Follicular lymphoma treatment decisions: put GELF on the shelf?

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The decision to initiate or defer treatment for a newly diagnosed patient with low-grade follicular lymphoma (FL) presentation is challenging, and for nearly four decades a leading discriminator to help with that decision in clinical practice and in clinical trials has been the Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria.

In this issue of Haematologica, Barraclough and colleagues identify that the GELF criteria are in fact not well correlated with treatment initiation in the Australasian health-care system that is unique in supporting only immunochemotherapy or observation as initial FL management options.[1] This report expands the scope of observations from Japan and the US suggesting that in clinical practice, the GELF criteria are not strong discriminators of who is immediately treated *versus* who is observed.[2,3]

The authors appropriately highlight concerns that clinical trials uniformly populated with patients who have GELF criteria may yield results disparate from the patient populations that actually receive systemic therapy at diagnosis. They further highlight the lack of prognostic value for GELF criteria in their cohort. Together, these illuminate the limited effectiveness of the GELF criteria in determining who "should" get enrolled in trials of systemic chemotherapy, yet they have remained a stalwart for nearly four decades.

The GELF criteria were initially utilized in a 1986 trial design by a multicenter cooperative group in France and Belgium (Groupe d'Etude des Lymphomes de l'Adulte) with a goal of identifying large tumor burden or adverse prognostic factors to select FL patients for a randomized study of cyclophospamide, doxorubicin, vincristine and prednisone (CHOP) +/- interferon α-2b.[4] Although citing an earlier St. Bart's cohort on prognostic factors for response and survival in 148 FL patients, there is little homology between the two.[5] Only two of the seven GELF criteria - B symptoms and splenomegaly - were actually prognostic in that citation.

Since 1986, there has been immense evolution in the treatment of FL most notably with rituximab replacing interferon α-2b as the immunologic component of immunochemotherapy despite the improved OS reported in the above trial for the interferon-treated patients. Bendamustine, lenalidomide and more recently bispecific antibodies have enhanced the spectrum of management tools. Furthermore, prognostic indices in FL such as FLIPI, FLIPI-2, PRIMA-PI, and M7-FLIPI have all been subsequently developed based upon newer cohorts numbering up to the thousands with rigorous modeling strategies all of which makes GELF criteria a bit harder to defend as the optimal therapy selection tool (Figure 1).[6-9] Nonetheless, clinical trial criteria and prominent treatment guidelines commonly still utilize GELF criteria to establish appropriateness of systemic therapy initiation.[10]

This raises the question as to what are the actual clinical practice discriminators of who is treated and who is observed and furthermore raises the fundamental question of what should be justification to treat FL patients at diagnosis. Randomized clinical trials of upfront therapy in FL patients showing prolonged survival compared to observation are famously lacking, and our best current measure of those at high risk for early mortality rely on outcomes in the first 2 years following immunochemotherapy. Perhaps rigorous development of an effective prognostic model that identifies at diagnosis those with a high risk of early death from lymphoma would be useful. Model developers often gravitate toward lists of differentially weighted variables resulting in scores to answer such questions. Likely all would agree that the presence of symptoms such as pain, dyspnea, cough or fatigue would justify initial treatment. These variables can be hard to quantify but are generally easy to document. Patient concerns related to fear or anxiety can be hard to quantify or even document and can perhaps sometimes be addressed with support and education thereby avoiding systemic therapy yet may be an important treatment-seeking factor for patients.

Ongoing work expands on surrogates for tumor burden,

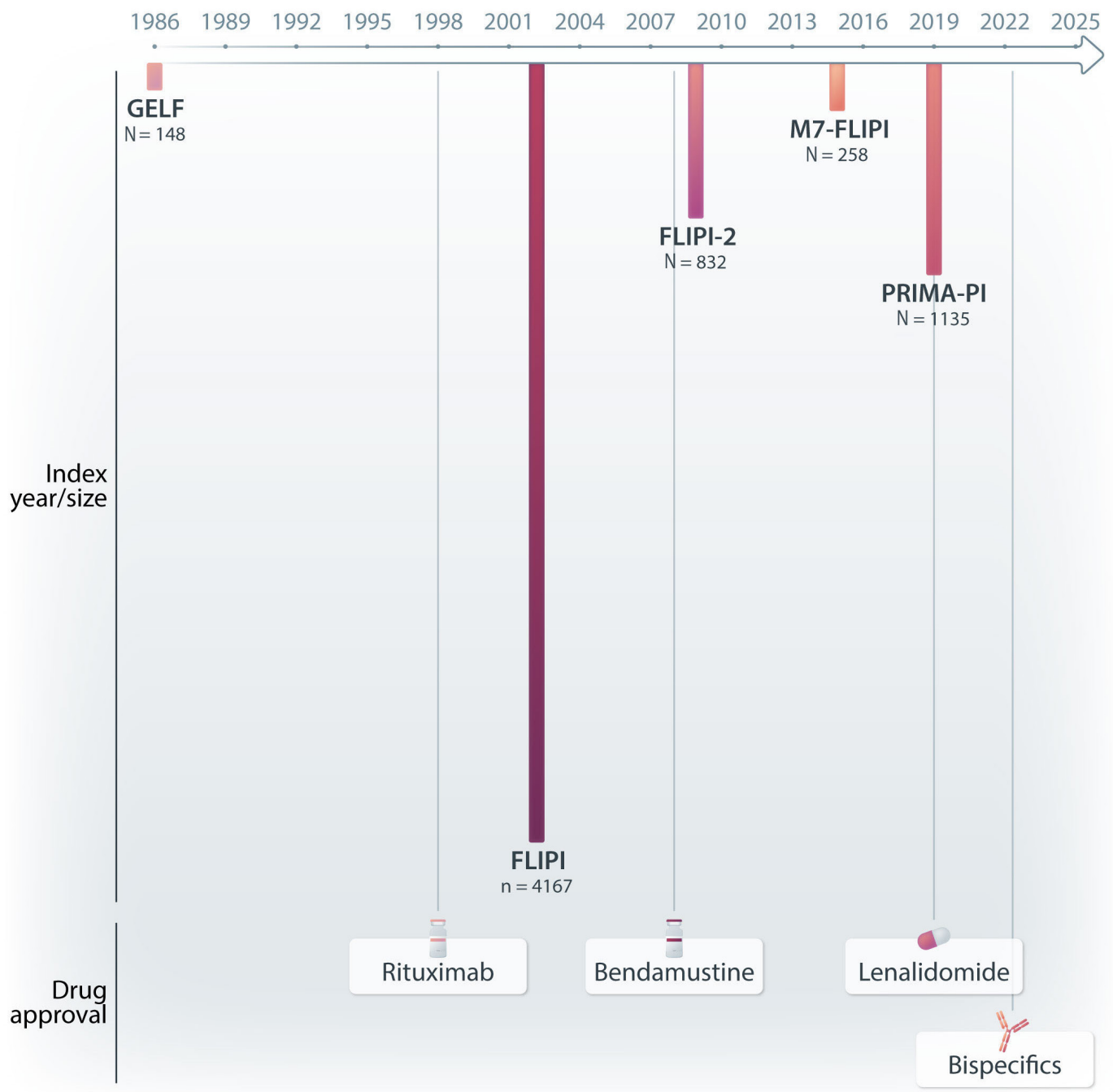

Figure 1. Timeline of new relevant prognostic indices and systemic treatments in follicular lymphoma since 1985. GELF: Groupe d'Etude des Lymphomes Folliculaires; FLIPI: follicular lymphoma International Prognostic Index; Bispecifics: bispecific antibodies.

general patient well-being, and response to initial therapy by focusing on tumor mutational analysis, functional tumor imaging, and tumor microenvironment biomarkers. In addition to risk from therapy, another probably powerful missing element in decision models on whom should be treated early on is the opinion of the FL patients. This information is readily available to the clinical practitioner (though challenging to document or measure) and likely explains much of the repeatedly demonstrated discordance between GELF criteria and treatment patterns. Research priorities moving forward should seek to ascertain what patients find important at the time of diagnosis, which management tools might best address those needs, and develop appropriate endpoints to measure successes.

There will be no perfect model to determine which patients diagnosed with FL should undergo early treatment unless a risk-free curative treatment option becomes available. Until then, new models should incorporate as many of the previously mentioned factors as is useful to individualize the treatment decision. Simple need not be an important criterion - we should be well past the need for an index that we can memorize or print on a 3x5 inch index card stored in our jacket pocket. Factors readily ascertainable at diagnosis should be a critical component of any new option. However, every model will run the risk of obsolescence with new treatment modalities and adaptability should be incorporated. Whatever or whenever new predictive models are available, the accumulating data added to by Barraclough *et al.*, suggests that it is probably time to put GELF on the shelf.

Disclosures

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