Frailty and Diffuse Large B-Cell Lymphoma: Where Do We Go From Here?

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Older adults with diffuse large B-cell lymphoma (DLBCL) or transformed follicular lymphoma represent a prevalent and highly problematic malignancy. DLBCL is the most common lymphoma, accounting for approximately 30% of all non-Hodgkin lymphomas. Median age at presentation is approximately 67 years, and the percentage of patients >70 years of age continues to expand as the population ages. Therapy is potentially curative in a significant percentage of patients, even in those aged ≥80 years, highlighting the critical importance of delivering therapy safely to this vulnerable population. However, older adults also have inferior survival and augmented risk of treatment toxicity due to comorbid illnesses, altered physical and cognitive function, and impaired metabolism of chemotherapeutic agents. Thus, identifying which older adults are likely to do well with chemoimmunotherapy, and which will do poorly and should receive other novel therapies remains a critical question for the field.

Frailty refers to the loss of functional reserve that compromises the ability to cope with physiologic stressors, and is well recognized in oncology as an important factor associated with clinical outcomes, including survival and treatment toxicity. Frailty can be measured by a comprehensive geriatric assessment (CGA), a formal evaluation of functional status, comorbid conditions, medications, psychological state, social support, and nutritional status, but CGA utilization is infrequent in oncology. To address this, additional tools aimed at identifying frailty in DLBCL have been developed, such as the Fondazione Italiana Linfomi Simplified Geriatric Assessment (sGA). The sGA incorporates age, comorbidity score, activities of daily living (ADL) score, and instrumental activities of daily living (IADL) score and stratifies patients into fit, unfit, and frail categories, with frail patients having a 2-year overall survival (OS) of approximately 50% compared with approximately 80% for fit patients. Additionally, other tools such as the Vulnerable Elders Survey-13, a patient survey, and the 4-meter gait speed test—an objective physical test measuring the length of time for a patient to ambulate 4 meters at a normal pace—have been shown to be associated with OS in patients with DLBCL. This literature has significantly advanced our understanding of frailty and its association with outcomes, but most of these instruments require either a patient evaluation or administration of a patient survey, and a sizeable amount of this work derives from tertiary care settings.

Elsewhere in this issue, Vijenthira et al report on a timely and important analysis assessing the relationship of frailty with survival and healthcare utilization using a population-based retrospective cohort. In this study of adults aged >65 years with newly diagnosed DLBCL receiving chemoimmunotherapy, the authors defined frailty utilizing population-based health administrative data to generate a modified generalizable frailty index (FI). The FI incorporates 30 variables across myriad dimensions and has been studied in the surgical population. The analysis included >5,000 patients, the vast majority of whom had de novo DLBCL, with a median age of 75 years. Across this population-based data, almost half (49%) of older adults were frail. Frailty was associated with healthcare utilization, including emergency room

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visits, admissions, and ICU admissions. In multivariate analyses adjusting for potential confounders, frailty was associated with 1-year survival. Among frail patients, 14% received only 1 cycle of chemoimmunotherapy and fewer than half completed 6 cycles. Interestingly, frail patients were more likely to die during cancer therapy but not more likely to die from lymphoma compared with nonfrail patients, and 22% of frail patients were admitted due to an infectious complication and 19% were admitted to an ICU.

This work is an important contribution to the literature on frailty for patients with DLBCL, because it demonstrates the prevalence of frailty in a large population-based sample, underscoring its significant impact on mortality and treatment-related complications. The use of a modified version of the FI is innovative and helpful as a tool for assessing frailty in population-level data given the noted limited utilization of the CGA and lack of current integration of patient-reported assessment of frailty into clinical practice. Notably, the median OS for the frail population was still 3.5 years, underscoring that frailty defined by the FI should not preclude the use of curative-intent chemoimmunotherapy. An important limitation to highlight is the absence of data on international prognostic index scores or administered regimens, including anthracycline dosing.

In sum, Vijenthira et al describe important associations of frailty with clinical outcomes in a large population-based sample of older adults with DLBCL, further cementing our understanding of the importance of baseline frailty as a predictor of poor clinical outcomes. A number of questions remain to be answered moving forward. Whether excess mortality in frail patients is due to worse disease biology, augmented treatment toxicity, or other factors remains incompletely understood. Moreover, though frailty is clearly associated with poor outcomes, we lack the ability to predict prospectively with a high level of certainty which patients will not benefit from curative-intent therapy. Critically, we lack studies examining how identification of frailty through CGA or other instruments should impact treatment selection, such as with modification of chemoimmunotherapy dosing. Additionally, there remains an unmet need for interventions to improve treatment tolerability. Prior studies show that prephase steroids, given alone, with rituximab, or with vincristine, improve performance status and reduce infectious complications. However, additional supportive care interventions and novel prephase regimens, perhaps using targeted agents or bispecific antibodies, to further debulk patients are sorely needed. Prioritizing clinical trials aimed at improving the clinical outcomes of frail older adults with DLBCL has the potential to significantly alter the care of this vulnerable and prevalent population.

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References