in selected elderly fit DLBCL with double-hit or triple-hit rearrangements (careful dosing and toxicity profile consideration specifically in fit patients >70 years old) (30-32).

Elderly fit with cardiac comorbidities

Non-pegylated liposomal doxorubicin (NPLD/Myocet™) was developed as an alternative drug to address doxorubicin's potential cardiac toxicity (33,34). Multiple studies have investigated R-COMP (R-CHOP but with NPLD replacing doxorubicin) (33-37). The randomized phase 2 trial from the GELTAMO group compared R-COMP with R-CHOP (90 subjects and 45 patients in each group) as first-line therapy for DLBCL patients ≥60 years (ECOG <2 in more than 80% of the subjects). The study found no significant differences in 2-year event-free survival (EFS) and PFS and OS probabilities between the two cohorts (EFS of 46% in R-CHOP *vs.* 62% R-COMP and P=0.083; PFS of 59% in R-CHOP *vs.* 62% in R-COMP and P=0.505; OS 75% in R-CHOP *vs.* 73% R-COMP, P=0.751). However, a significantly higher percentage of the R-CHOP group experienced increased troponin levels than the R-COMP group in cycle 6 (100% *vs.* 63% and P=0.001) and one month after treatment (88% *vs.* 56%, respectively, P=0.015). Further, nine episodes of cardiovascular AEs were seen in five patients in the R-CHOP patients (four were grade ≥3), and five episodes were seen in four patients in the R-COMP cohort (all grade 1–2) (38). A recent systematic review compared the efficacy of R-COMP with R-CHOP and has shown significantly higher OS (85.9% versus 70%) and PFS (77.0% versus 60 %) pooled estimates in patients who received R-COMP regimens. The authors deduced that R-COMP might represent a safe and effective option for the elderly with DLBCL, specifically for those with cardiac impairment at baseline (39).

R-CEOP (substituting doxorubicin with etoposide in R-CHOP) is another modified regimen designed to lower cardiac risk. Prusila *et al.*, in a recent matched-pair retrospective analysis, compared PFS among patients who received R-CHOP, R-CEOP, and R-CIOP (doxorubicin replaced by epirubicin) and found a reasonable 2-year PFS of 87.7% (40). Another recent retrospective study compared the safety and efficacy of R-CEOP treatment in 70 *de novo* DLBCL patients (median age of 73) with a matched control group of 140 subjects who received R-CHOP. The median follow-up time of the study was 12 years. No significant differences were seen between the two cohorts concerning the 10-year time to progression and disease-specific survival. However, the 10-year survival was significantly lower in the R-CEOP group than in the control group (30% *vs.* 49% and P=0.002) due to concomitant comorbidities. The study outcomes proposed that R-CEOP may only be considered an alternative curative option for elderly DLBCL patients with absolute contraindication for anthracycline administration (41).

Mitoxantrone is a synthetic derivative of doxorubicin that works against malignant cells by intercalating DNA. R-CNOP has all R-CHOP components, but doxorubicin is replaced by mitoxantrone. R-CNOP has been previously studied for the treatment of elderly DLBCL patients. Three randomized trials compared R-CNOP with R-CHOP in elderly patients (including DLBCL >80 years) and found it to be inferior for OS, complete remission (CR), and treatment failure (TTF) (42-44).

Unfit and frail category, candidate for curative intent therapy

The concept of lower toxicity and overall better or equivalent survival outcomes while using a lower dosage of CHOP portion or 'R-miniCHOP' has been investigated previously. GELA group investigated the safety and efficacy of R-miniCHOP in untreated elderly DLBCL subjects >80 years old (median age of 83 with a range of 80–95 years). The study included one hundred forty-nine patients; the median follow-up was 29 months. Study analysis showed a two-year PFS of 47% with a median PFS of 21 months. The most common side-effect was hematological toxicity [neutropenia in 95 (64%) of patients with grade 3 toxicity or higher in 59 patients and thrombocytopenia in 56 (38%) patients] (45). A recent retrospective study examined intended dose intensity (IDI) and relative dose intensity (RDI) in elderly DLBCL. IDI was defined as the average dose of doxorubicin and cyclophosphamide received in cycle 1. RDI was defined as the total cumulative dose of cyclophosphamide and

doxorubicin patients received across all cycles. The study investigated the influence of IDI and RDI with factors including age, Eastern Cooperative Oncology Group performance status (ECOG PS), CIRS-G score, lactate dehydrogenase (LDH), tumor bulkiness, hemoglobulin level, and albumin on outcomes for DLBCL patients ≥70 years. Study findings showed that patients 70–79 years of age treated with IDI ≥80% had superior PFS and OS than those treated with an IDI <80%. However, comparing the same IDI range (IDI ≥80% *vs.* IDI <80%), no significant differences were seen in patients ≥80 years. Further, multivariable analysis showed that patients 70–79 years treated with IDI <80% had increased CRR, whereas this was not observed in patients 80 years and older treated with IDI <80% (46). Hounsome *et al.*, in their recent population-based study, analyzed 3-year Real World data from Public Health England's National Cancer Registration and Analysis Service and examined treatment and outcome patterns among patients >65 years who received R-CHOP (n=4,079) *vs.* R-miniCHOP (n=313 or 7%) between 2013 and 2015. The study results showed that the choice of R-CHOP or R-miniCHOP had no influence over 3-year OS (54% for both) in each group, and both regimens had similar efficacy, specifically in DLBCL patients aged ≥80 years (47).

Bataillard *et al.* conducted a systematic review investigating the challenge of treating elderly DLBCL cases with a full dose versus reduced dose intensity (DI) of R-CHOP. Thirteen retrospective trials (4,499 subjects) were included in the study. Most of the included high-quality studies showed an association between reduced DI and poorer outcomes in fit patients aged <80. However, in the subgroup population aged ≥80, survival was not consistently affected by reduced DI, and dose-reduced R-CHOP did not compromise survival (48). A recent systematic review analyzed 633 articles exploring the best R-CHOP-based treatment for elderly fit patients with DLBCL. From 2007 and 2020, 64 trials were deemed eligible for the analysis. Most R-CHOP/modified R-CHOP-based studies, including R-miniCHOP, had a CR of over 60% compared to anthracycline-free trials. Moreover, elderly patients >80 years in this subgroup and other groups that received immunochemotherapy with an alternative anthracycline had the highest OS range (46% to 64.7%). Evidence from this systematic review and analysis favored R-miniCHOP or reduced-dose R-CHOP implementation for elderly fit patients >80 years (49).

Ofatumumab is a second-generation, fully human, anti-CD20 monoclonal that inhibits early-stage B lymphocyte activation. It has been used alone or combined with other regimens to treat leukemia and lymphoma (50). Eyre *et al.*, in a phase two randomized trial, investigated CHOP-21 with ofatumumab induction/maintenance therapy (six cycles) in the treatment of forty-three patients (73% aged >60) with Richter transformation of chronic lymphocytic leukemia (CLL). The overall response rate (ORR) was 46%, and the median PFS and median OS were 6.2 and 11.4 months, respectively. The most common adverse effects were fever and infection, and no treatment-related mortality was observed. Comparing the historical outcome authors concluded minimal benefit in the administration of ofatumumab after R-CHOP in treatment for this type of AL (51). A recent metanalysis compared the efficacy and safety of rituximab and anti-CD20 monoclonal antibodies as induction therapy for NHL. Comparing ofatumumab and rituximab, study results did not show any superiority concerning ORR, OS, and CRR but a higher incidence of AEs for patients who received ofatumumab (52). The phase 2 trial from the LYSA group investigated the safety and efficacy of ofatumumab in combination with reduced-dose CHOP in elderly DLBCL patients. The study included 120 DLBCL patients aged 80 years or older (53% had intermediate or high CGA scores). The study results found comparable OS (64.7%) to R-miniCHOP in the past (OS 59%) and the most common adverse effect was grade 3–4 neutropenia (24 subjects or 21%). These results were suggestive that ofatumumab + miniCHOP is safe and effective in elderly DLBCL patients (>80 years old), although it is not superior to R-miniCHOP (53).

Spina *et al.*, in their prospective trial, examined the efficacy and safety of modulated chemotherapeutics based on modified CGA in the newly diagnosed DLBCL elderly population (aged 70 years). Using CGA, they stratified 100 subjects into the fit, unfit, and frail cohorts but administered modulated regimens or doses based on comorbidities and ADL and IADL scores. Step one of stratification was based on the severity of cardiomyopathy using the New York Heart Association or NYHA classification, diabetes, and neutropenia. Patients without comorbidities received either CHOP or R-CHOP regimens. Patients with mild cardiopathy (NYHA class II or CIRS-G grade 2) received CEOP (epirubicin, 70 mg/m^2 i.v. on day 1 replaced doxorubicin in the CHOP regimen) or R-CEOP (epirubicin, 70 mg/m^2 i.v. on day two instead of doxorubicin). Anthracyclines were omitted for patients with moderate or severe cardiopathy (NYHA class III or class IV

or CIRS-G grade 3 or 4), and they were treated with either CVP (cyclophosphamide, vincristine, and prednisone) or R-CVP (rituximab plus CVP regimen). In step two, the dosage of chemotherapies modulated based on ADL or IADL (full dose in ADL score of 6 and/or an IADL score of 7 or 8, 75% of the full dose in patients with an ADL score of 5 and/or an IADL score of 5 or 6 and 50% full dose in patients with ADL score five or an IADL score 5). The treatment resulted in an 81% complete response rate and 80% of 5-year disease-free survival (with 5-year OS rates of 76%, 53%, and 29% (P=0.001), in fit, unfit, and frail subjects, respectively, and similar relapse rate in all three subcategories). Moreover, the rate of grade 3 or 4 hematological and non-hematological toxicities was not significant among the fit, unfit, and frail cohorts. However, frail patients experienced significantly more episodes of febrile neutropenia (33%) than unfit (13%) and fit patients (5%). Further, no significant difference concerning deaths related to toxicity was seen among the fit, unfit and frail cohorts. It was concluded that adjusting R-CVP based on CGA scoring is associated with promising survival outcomes with manageable toxicity in elderly DLBCL patients, especially in fit and unfit subcategories (54).

Unfit and frail category, non-candidate for curative intent therapy

Very old patients with comorbidities and low functionality are considered the most challenging population for treatment. In the unfit and frail elderly for whom a curative regimen is not an option, less intensive treatments with palliative intention are considered a better approach. Patients receiving palliative treatment burden a high risk of death and an overall dismal prognosis (55).

Rituximab mono or in combination have been tested as a palliative treatment. Rituximab, in combination with trofosfamide (alkylating agent), was tested in 11 patients >75 years old (median of 83). CR and PR were seen in 45% and 27% of patients, respectively and the one-year estimated OS was 54.5%. Rituximab-DEVEC is another regimen that showed promising results as a palliative approach. Cox *et al.* investigated oral regimen, DEVEC (Deltacortene®, etoposide, vinorelbine, cyclophosphamide, +/– rituximab), in 51 elderly DLBCL (including both R/R and treatment naïve frail or unfit) subjects. The treatment naïve (17/51 or 33% of subjects) had a one-year OS of 67% and PFS of 61% (56,57).

For extremely elderly and frail patients, who cannot tolerate curative intent therapy, the lack of application of universal assessment tools in different trials has made the selection of treatment strategies more challenging. A phase II multicenter study in Italy used rituximab combined with bendamustine (BR), an alkylating DNA crosslinker, as front-line therapy in frail DLBCL patients aged >70. Based on the CGA assessment, 78% of subjects were unfit, and 22% were frail. Treatment protocol comprised bendamustine (90 mg/m^2, day 1–2) with rituximab (375 mg/m^2, day 1) every 28 days. Patients with age-adjusted IPI (aaIPI) =0 and without bulky disease received four cycles of BR followed by two cycles of rituximab. The rest of the patients received six cycles of BR followed by two cycles of rituximab. During the median follow-up of 33 months, the overall CR was 54% (24 patients), the overall response rate was 62%, and the median PFS was ten months. The most frequent adverse event was neutropenia (37.8% of which were grades 3–4) (58). Zeremski *et al.*, in their retrospective multicenter study, ECOG PS as the assessment tool for patient inclusion, comparing BR with R-CHOP. They included patients aged ≥65 with ECOG with PS ≥2 or ≥75 years regardless of PS. One hundred forty patients were included in the study. The study results showed that BR was associated with marked inferior OS (16.3 *vs.* 75.4 months; P=0.006) and PFS (11.0 *vs.* 62.3 months; P<0.001). Incorporating multivariate analysis, they concluded that only the high age-adjusted Charlson Comorbidity Index (aaCCI) was associated with inferior PFS in the R-CHOP cohort. Hence, R-CHOP did not show any superiority in older DLBCL patients with comorbidities, and the authors concluded that BR might be an alternative option for elderly DLBCL patients with comorbidities (59).

Palliative radiation (PT) is another modality that may be considered in patients with bulky tumors and multiple comorbidities such as cognitive and physical dysfunction making them poor candidates for any regimen. The dosage and number of fractions can be adjusted based on the type of lymphoma (higher dose in DH/TH DLBCL), site of the tumor, and overall patient functionality and prognosis. While implementing PT in patients with poor prognosis it is crucial to alleviate symptoms while considering factors such as toxicity, quality of life, and patient's goals of care (60).

Post treatment multidisciplinary care and follow-ups

Aging results in a decrease in renal function and liver volume and consequently alteration of therapies'

pharmacokinetics. In addition, if present, concomitant comorbidities decrease the threshold of therapy-related toxicity and organ damage. DLBCL patients may experience a higher risk of morbidity and mortality from organ impairments and noncancer disorders during and after treatment (1). Close clinical and laboratory monitoring and follow-ups by the outpatient care team have vital roles in risk management during and after treatment.

In a recent cohort population-matched study, Jull *et al.* investigate the cardiovascular risks in elderly DLBCL patients after treatment. After analyzing data from 1,009 patients and comparison to matched cohort, the authors concluded that fit DLBCL patients aged >75 who received doxorubicin in the context of R-CHOP or attenuated R-CHOP regimen are at increased risk of heart failure. Further, the study found a higher risk of venous thromboembolism (VTE) during the six months after diagnosis (61). These findings justify routine monitoring of elderlies' cardiac functions [including echocardiogram and electrocardiogram (EKGs)] and assessing any anticoagulation indication after treatment (61,62).

Using US SEER database, Howlader *et al.* assessed the noncancer causes of mortality among DLBCL patients after immunochemotherapy. From 2002 to 2011, 8,274 deaths from 18,047 DLBCL patients were recorded and included in the analysis. Within the five years after DLBCL diagnosis, infections had the highest standardized mortality ratios (SMRs) after blood disorders (63). A recent retrospective study examined the morbidity and mortality among 690 DLBCL geriatric patients in 8 different centers in the United Kingdom. Study results showed that cumulative incidences of death due to infections were directly associated with IPI scores (3 to 5), CIRS-G scores (≥6), and low albumin, and it increased up to 5 years after DLBCL diagnosis (3.3% at six months to 11.1% at five years) (64). Besides infection, a higher rate of other immune disorders such as humoral deficiencies and autoimmune cytopenias have been detected in DLBCL survivors. These findings on immune system disorders post-DLBCL treatments motivate close surveillance and long-term follow-up.

Besides organ function, nutritional status at baseline, during, and after cancer treatment directly affects survival outcomes. Studies showed that losing weight during the treatment period is associated with a decrease in the number of treatments received and a lower survival rate (65). Chemotherapy by itself affects weight and calorie intake. A recent retrospective study investigated protein-energy malnutrition (PEM) in cancer-related mortality. Data from 76,425 DLBCL cases also diagnosed with PEM were collected using the National Inpatient Sample database. Study results showed that PEM was directly associated with a higher length of hospital stay, neutropenia, candida sepsis, septic shock, bacteremia, and acute kidney injury. These results encourage close and adequate nutritional monitoring and follow-up during and after DLBCL treatment (66).

Future direction

Currently, there is a clear need for a standard and accepted regimen for the elderly DLBCL. Toxicity is one of the major dilemmas with full dose R-CHOP (67,68). Trials incorporating novel targeting agents with attenuated dosing of R-CHOP, such as R-miniCHOP are being evaluated. R-miniCHOP has been studied in multiple trials in the elderly population and is a regimen that is deliverable. The POLAR BEAR trial is currently examining the efficacy and safety of R-miniCHOP and polatuzumab vedotin (antibody-drug conjugate) in frail DLBCL patients >75 or fit >80 years old (NCT04332822). SWOG 1918 is another randomized phase II/III trial that is investigating R-miniCHOP plus/minus oral azacitidine (synergistic effect by DNA hypomethylation) in elderly DLBCL >75 years while incorporating FIL Tool and GCA for frailty assessment (69).

The results of these studies may change the clinical approach and standard treatments in elderly DLBCL patients with or without comorbidities. Considering the effect of novel multi-target therapeutics, prospective treatment strategies also require careful patient stratification with a focus on both elderly's quality of life and survival outcomes.

Conclusions

AL survival rates have increased in the elderly population during the last three decades. Initial treatment of elderly patients with DLBCL requires a multidisciplinary approach. Multiple functional domains such as physiological, psychological, social, and environmental factors (including support and polypharmacy) must be considered, investigated, and addressed before initiating trials or treatments. Integrative geriatric assessment tools are adjunctive modalities developed for further risk stratification and prognostic evaluation of treatment outcomes. When combined with genotyping categorizations, implementing these multi-domain assessment guidelines has resulted in less biased patient selection, better optimization of the

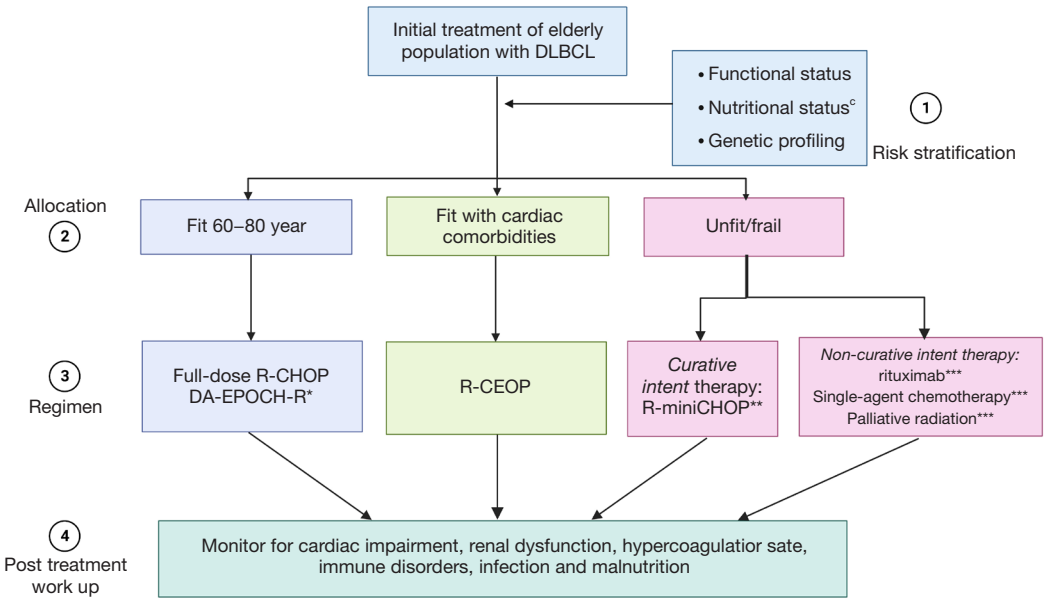

Figure 1 Stratification, patient allocation and treatment algorithm of elderly patients with DLBCL. [c], needs to be considered for risk assessment. *, EPOCH adjusted dose can be considered in patients >70 years with double hit and triple hit rearrangements; **, patient is a candidate for curative intent therapy/applicable in fit, patients >80 years; ***, patient is not a candidate for curative intent (palliative therapy). DLBCL, diffuse large B-cell lymphoma; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; DA, dose adjusted; EPOCH-R, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin and rituximab; R-CEOP rituximab, cyclophosphamide, etoposide, vincristine and prednisone.

protocols, and more consistent outcomes.

Despite developments of newer chemoimmunotherapeutic regimens that can be applied for octogenarian DLBCL subgroups, R-CHOP and R-CHOP modified regiments remain the best initial options. R-CEOP may be considered an alternative option for fit elderly populations with significant cardiac impairment. When dealing with the very elderly, R-miniCHOP has shown promising results for fit patients >80 years old. Before administering such treatment, one must determine if potential curative treatment can be administered, and if it can, R-miniCHOP is worth considering. Patients for whom curative intent therapy is too toxic, then one must consider simple palliative maneuvers like external beam radiation, single-agent rituximab, or R-CVP (see *Figure 1*). Post-treatment close laboratory, clinical monitoring, and follow-up are critical concepts for achieving optimum outcomes. For future perspectives, clinical trials investigating new initial regimens need to implement equally reliable integrative assessment tools, perform biological profiling, and plan long-term follow-ups to achieve the most favorable outcomes.

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