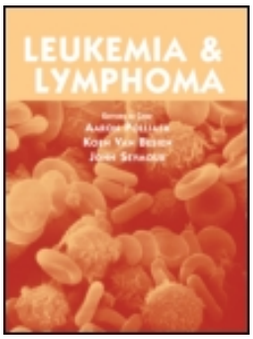

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COMMENTARY

Are we close to a prognostic index for cutaneous T cell lymphoma?

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In recent years it has been difficult to read through a hematology journal's table of contents without discovering a manuscript that describes some novel prognostic factor ascribed to any number of specific hematological malignancies. The authors of such papers search for prognostic factors which aim to predict patient outcomes. The first step is to identify individual predictors based on univariate analysis. More often than not, most of these are subsequently found to be influenced by other variables; these different prognostic markers overlap and may influence each other. This has led to the common use of multivariate analyses – an attempt to find prognostic markers that are independent of each other. The next step has been to integrate these independent prognostic indices to form a prognostic scoring system that can stratify patients into risk groups. Such "prognostic indexes" have become commonplace in hematology: classic examples include the International Prognostic Index (IPI) for diffuse large B-cell lymphoma (DLBCL), the follicular lymphoma international prognostic index (FLIPI) and the international prognostic scoring system (IPSS) for myelodysplastic neoplasms. The prognostic indexes assist us every day to prognosticate for our patients. Sometimes they will help us modify therapy. For academic purposes they help us to compare outcomes across trials; trials with a high proportion of poor-risk patients are likely to have relatively inferior outcomes.

However, for such prognostic markers and scoring systems to be useful they must meet some important criteria. First, they should use parameters that are easily accessible to the treating clinicians (for example gene expression profiling is not readily available to most clinicians, whereas lactate dehydrogenase generally is). Second, the prognostic scores should divide the populations into reasonably sized groups (there is little point in having a very powerful prognostic score which only occurs in a very small percentage of patients). Finally, the scoring system must demonstrate meaningful differences in outcome across the groups.

Indeed, in hematology there is frequently substantial overlap between our routine "staging" systems and prognostic scoring systems. With respect to DLBCL, the IPI incorporates disease stage as one of its parameters. Conversely, in myeloma, the clinician consortium set out to define adverse prognostic markers, but what resulted was an entirely new staging system, the International Staging System (ISS), which utilizes just two parameters, albumin and β_2-microglobulin (B2M), to separate patients into three well differentiated groups. It has now reduced the previously ubiquitous Durie–Salmon staging system to a historical memory.

So where are we with primary cutaneous T cell lymphoma (CTCL)? First, it is important to recognize that not all types of CTCL "are created equal." We now recognize that the pathobiologies of the various subtypes of CTCL are quite different. Thus, with respect to CTCL, we should restrict any prognostic systems to specific pathological entities. Thus, I will restrict my subsequent comments to mycosis fungoides/Sezary syndrome (MF/SS) (indeed there is a growing body of evidence that biologically SS is very different from MF, akin to DLBCL being subdivided into activated B cell versus germinal center types). It has now been 34 years since the staging system for MF was described [1]. It broadly divides patients into early- versus advanced-stage disease, with tumors, erythroderma, nodal and visceral involvement defining advanced-stage. This system has served us well, separating patients with stage IA disease who have a prognosis equivalent to that of the age-matched normal population, from patients with stage IVB disease who have a survival of less than 2 years. Nonetheless, we recognize that this is an imperfect staging system. Indeed, one obvious flaw is that patients with stage IIB (tumor-stage) disease have an inferior outcome to patients with stage III (erythrodermic) disease [2]. Moreover, we know that patients with stage IA disease generally do well, but there is the occasional patient who progresses relatively rapidly. Thus, prognostic markers are needed. But do we attempt to follow our myeloma colleagues and abolish the staging system and start from scratch, or do we work within the current staging system and start by broadly dividing patients into early stage versus advanced stage disease?

In this edition of the journal, Vonderheid *et al*. restrict their analysis of potential prognostic markers to patients with patch or plaque disease (stage IA–IIA, i.e. early-stage disease) and attempt to tease out subgroups that are destined to do poorly [3]. They identify large Pautrier microabscesses,

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atypical lymphocytes with hyperchromatic or vesicular nuclei in the dermal infiltrate, less than 20% CD8+ cells in the dermal infiltrate and elevated serum immunoglobin E (IgE) levels. They then use these prognostic factors to construct prognostic groupings. They seem to have successfully achieved at least one of the major criteria of a successful prognostic tool – to be able to differentiate the groups in a clinically meaningful way. As the authors conclude, the next step is validation of their findings. Obviously, this could be undertaken by either examining a large existing database or better still undertaking a prospective validation. Needless to say, the success of their prognostic tool will depend on hematopathologists agreeing on the pathological criteria that the authors describe – perhaps easier said than done. Furthermore, serum IgE levels are generally not routinely performed in patients with MF/SS at most centers, and thus a retrospective validation may not be possible.

The International Society of Cutaneous Lymphoma (ISCL) with the United States Consortium on Cutaneous Lymphoma (USCLC) are planning to tackle the task of developing a cutaneous lymphoma prognostic index. The first step is to determine the relevance and "collectability" of important adverse prognostic markers identified to date. These include, but are not limited to, stage, advanced age, male gender, folliculotropic variant, blood eosinophilia, serum lactate dehydrogenase (LDH), plaque disease, multifocal disease, disease transformation and presence of the tumor clone in the blood [4–15]. To complicate matters further, some of these parameters are only relevant if used to distinguish subpopulations within early- and advanced-stage disease, and are not applicable across all stages of MF/SS. Developing a robust prognostic index for MF/SS thus leaves us with many challenges, some of which are highlighted by Vonderheid's publication. If we are to use pathological features we must have consistent agreement across the pathology community, we may need to start prospective collection of potentially important blood markers (the myeloma community now assess B2M routinely), and we may need to consider the costs and availability of testing of blood for T cell receptor gene rearrangements in all patients. Finally, we face a further challenge. CTCL is not like DLBCL and acute myeloid leukemia where there are clearly defined gold-standard therapies. Indeed, treatment options are often individualized, and furthermore the availability of therapies varies considerably around the world: bexarotene, the histone deacetylase inhibitors, extracorporeal photophoresis and total skin electron beam therapies, to name a few, are not consistently available across the globe, making the situation particularly complex for advanced-stage disease. The data presented by Vonderheid *et al*. provide additional pieces of the puzzle of our understanding of prognosis in patients with early-stage MF. The next step must be to validate both their findings and those of others working in this field, and that must be done through a large international collaborative effort.

Potential conflict of interest: A disclosure form provided by the author is available with the full text of this article at www.informahealthcare.com/lal.

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