develop with the psoriatic phenotype could have important effects on both of these variables. Prior studies suggested that L-SNAs could penetrate to the dermis in explants of psoriatic skin (Lewandowski et al., 2017), but the efficiency of this process is unknown. In the current models, L-SNA treatment of essentially normal skin in these prevention models reduced IL-17RA mRNA by 57% in mouse skin and as much as 72% in cytokine-treated human 3D skin cultures, and the reductions were time dependent. In established psoriasis, the barrier is more pronounced, the epidermis is thicker, target keratinocytes are more numerous, and IL-17A receptor expression is upregulated, all of which suggest greater challenges for effective L-SNA delivery. It is difficult to predict how much and how often topical L-SNA application will be required for clinical efficacy. Limitations in current psoriasis models suggest that these issues can only be addressed through clinical trials, which are now underway.

Despite remaining challenges, the current studies provide important proof of concept for the future development of topical L-SNA therapies for the treatment of psoriasis. They also support the feasibility of L-SNA delivery for the treatment of other skin diseases. In particular, L-SNA delivery has the potential to be effective for skin pathologies in which the skin barrier may be normal or compromised, and, thereby, presents less of an obstacle to delivery, such as wound healing, immunobullous diseases, and disorders of the hair follicle. L-SNA delivery has the potential to be an enabling technology for the topical delivery of molecularly-targeted therapies, dramatically expanding the scope of topical interventions available to dermatologists and other healthcare providers.

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CONFLICT OF INTEREST
LDF is a scientific advisor for and holds an equity position in BrainStage and SkinJect. Ek states no conflict of interest.

ACKNOWLEDGMENTS
LDF is supported by National Institutes of Health grants R01AR074285, R01AR071277, R01AR068249, and P50CA121973.

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Survival in Mycosis Fungoides and Sezary Syndrome: How Can We Predict Outcome?

Julia J. Scarisbrick

Early-stage mycosis fungoides (MF) has been associated with long survival. A recent meta-analysis including 6,279 patients with MF and Sezary syndrome found that about 10–20% of stage IB patients don’t survive 5 years, whereas patients with advanced-stage MF and Sezary syndrome have a 5-year survival chance of about 20–60%. Identifying prognostic markers to better identify those at risk of limited survival may allow improved management choices and this, coupled with newer treatments, could improve survival.


Cancer staging systems are used to estimate the survival of patients with specific cancers and help to determine best management. However, there are ranges of survival within individual cancer stages. Mourad and Gniadecki (2019) performed a systematic review and metanalysis of overall survival (OS) in patients with stage IB–IVB mycosis fungoides (MF) and Sezary syndrome (SS). They identified 10 studies including 6,279 patients. All were retrospective cohort studies that were mostly limited to single centers, and thus there is no uniformity in definitions. The median age at diagnosis ranged from 52–62 years and all studies had a male predominance of 1.6 (male:female ratio 6:4) in accordance with previous reports (Willems et al., 2005). The authors concentrated on OS because detailed information on cause of death was not available. This is a logical approach in retrospective
cohort studies when data may be inconsistently defined between centers or incomplete.

Mourad and Gniadecki (2019) reported a median survival and included best- and worst-case scenarios. The authors achieved this by calculating median 5-year OS rates and then defining best case as the upper 10th percentile for each stage and worst case as the lower 10th percentile. They showed OS to be 85.8% in stage IB, reflecting significant mortality in these patients with early-stage MF, with a best case of 88.8% and a worst case of 82.1%. The authors showed that development of tumors (progression from stage I to IIB), Sézary syndrome (stage IVA1), nodal effacement (stage IVA2), and metastatic spread (stage IVB) had powerful, negative impacts on survival. However, these features are reflected in the staging algorithm and don’t give additional information on the patients’ clinical or pathological phenotypes, which may provide further prognostic information.

The Prospective Cutaneous Lymphoma International Prognostic Index (PROCLIPi) study is a global prospective effort collecting clinical, pathological, genotypic, treatment, and health-related quality of life (HRQoL) data on all stages of MF and SS with the aim to develop a prognostic index to stratify all stages of MF and SS with the aim to collect detailed information on OS to be available for patients but also show a 10–20% difference in the best- and worst-case scenarios. This may be confusing for patients until we can identify those factors that may better differentiate survival risks. It is likely patients will want to know if they are more likely to survive >10 years for future life and family planning.

Deciding how best to inform patients regarding 5-year OS may also be challenging for physicians, especially in metastatic disease (stage IVB) where the best-case scenario gives a 40% 5-year OS compared with just 10% in the worst case. Factors previously reported to be associated with worsened survival in advanced stages of MF include age greater than 60 years at diagnosis, partially or completely effaced nodal involvement (N3), B2 blood involvement (as defined by ≥1000 IU aberrantly circulating lymphocytes), visceral involvement, LCT in skin, and raised serum LDH (Benton et al., 2013; Scarisbrick et al., 2015). PROCLIPi is recording these factors as well as histological markers such as CD30% and Ki-67 (Gru et al., 2018).

Variation in survival within the stages of MF and SS is acknowledged and the importance of poor prognostic indices outside the staging system has been recognized. The International Society for Cutaneous Lymphoma and European Organisation for Research and Treatment of Cancer Cutaneous Lymphoma Task Force recommend the tracking of patients with FMF or LCT to determine if either warrants a different staging system from classical MF and SS. A staging system that relates to prognosis is vital, as this dictates treatment choices for patients with MF or
Patients with early-stage MF (stages I A—II A) are treated with skin-directed therapy. Patients with advanced-stage MF or SS (stages III B—I V B) typically require immunotherapy or chemotherapy, and sequential treatments are given as the disease progresses (https://www.nccn.org/professionals/physician_gls/pdf/primary_cutaneous.pdf). Treatment is frequently palliative and decided on an individual patient basis. Allogeneic stem cell transplant may be considered for eligible patients with poor survival risk. It produces some good responses, but careful consideration is required as transplant-related mortality at year 1 is significant (>34%) (Duarte et al., 2010).

Treatment of MF and SS rarely results in complete responses, and partial responses or stable disease is common (https://www.nccn.org/professionals/physician_gls/pdf/primary_cutaneous.pdf). Patients therefore live for long periods with significant morbidity from skin tumor burden, which impacts quality of life. Molloy et al. (2019) recently reported on HRQoL, as measured by Skindex-29, in patients with MF and SS. HRQoL was found to be worse in women, patients with SS, patients with alopecia, those with high skin tumor burden, and those in advanced-stage disease. Female sex and alopecia were the only independent predictors of worsened global HRQoL. Item-level analysis showed that the HRQoL impairment in women occurred because of a higher impact of the symptoms of burning/stinging, pruritus, and irritation and worse emotional scores of depression, shame, embarrassment, and annoyance with their diagnosis of MF or SS (Molloy et al., 2019).

The likely survival outcomes of individual patients is often their greatest concern. Identifying prognostic markers will provide more relevant personalized information for patients than stage alone and allow better management decisions. More specifically, if prognostic markers can be modeled into a prognostic index, this may provide individualized survival outcomes and allow personalized management choices. A prognostic index for aggressive non-Hodgkin lymphoma was developed in 1993, and it has been widely used to stratify patients for treatment (Shipp, 1994). Development of a useful prognostic index requires international collaboration, and it must be done prospectively with well-defined criteria to ensure comparable measures. Retrospective data may be flawed because of poor recording, differing definitions, and inaccurate recall. The PROCLIPI study provides an established registry with centrally reviewed clinicopathological data (Gru et al., 2018) with the aim of producing a prognostic index in MF and SS to stratify patients according to survival. It is hoped that such an international prognostic index will provide an improved basis for selecting patients for appropriate therapies and for stratification into clinical trials, and that it will improve survival in this group of patients with poor outcome. Mourad and Gniadecki (2019) have provided a useful data source that can be used to give guidance to patients and treating physicians in the likely survival outcomes of patients with MF and SS according to stage.

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CONFLICT OF INTEREST
The author states no conflict of interest.

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