Prognostic tools for older patients with diffuse large B-cell lymphoma: complex patients require complex solutions and a personal touch

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In this volume of *Haematologica*, Isaksen *et al.* describe a new prognostic index that has been developed and validated to estimate the survival of those older patients with diffuse large B-cell lymphoma (DLBCL) who are treated with standard immunochemotherapy. This new index combines the Activities of Daily Living (ADL) scale and the Charlson Comorbidity Index (CCI), along with age, sex, albumin, stage, Eastern Cooperative Oncology Group (ECOG) score, and lactate dehydrogenase (LDH) level. There are three distinct prognostic groups, which differ significantly in terms of overall survival (OS). The authors demonstrated that the new index performed better than conventional prognostic indices like the International Prognostic Index (IPI), the Revised (R)-IPI, and the National Comprehensive Cancer Network (NCCN)-IPI.[1]

The authors should be commended for their efforts in carrying out such a study in a difficult-to-treat population, combining lymphoma-related parameters with patient-specific features, which are not well accounted for in the conventional approach to DLBCL prognostic assessment. For many years, the IPI was the only prognostic tool available to estimate survival in patients with aggressive lymphomas. However, this tool oversimplified the complex characteristics of older subjects, assuming a categorical role for age, and limiting patient description to a simple assessment of performance status. It has become clear over time that lymphoma does not get more aggressive with age per se, and that, with the improvement in both prevention measures and living conditions, the consensus on the definition of "old" has shifted upwards, to 75-80 years of age. No matter the age cutoffs, the ECOG performance status (PS) measure is just another ineffective effort to describe patients' problems. Typically, PS understates or completely ignores the presence of geriatric impairments, which have been proven to be determinants for the patient's geriatric evaluation. Moreover, PS describes a condition that can frequently be reversed by treatment. Over time, geriatric assessment has gained an

important role in describing patient status, allowing the reporting of multiple domains of a patient, ranging from the assessment of the ability to perform simple daily activities to the description of the emotional status or of cognitive functioning. Several now-validated scales have been proposed to describe the fitness of an older patient in an attempt to provide valuable objective and reproducible clinical tools. After several retrospective and prospective studies, Merli *et al.*[2] were able to build and validate the first prognostic index (Elderly Prognostic Index, EPI) designed for the older patient with DLBCL which combines disease-related features with an objective, reproducible, validated tool to define patient frailty (simplified geriatric assessment, sGA). Isaksen *et al.*'s Geriatric Prognostic Index (GPI) follows in the same vein, but, unlike the EPI, it calculates a score for patients who are eligible for immunochemotherapy with curative intent. This new tool contributes to the ongoing search for accurate prognostic models to support clinical or therapeutic decisions for the management of older DLBCL patients. Additional tools are expected in the future which will explore different scales or proxies of patient status, including patient domains that remain unexplored or for which there is little evidence (i.e., sarcopenia, senescence biomarkers, etc.).

To advance clinical research on older patients with lymphoma, it is critical to remember that one of the primary goals of prognostic studies is to provide actionable features or predictive factors that can be used to support clinical decisions. In this setting, prognostic evaluation in older DLBCL patients requires a slightly different strategy than that in younger individuals. Firstly, an older patient cannot be treated using the same guidelines as those for a younger one. In other words, older patients may benefit more from risk-adapted treatments that take an inverted approach rather than the linear association between rising risk and treatment intensity used for younger patients. A palliative approach that protects the patient from needless toxicity and from further loss of quality of life may

be a more acceptable goal of therapy in a high-risk patient than it would be in a low-risk older patient with cancer. The second significant difference between younger and older DLBCL patients regards the varied nature of risk in older patients as well as the individual patient's therapeutic aims. The effectiveness and worth of a treatment are established by a number of factors that are added to the simple risk of mortality or disease progression. The risk of being hospitalized, the loss of independence and of physical or social functioning, or simply the loss of quality of life are some of the pertinent endpoints for a frail patient. Thirdly, compared to younger individuals, the risk variables for older patients with DLBCL are much more diverse and the relationships between these variables are complicated.

In conclusion, older patients with DLBCL pose a clinical and therapeutic challenge for physicians, and prognostic tools capable of describing the high complexity of these subjects are eagerly awaited. We must be prepared to manage a complex problem with tools that are, by definition, difficult to manage and use. However, no tool will be able to replace the fundamental role of a dedicated physician, whose experience, compassion, and personal touch are invaluable in determining a patient's outcomes.

Disclosures

References

1. Isaksen KT, Galleberg R, Mastroianni MA, et al. The Geriatric Prognostic Index: a clinical prediction model for survival of older diffuse large B-cell lymphoma patients treated with standard immunochemotherapy. Haematologica. 2023;108(9):2454-2466.

2. 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. J Clin Oncol. 2021;39(11):1214-1222.