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Older patients with lymphoma: navigating a landscape of clinical controversies and barriers to innovation

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Abstract:

Older patients with lymphoma represent a growing, heterogeneous population whose care is challenged by diverse outcomes, limited evidence, and one-dimensional age definitions. Historically, arbitrary age thresholds such as ≥60 or ≥80 years have guided treatment decisions, yet they fail to capture the biological and functional diversity of aging and can limit opportunities for cure and progress. Current practice relies on arbitrary dose reductions in old age, such as R-miniCHOP, despite limited data for optimal intensity and benefit–risk trade-offs. Likewise, novel agents and combination therapies frequently demonstrate discrepant efficacy and safety across age groups, but systematic attempts to optimize dose for the older patients are rarely prioritized. When it comes to clinical trials, documenting benefit of new therapies is more challenging in older patients due to high background mortality that complicates interpretation of overall and progression-free survival and may led to underpowered trials. Moreover, prognostic models developed in younger populations have limited applicability in older patients, as they overlook the broader range of clinically relevant outcomes in older patients, including treatment-related mortality, functional decline, and quality of life. Pre-therapeutic geriatric assessments are prognostic, but their predictive capability remains to be demonstrated in prospective trials before use as treatment decision support tools.

Addressing these challenges requires reframing of “old age” to a multidimensional construct, incorporating geriatric assessment, patient preferences, and biological age. More inclusive trial designs, dedicated dose-finding in older patients, and development of holistic, predictive models are critical to advance care. Without this, progress risks stalling for a growing group of our patients.

Background:

Historically, older patients with lymphoma were defined solely by chronological age based on chemotherapy-era toxicity concerns and thus limited treatment options. However, managing lymphoma in older patients has evolved beyond this niche scenario with outdated, low survival expectations. Older patients should receive individualised care that addresses personal beliefs, goals and acceptance of toxicities that potentially cause functional decline in the context of a naturally limited life expectancy. Quality-of-life aspects like independent living and treatment convenience may be prioritised over crude survival duration, in contrast to younger patients.[1] The breadth of clinically relevant and possible outcomes in older patients are much more diverse and includes cure with or without decline in independent living ability as well as death from progressive lymphoma versus treatment toxicity in the setting substantial competing risk of deaths from other causes. Traditionally used endpoints like overall survival (OS) and progression-free survival (PFS) fail to disentangle these important events, which are nevertheless critical for making treatment decisions that align with patient preferences. The complex balance of treatment-related benefit and risks in older patients requires careful clinical judgement and respectful, open evidence-informed conversations with greater level of nuance than those held with younger patients. The science of aging is advancing, enabling improved understanding of age as a highly individual biological and functional measure rather than purely chronological. This progress is critical with a projected 115% increase of ≥85 year-olds from 2020 to 2040 in the US which means that managing lymphoma in octogenarians and above will become a substantial proportion of future clinical practice.[2] The drastic changes in age distributions are already tangible. A Nordic population-based newly-diagnosed diffuse large B-cell lymphoma (DLBCL) study showed median age increased from 67-70 in 2007 to 72-74 years in 2021.[3] Other recent database/registry studies from Germany, UK, and US observed similar median age at DLBCL diagnosis of 70-75 years.[4–6] Paradoxically, while ~50% of DLBCL patients are now +70-years old segment, high-quality evidence is limited for even the most common treatment decisions in the oldest patient populations causing considerable clinical challenges. This review addresses controversies in management of older lymphoma patients, focusing mostly on DLBCL, but also relevant to hematology in general.

Age-related prognostic implications should not automatically define 'old' patients

Definitions of old age require consideration of clinical rationale for any age-threshold in lymphoma, which is meaningful if clear age-related differences in treatment outcomes and tolerability exist.

The World Health Organization[7] (WHO) definition of 'old' is persons ≥60 years, but using this definition, most patients with lymphoma are 'old'. Correlations between age and outcome are also highly dynamic and change with treatment landscape, supportive care improvements, and societal risk tolerance. Notably, with the observed increase in life-expectancy over the past three decades, age-matched fitness has also improved.[8] While the WHO definition is not meaningful today, it may have been historically appropriate. Pivotal DLBCL studies conducted two decades ago enrolled "elderly" patients. The landmark study showing superiority of Rituximab (R)-CHOP over CHOP enrolled 60-80 year-olds with no significant co-morbidities and ECOG performance ≤2.[9,10] The prior 60-year age-cut was supported by strong survival correlation with age in lymphoma prognostic models and associated perceived higher unmet needs.[11,12] Later real-world studies identified 70 years a better OS discriminator in the R-CHOP era suggestion that these associations are dynamic and heavily influenced by the studied patient population.[13]

However, categorical age thresholds for prognostic association with OS generally translate poorly into operational old-age definitions (Table 1). Limitations of binary age cut-offs are demonstrated by improved performance of models using age as continuous variable which do not erroneously assume constant hazards for deaths on each side of a binary cut off.[14] Defining old age based on associations with worse progression-free survival (PFS) and OS is also generally problematic because both measures include all-cause mortality. In DLBCL where cure is a realistic goal for approximately 50% of older patients ≥80-years, the high background mortality adds events to PFS and OS that are not directly modifiable by treatment adjustments and therefore, less relevant for treatment decisions per se.[15,16] In a Swedish multistate modelling study[17] of 2,941 DLBCL patients in remission, transitions to death from first remission (no relapse) accounted for a substantial proportion of total mortality in older patients, especially those >80 years. While it is difficult, if not impossible, to truly delineate causes of death in this population, where treatment-related toxicities contribute directly or indirectly to deaths in remission, the results highlight two important aspects. First, there are likely a substantial number of events that are not directly influenced by treatment decisions but nevertheless contributes to outcomes measures like OS and PFS used in prognostic models. If dichotomized age-thresholds are relevant for treatment decisions at all, they should optimally be identified in studies that can separate deaths from lymphoma progression from other causes (including background and treatment-related mortality). Clinical decisions based on identified high risk of deaths from lymphoma progression differ from those made in response to high risk of treatment-related deaths or deaths from competing causes. Second, the high mortality

for patients in first remission underscores the continues need for effective treatments that induce durable remissions in older patients, while minimizing toxicity to reduce the number of deaths in remission, both those occurring as a direct consequence of treatment toxicity as well as indirect causes through worsening of pre-existing comorbidities and/or events that lead to functional decline.

Age may define treatment regimen but not treatment eligibility.

Treatment-specific elderly designations are often employed to define the age where benefit/risk of therapy changes to become unfavourable due to poor tolerability. However, these are only meaningful in clinical decision making if rooted in clinically, reliable measures of treatment tolerability and not just crude survival. Age-related dose-reductions, premature treatment cessation, or treatment mortality are important metrics for these assessments. While age strongly correlates with poor treatment tolerability and treatment-related mortality, more granular data on these metrics could characterise age-related risks. Improved understanding of the biological/clinical reasons for poor tolerability may alleviate potential concerns regarding serious treatment complications in some cases where more tolerable treatments are needed, but also avoid undertreatment of fit older patients due to unfounded perceived high risk of complications. Supporting the notion of perceived tolerability related to age, a Danish population-based study showed that 35% of patients with DLBCL between 80-84 years old received substandard therapies, including palliation.[15] Consistently, US database study found that less than 50% of all patients with DLBCL ≥80 years received R-CHOP (including R-miniCHOP) and a large proportion received no treatments at all.[18] These numbers emphasize the need for more tolerable treatment options for older patients, but also raises a concern that poor outcomes may be in part due to a risk averse approach leading to substandard treatment in older DLBCL patients.

In modern first-line phase III DLBCL trials, the upper age for inclusion has been 80 years due to perceived poor tolerance to full-dose R-CHOP in patients exceeding this age (NCT06047080, NCT05578976, NCT06356129).[19–21] R-miniCHOP eligibility is also pragmatically set to ≥80 years in the recently published ESMO guidelines for lymphoma.[22] Old age definitions for expected benefit/risk tipping points are heavily treatment specific and should change as treatment landscapes evolve to reflect better supportive care and/or less toxic agents. Such decisions are evident in clinical practice for 50–60-year-olds with Burkitt lymphoma, where trade-offs between tolerability of intensive chemotherapy and potential efficacy must be made. In contrast, no fixed age limits

exist for treatment-naïve, low-tumour burden follicular lymphoma where rituximab monotherapy can be used safely for all ages.[23] The age cut-offs are among key eligibility criteria in clinical trials and often reflect a conservative approach to risks, especially when older patients are excluded on the basis of chronological age alone. While modern first-line studies of DLBCL typically operate with an upper age threshold of 79-80 years (NCT06047080[24], NCT05578976[25], NCT06356129[26]), recent first-line studies of mantle cell lymphoma (MCL) used broader definitions of "elderly," including patients as young as 60-65 years. For example, the ECHO, SHINE, and ENRICH trials enrolled newly diagnosed patients with MCL with ECOG Performance 0-2 that were older than 60 (ENRICH) or 65 (SHINE and ECHO) years considered transplant-ineligible.[27–29] The eligibility for intensive cytarabine containing regimens with high-dose therapy and autologous stem cell transplant (HDT/ASCT) was historically <65 years, for example in the Nordic MCL2 and MCL3 trials.[30] However, real-world data (RWD) studies have shown, that treatment with HDT/ASCT is not uncommon in patients with MCL and age >60-65 years and in other lymphomas, such as CNS lymphoma, and a more recent MCL trial, HDT/ASCT were used in age up to 70 years.[31,32] In contrast to SHINE and ECHO, the TRIANGLE trial, which included patients up to the age of 65 years, documented an OS as well as a PFS benefit when ibrutinib was combined with cytarabine-containing chemotherapy regimens.[33] It is likely, that fit patients >65 years could have been included without safety risks in TRIANGLE, aligned with normal clinical practice, and the most recent European MCL guidelines recommends use of TRIANGLE-based therapy in up to 70 years.[34] Rather than moving the testing of tolerability to the post marketing setting, it would be optimal to study those older individuals in the clinical trials to capture safety data in a systematic way.

The risk of serious adverse events does increase with age and is a major limitation for effective treatment of older patients, especially for chemotherapy but also targeted therapies.[19,35] However, arbitrary old-age treatment eligibility definitions can potentially derail development of new, effective therapies for elderly populations – particularly for desperately needed less toxic therapies. Age-based dosing schedules should be explored over age-determined treatment eligibility already early in clinical development programs (Table 1). Unfortunately, older patients with cancer are significantly underrepresented in early phase clinical trials with >75 year-olds accounting for as few as 9-18% of participants but 28-50% of the total cancer patient population.[36] In a review by FDA of hematology trials submitted between 2005-2015 (all phases), <10% of 11,425 patients enrolled in lymphoma trials were >75 years, although they constitute a much greater proportion of the total

patient population.[37] Even in registrational trials submitted to the FDA and EMA between 2014-2024, the proportion of patients >75 years (now close to the median age of newly diagnosed DLBCL) was either low or not even reported.[38] Thus, older patients are underrepresented throughout all clinical development phases and establishing the benefit/risk for older patients is deferred to the post-marketing setting through clinical experience and in the absence of systematic data collection.

Existing phase I trial dosing schedules also typically rely on early detection of protocol-defined dose-limiting toxicities and not long-term tolerability, despite novel agents often being administered for longer than historical chemotherapy regimens and often intended for use until progression. Objective age-related differences in treatment tolerability in DLBCL have been demonstrated in studies such as the PHOENIX trial[19] where ibrutinib plus R-CHOP showed superior OS in patients aged <60 years over R-CHOP alone, yet detrimental OS for over 60 years. The latter group experienced more serious adverse events and higher failed completion rates for full R-CHOP. Similar observations were made in ibrutinib-chemotherapy treated mantle cell lymphoma (MCL). Adding ibrutinib to intensive immunochemotherapy provided OS benefit in younger, transplant-eligible MCL in TRIANGLE[39], but no OS benefit was achieved with ibrutinib plus R-bendamustine in transplant-ineligible patients in SHINE[27]. The sizeable PFS advantage in SHINE in the ibrutinib-R-bendamustine arm with reduction in deaths from lymphoma progression was offset by higher risk of toxicity-related deaths.[27] However, it would be wrong to conclude that these treatment combinations are only efficacious in younger patients. The ongoing Arched/GLA 2022-1 study investigates first-line acalabrutinib combined with R-miniCHOP in older patients with DLBCL (+80 years or 61-80 years unfit to receive full-dose R-CHOP) and the combination of a BTKi with better tolerability and reduced dose chemotherapy may lead to a more tolerable regimen for this group.[40,41] Rather than narrowing treatment-eligibility, focusing more strongly on dose-optimization in older populations prior to pivotal studies could establish more tolerable treatments and inclusive, successful late stage clinical development (Table 1). Studies which enrich for elderly populations, while simultaneously evaluating new treatment in younger patients have shown promise. The Hodgkin Lymphoma HD21 study randomized young patients between BreCADD and the more intensive BEACOPPesc chemotherapy, which is undeliverable to older patients. BreCADD showed both superior PFS and lower toxicity.[42] The deliberate addition of a single-arm cohort of 85 older patients aged 61-75years to receive BreCADD within HD21 provided some safety, feasibility, and efficacy data for older patients, in the absence of exposure to the high

intensity control regimen.[43] This study serves as an example of successful inclusion of older patients in the pivotal study, although the collected data was not considered sufficient to establish formally benefit/risk in patients >60 years.[44] Unfortunately, the current fast-paced drug development programs give little attention to dose-optimizations, exploration of true target doses, and strategies to include underrepresented older cohorts. This raises unacceptable ethical issue with missed treatment opportunities for a large patient population. Growing rationale for rethinking drug development is evidenced by the recent advent of novel, highly effective therapies harbouring predictable and narrow toxicity profiles, such as bispecific antibodies, in the context of surging DLBCL rates in older patients.[45] Strategies for inclusion of older patients with lymphoma in studies of novel therapies should be prioritized by critically reviewing structural barriers for inclusion. For example, hard upper age-ceiling in in- and exclusion criteria should only be used if some data suggest that there is a strong chronological age-related impact of benefit/risk of the investigational therapy that does not go through age-related fragility measures and comorbidities. Other measures to increase inclusiveness towards older populations would be to relax some of the organ-based eligibility criteria. While patients that do not fulfill organ-based eligibility criteria have worse lymphoma outcomes and many of those are older patients, the better approach would be to explore posology adapted to these impairments in the hope of benefiting this population with higher unmet needs rather than excluding them.[46,47] Inclusion of older patients could also be increased by rethinking the typical setup of clinical trials. which are often performed at selected tertiary academic centres.[48] While this is a burden for younger patients, it can be insurmountable for the older patients, that also constitute a larger proportion of the patient population in the rural areas and may have to travel longer distances to participate.[48] There are now several opportunities to conduct trials with decentralized elements, which means that trial-specific procedures can be performed closer to home and sometimes even at home (Table 1). The increasing use of decentralized elements in clinical trials could facilitate inclusion of older patients, but decentralized elements are unfortunately still rarely used to a larger extent in clinical trials involving novel cancer therapies and there are still logistical and legal challenges that should be addressed.[49,50]

Weak evidence levels for key decisions - the mini-CHOP example

Older patients with lymphoma, particularly aggressive subtypes, experience universally inferior outcomes but this does not justify accepting lower evidence levels nor disincentivise new studies. Randomised trials are feasible and urgently needed to inform clinical care.[51] Dose-reduction for

treatment-naive DLBCL patients ≥80 years is now common with (R)-mini-CHOP (roughly 50% of full CHO doses) becoming standard and the control arm in recent DLBCL clinical trials in older and frail adults.[51,52] Replacement of standard R-CHOP with R-miniCHOP is a major decision, as treatment failures were historically associated with very dismal outcomes due to the lack of effective, tolerable salvage therapies, although this is changing with newer therapies.[53] The GELA R-miniCHOP study was a single-arm, phase II enrolling 149 patients ≥80 years.[16] All patients were ECOG performance 0-2 and 47% had no significant daily function limitations. The 58 on-study deaths were mostly secondary to lymphoma progression, but 12 were treatment-related toxicity including infections. The 2-year PFS was 47% (38–56) which is substantially lower than full-dose R-CHOP in studies of younger patients.[10] In contrast to patients in the GELA study, older patients now commonly receive G-CSF and viral/antibiotic prophylaxis as well as pre-phase steroids which likely improves outcomes. Despite the relatively low efficacy, this study led to wide adoption of R-miniCHOP patients with DLBCL ≥80 years old. Taken with supportive care improvements, a critical question remains: would a carefully increase in dose-intensity lead to better outcomes despite more toxicity? Or are worse outcomes for older DLBCL patients intrinsic to different disease biology that is more resistant to immunochemotherapy? A large proportion of older patients with DLBCL have ABC subtype which confers inferior prognosis: 28-33% of patients aged 50-60 years versus 54-67% in patients >80 years.[54,55] Interestingly, replacing vincristine with polatuzumab vedotin (pola-R-CHP) conferred greater benefit in the ABC subtype of DLBCL than for the GCB subtype and greater PFS improvement in 70–80 year-olds patients.[56, 57] These observations are now explored in the ongoing Nordic phase III POLARBEAR study[52] where pola-R-miniCHP is tested against R-miniCHOP in newly-diagnosed patients ≥75 (NCT04332822). The addition of BTKi (acalabrutinib) to R-miniCHOP is another strategy that may successfully target the prevalent ABC subtypes of DLBCL among older patients.[40]

Worse outcomes in elderly patients could also partially be explained by suboptimal dose-intensity. Although R-miniCHOP is curative in some, the optimal R-CHOP dosing strategy has never been explored in prospective randomized elderly studies. Real-world studies are mixed. In a systematic review of dosing strategy of 5,188 newly diagnosed DLBCL from 13 studies, 10 performed multivariable analyses and 6 reported significantly poorer outcomes with reduced dose-intensity. However, in subgroups aged ≥80, lower dose-intensity did not consistently impair OS. There was substantial heterogenicity in dose-intensity calculations and definitions of reduced dose-intensity. Furthermore, most studies had very few patients ≥80 years which limited power to determine

smaller, yet clinical important effects of dose-reductions in this cohort.[58] Two recent observational studies specifically explored R-miniCHOP versus R-CHOP. A UK study included 746 DLBCL patients ≥80 years old receiving R-CHOP and 158 R-mini-CHOP.[59] Patient characteristics were balanced, with identical 3-year OS (54%) maintained in multivariate analysis (HR 0.95, 95%CI 0.73-1.22, R-CHOP reference). Due to R-CHOP definitions including some dosing concessions, the R-CHOP cohort likely included patients receiving reduced doses. A Dutch population-based DLBCL study evaluating age 65 years or above reached different conclusions. Using propensity scores 384 R-mini-CHOP-treated patients were matched to 384 of the 3,847 R-CHOP-treated patients. R-miniCHOP was associated with statistically significant worse survival (PFS 51% versus 68%; OS 60% versus 75%; relative survival [RS] 69% versus 86%). ECOG performance was not available for either study's matching, despite being strongly predictive of OS. Attributing inferior OS to dose reductions therefore needs caution as it is likely confounded by ECOG performance and frailty. Whether higher chemotherapy dosing would lead to different outcomes for elderly patients remains unclear. While uncertainties remain around the optimal dosing strategy in older patients, an Italian study focusing on 370 patients ≥80 years showed that the inclusion of anthracycline, regardless of dosing strategy, correlated with better survival outcomes. Outcomes by R-CHOP intensity (here >70% versus 50-70% of standard dose intensity) did not impact outcomes, although these comparisons where not adjusted for confounders. In general, escalation/de-escalation strategies warrant prospective, randomized investigations to control for all known and unknown confounders linked to dosing strategy in older patients. Confounding response-adapted treatment decisions during therapy could also impact these analyses. For example, dose intensity may be reduced more often in a patient with signs of poor treatment tolerability if interim response assessment shows remission as compared to those with partial remissions. Finally, most of the published studies exploring R-CHOP dosing strategies use reduced-dose definitions for doses that were much higher than the conventional R-miniCHOP schedule. For example, a large US study showed no detrimental effects of R-CHOP given in <80% of standard dose intensity (cyclophosphamide or doxorubicin) to patients with DLBCL >80 years.[60] However, considering many promising new therapies in development, chemotherapy dose-optimizations may not be a high priority at all. Older patients with DLBCL may potentially look forward a chemotherapy-free future, as shown by the preliminary data of the triplet polatuzumab, rituximab, and glofitamab in the AGMT□NHL□16/GLA2022□10 trial where CR was achieved in 82% of patients ineligible for full dose R-CHOP (median age 80 years, range 66-92).[61] Numerically, the CR rate of +80% is identical

to what is achieved with full-dose R-CHOP in younger patients.[20] While durability of response remains to be seen, these early data question the future of chemotherapy in older patients with lymphoma in high-income countries that can afford these expensive combination therapy. However, optimisation of the chemotherapy dosing strategies may still be the most cost-effective way of improving outcomes on a global scale. While RWD may help by providing descriptive data about treatment tolerability, the causal inference between different dosing strategies and outcomes are complex even with advances in statistical methodologies for comparative effectiveness studies and more granular RWD. Pragmatic clinical trials where patients are randomized to different dosing strategies but otherwise managed in a setting very close to normal routine practice and where events are captured in national registries if possible could be a cost-efficient way of reaching more firm conclusions concerning dosing strategies.

Trials in older patient with lymphoma risk a higher bar for success and missed safety signals

Treatment- and disease-unrelated deaths in clinical trials are a unique challenge in elderly populations. Highlighting this, the UK study observed a marked difference between OS and lymphoma-specific survival (LSS) (3-year OS 54%; LSS 80-90%).[59] The exact contributors to cause of death are difficult to elucidate despite OS remaining the most important clinical outcome to industry, policy makers and regulatory bodies. Background mortality estimates can provide some clarity; the 2020 5-year mortality for 80-year-old Danish men and women were 30% and 22%, respectively.[62] Corresponding estimates for 50-year-olds were 2% and 1%. The high background mortality of elderly populations impacts clinical trial performance and results. Paradoxically, it can raise the bar for success in older lymphoma patients despite higher unmet need. Our case example illustrates this. Consider a novel immunotherapy which is very effective in combination with first-line chemotherapy for high-risk DLBCL. The experimental therapy (ET) reduces the risk of dying from lymphoma by 10% after 5 years regardless of age and has no negative or positive influence on lymphoma-unrelated deaths. Two trials are performed – Trial I exclusively enrols 50-year-olds and Trial II enrols only 80-year-olds. The 5-year LSS is set to 80% and 50% for 50-year-olds and 80-year-olds, respectively.[63] Utilizing Danish background mortality[62], Table 2 illustrates how the two hypothetical trials differ in terms of survival between the arms, with Trial I having an HR between the arms of 0.50 and Trial II an HR of 0.82, resulting in Trial I having clearly superior power to Trial II with similar enrolment numbers. Thus, transferring efficacy results (for example observed HR for OS) from younger to older patients without considering background mortality differences

can result in underpowered studies and higher bar for success. At the same time, high background mortality may inadvertently obscure excess mortality from toxicity. PFS is the common primary endpoint in DLBCL trials, but OS is increasingly considered as a safety endpoint where trends towards worse OS in an experimental arm, even if not statistically significant, would raise concern despite a PFS gain.[64] Again, paradoxically, the bar will be higher for detection of detrimental effects on OS in studies of older patients, despite their excess risk of fatal toxicities. We illustrate this with similar survival assumptions as before, but a fixed number of 500 patients (250 per arm) in a scenario where the ET is associated with excess mortality of 1%, 2%, 3%, 4%, or 5% after 5 years. The corresponding hazard ratios (HRs) for OS in younger patients would be 1.05 (Power (P): 4%) , 1.11 (P: 8%) ,1.16 (P: 12%), 1.22 (P: 19%), and 1.27 (P: 25%) whereas HRs for older would be 1.02 (P: 4%) ,1.04 (P: 5%), 1.06 (P: 8%), 1.08 (P: 19%), and 1.11 (P: 15%). Thus, while excess mortality caused by the ET is similar, it is more likely to go unnoticed in the oldest patients. Overall, designing and conducting trials in older patients is more complex and associated with lower likelihood of success for several reasons. This may limit the pharmaceutical companies' willingness to invest in the development of novel therapies for the oldest patients with lymphoma. The fact that novel therapies are, as a rule, associated with more toxicity in older patients and because OS outcomes are worse, could also lead to a perception of poorer cost-effectiveness among payers and more questions raised in the post-marketing access discussions. Such negative perceptions will exacerbate the already existing disparity between younger and older cancer patients. Ultimately, there is a role for regulatory agencies like FDA and EMA as well as ethics review boards to strongly encourage, if not reinforce, inclusion of more older patients in clinical development programs already at early stages to optimize dosing strategies for the older patients groups.

Prognosis and prognostic models in old patients

Prognostic models for older patients require several considerations to maintain clinical relevance. For example, endpoints predominantly related to progression or all-cause mortality do not adequately recognize the broader range of clinically relevant events among older patients, where treatment-related mortality and loss of function are substantial risks of interest for patients. Accurately predicting these outcomes in real-world settings also requires models developed on representative patient populations as models developed in younger may not apply (Table 1). The Advanced-stage Hodgkin Lymphoma International Prognostic Index (A-HIPI) developed for

patients aged 18-65[65] years was applied to patients aged 65-90 years resulting in a C-index for OS of 0.55, indicating low discriminatory power, almost at the level of random guessing.[66] A recent validation study of several commonly used DLBCL prognostic indices also reported lower predictive accuracy in patients >60 years, likely due to focus on measures of disease burden and failure to account for geriatric performance measures and comorbidities.[67] Dedicated prognostic models for older patient models have been developed with better performance for outcome predictions.[68–70] Merli et al.[69] integrated a simplified geriatric assessment (GA) in a prognostic model for older patients with DLBCL, which have been externally validated both in the original publication as well as in a Chinese study.[71] However, caution must be taken when utilizing GA's in older patients with lymphoma. While the ASCO guideline recommends GA-guided management of patients ≥65 years planned for systemic therapy when GA deficits are identified, the evidence supporting this practice in lymphoma is insufficient. The ASCO recommendation was based on nine clinical trials, of which only five included patients with lymphoma. Among these, two trials enrolled very low proportion of lymphoma patients (grouped in the "other cancers")[72,73], two included fewer than 10% lymphoma patients (N=33 and N=46 patients) [74,75], and only one trial[76] in which a substantial proportion of patients enrolled had lymphoma (N=50, 31%). Evidence derived from patients with solid cancers may not apply in lymphoma, as patients with lymphoma and GA deficits may improve substantially and fast on lymphoma therapy if deficits were partially caused by high disease burden. Routine use of GA's can also be challenging due to limited resources and absence of a simple commonly agreed standard assessment tool.[77] A consensus statement from experts in the field would facilitate more standardize practices and accelerate implementation in clinical trials and routine practice. Alternatives ways of assessing comorbidity and fragileness through readily available surrogate measures may be an option. For example, prescription drug overviews and polypharmacy can predict various different patient outcomes such as hospitalizations and severe infections and not just OS.[78]

Finally, the validity GA assessment for use in treatment decision algorithms is sensitive to changes in therapy. Newer agents, including small-molecule inhibitors such as BTK inhibitors and BCL2 inhibitors, as well as bispecific antibodies, and antibody–drug conjugates, brings distinct toxicity profiles compared with chemotherapy. This may fundamentally change the utility of current frailty scores for treatment decision.

When developing prognostic and predictive models for older patients, considering relevance of different outcomes and how they may differ between younger and older patients is important (Table 3). Discriminating between these outcomes is clinically important. If treatment-related deaths dominate OS events, increasing dose-intensity would be the solution. In contrast, if a high proportion of deaths is caused by progressive lymphoma with few treatment-related deaths, dose-escalations may be relevant. In general, endpoints should be more nuanced, recognizing that disease progression and death do not carry equal weight, and giving priority to understanding both the cause and timing of death. As a minimum, endpoints focusing on disease- and treatment-related events in older patients should try to account for the significant background mortality and how it contributes to the conventional OS and PFS measures (Table 3). Other survival endpoints, such as cause-specific mortality and relative survival, may provide more meaningful information for older lymphoma patients, although cause-specific mortality requires exact cause of death, which can be difficult to determine especially with multimorbidity. Incorporating cause-specific mortality could be combined with integration of prognostic scores that can distinguish treatment-related from disease progression–related mortality. Such prognostic tools could also guide treatment decisions and trial enrollment for older patients, enabling more intensive therapy for those at higher risk of disease progression and less intensive approaches for those at greater risk of treatment-related mortality. In contrast, relative survival rely on life tables for background mortality and is easy to obtain, but depends on model assumptions, which may not be fulfilled in hematology.[79]

Recent developments in the field of multistate modelling[80] allow handling of a wide array of different endpoints and aspect of the elderly health trajectory in a single model. Hematology comprehensive models have yielded clearer overviews of difficulties and adverse events in elderly cohorts, including DLBCL.[17,81]

Conclusions

Strict lymphoma therapy age cut-offs serve older patients poorly, both in clinical guidelines as well as a default selection criterion in clinical trials. They are arbitrary, outdated, and risk mismatching benefits and risks in these patients. They also inadequately accommodate patient wishes or goals of care. We must develop better frameworks for shared decision-making in older patients that focuses on informed therapeutic decisions based on likelihoods of a range of relevant clinical outcomes, which can vary in importance according to personal beliefs. Building robust and validated

predictive models that account for these outcomes at different time-points based on patient and disease characteristics will inform this process. Furthermore, a global overhaul of trial design in elderly populations is needed throughout the drug development pathway - from dose optimisation in early phase focusing on target doses rather than MTDs through to reviewing the backbone of randomised studies and harnessing RWD to inform applicability to clinical cohorts.

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TABLES

Table 1: Key topics that are considered barriers to development of novel, safe therapies for older patients with lymphoma, with suggested short- and long-term solution

Problem	Consequence	Short-term solution	Long-term solution
Dichotomized old age definition	Arbitrary age cut-offs (e.g., ≥60 or ≥70 years) exclude older adults that are fit and do not capture the biological heterogeneity of old age	Move away from chronological age-threshold to measures that use age more indirectly through relevant measures such as biological age, comorbidity, and fitness	Develop models that successfully integrate age, comorbidity, fitness, and functional status into a reproducible measure that can be used to select (and stratify) patients in clinical practice and clinical trials
Poor representation in clinical drug development	Limited efficacy/safety data for older patients, uncertainties about benefit-risk, and reliance on data generation in the post-marketing setting	Focus on systematic inclusion (possibly targeted enrollment of older patients to establish dosing age/frailty/comorbidity adapted dosing strategies in the earliest phases of drug development	Develop pivotal trial concepts that allow for differential dosing strategies within the trial, determined by age/frailty/comorbidity related treatment tolerability
Poor evidence for chemotherapy dosing strategies in	Suboptimal cure rates due to undertreatment versus risk of overtreatment/toxicity	Increase focus on possible outcomes in older patients and understand clinical risk factors and cultural	Develop and conduct pragmatic trial designs that enable dose explorations with minimal administrative burdens and trial costs to

older patients		reasons for undertreatment versus overtreatment	increase feasibility
Structural barriers to trial participation for older patients	Trials require activities and trial-related visits that leads to disparities based on residence (rural vs urban), ability to travel, and sufficient physical and cognitive capacity to participate	Review clinical trials protocols for activities that are not essential for safety and scientific integrity. Facilitate greater geographical diversity of clinical trial sites	Develop decentralized trial frameworks, home-based treatments and monitoring in hematology/oncology trials
Trials of older patients have higher bar for success when conventional endpoints like OS and PFS are used due to background mortality	Reduced statistical power; type 2 errors and missed efficacy for efficacious therapies. Excess mortality related to issues are more likely to go unnoticed.	Account for high background mortality in studies of the oldest patients. Consider risk of missed efficacy (type 2 error) when subgroup analyses are made for older patients in pivotal trials	Develop trial endpoints that separate mortality in deaths caused by lymphoma progression, treatment toxicity and competing background mortality
Lack of widely agreed and validated prognostic models developed for older patients	Uncertain, possibly poor predictive performance of the models when used in older patients	Carefully validate existing prognostic tools on older patients and utilize those which generalize best. Agree on a standard model to assess fitness and	Development of prognostic tools that can predict the wider range of relevant clinical outcomes that meaningful specifically for the older patients. Explore models as decision

		comorbidity in older patients with lymphoma for use moving forward	support tools for treatment intensity, including dynamic adaptions of treatment intensity during therapy if patients improve/worsen

Table 2: Two hypothetical clinical trial scenarios, one for patients aged 50 and the other for patients aged 80. In both scenarios, an experimental treatment increases the 5-year LSS by 10%. The table shows the resulting OS in each arm, the corresponding HRs, and power with different number of trial participants randomized in 1:1 ratio. Two-sided $\alpha = 0.05$ is used.

Abbreviations: BS = Background survival, LSS = Lymphoma specific survival, OS = Overall survival, HR = Hazard ratio.

	Trial I (patients aged 50)		**Trial II (patients aged 80)**	
	CONTROL	**EXPERIMENTAL**	**CONTROL**	**EXPERIMENTAL**
5-year BS	99%		74%	
5-year LSS	80%	90%	50%	60%
5-year OS	79%	89%	37%	44%
HR	0.50		0.82	
Power at enrollment				
• 200	47%		19%	
• 400	76%		34%	
• 600	90%		47%	
• 800	96%		59%	
• 1,000	99%		69%	
Enrollment to achieve 80% power	442		1,301	

Table 3: Overview of event types likely to occur in older patients with lymphoma and their clinical relevance, including how predictions would impact management.

Event	Special consideration for elderly populations	Clinical importance
Toxicity with impact on independent living and daily functioning	With lower baseline functional levels and reserve capacity, older patients are at risk of treatment-related functional decline that eventually reach levels that severely impact independent living with possible lifelong impact on quality of life.	Impact of toxicity underestimated using 'maximum grade' measures. Benefit/risk as reported in clinical trials may not translate to routine clinical settings and value to patients.
Dose interruptions, substantial dose reductions, or pre-mature termination of treatment	Older patients are more likely to experience toxicities lead to dose reduction or premature treatment discontinuation which may impair treatment efficacy. Threshold for when to reduce dose is lower for older patient.	Reduced dose intensity leading to lower efficacy and perceived lack of benefit in clinical settings. Undertreatment of older patients due to lack of knowledge about optimal dosing strategy/dose modifications for older patients
Primary refractory disease / early relapse	Frailty and genetically more complex cancer combined with less intensive therapies in older patients increase the risk of refractory disease and early relapse.	Refractory disease in older patients is more often associated with dismal outcomes due to lack of tolerable treatments. More risk in first-line treatment may be justified in older patients who express wish for curative treatment.
Late relapse and late treatment toxicities	Shorter follow-up due to competing risks make late relapses more difficult to capture accurately among the older patients. Shorter residual life expectancy, pre-existing comorbidities, and selection of fit older patients for treatments complicates evaluation of late treatment toxicities and their implications on the normal age-related	True long-term benefit of therapy and late toxicities not adequately measured, leading to lack of knowledge about the longer term benefit/risk ratio in older patients

	decline in general health.	
Deaths	Overall survival is an efficacy measure more difficult to interpret in older patients, especially in diseases with acceptable survival outcomes, due to competing deaths from lymphoma-unrelated causes. Incorporating information on cause of death and expected mortality is essential to respond to observations with relevant changes in clinical practice.	Deaths from unrelated erroneously attributed to treatment can lead to erroneous perceptions about tolerability and undertreatment of older patients. Relevant clinical response to high mortality requires more knowledge about the causes of deaths.