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A cutaneous lymphoma international prognostic index (CLIPi) for mycosis fungoides and Sezary syndrome

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Abstract ***Background:*** There is no prognostic index for primary cutaneous T-cell lymphomas such as mycosis fungoides (MF) and Sezary syndrome (SS).
Method: Two prognostic indices were developed for early (IA–IIA) and late stage (IIB–IVB) disease based on multivariate data from 1502 patients. End-points included overall survival (OS) and progression free survival (PFS). External validation included 1221 patients.
Findings: Significant adverse prognostic factors at diagnosis consisted of male gender, age >60, plaques, folliculotropic disease and stage N1/Nx for early stage, and male gender, age >60, stages B1/B2, N2/3 and visceral involvement for late stage disease. Using these variables we constructed two separate models each defined using 3 distinct groups for early and late stage patients: 0–1 (low risk), 2 (intermediate risk), and 3–5 factors (high risk). 10 year OS in the early stage model was 90.3% (low), 76.2% (intermediate) and 48.9% (high) and for the late stage model 53.2% (low), 19.8% (intermediate) and 15.0% (high). For the validation set significant differences in OS and PFS in early stage patients (both $p < 0.001$) were also noted. In late stage patients, only OS differed between the groups ($p = 0.002$).

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Interpretation: This proposed cutaneous lymphoma prognostic index provides a model for prediction of OS in early and late stage MF/SS enabling rational therapeutic choices and patient stratification in clinical trials.

1. Introduction

Primary cutaneous T-cell lymphomas (CTCL) comprise a heterogeneous group of non-Hodgkin lymphomas, of which mycosis fungoides (MF) is the most common variant with an incidence of 4.1/1,000,000 person–years, male predominance and older age distribution.[1,2] Whilst MF can be indolent,[2] Sezary Syndrome (SS), a leukaemic form of CTCL, has a poorer prognosis with a median survival of <3 years.[2,3]

Therapeutic strategies are primarily based on disease stage.[4–6] In 2007 a revision of the AJCC staging system was proposed incorporating stratification of early skin stage into those with patches alone (T1a/T2a) or patches and plaques (T1b/T2b), and molecular classification of lymph node and peripheral-blood involvement.[7,8] Early stage disease (IA–IIA) with limited skin involvement is generally treated with skin-directed therapies.[8–10] There is no standard treatment for late stage disease (IIB–IVB) but various immunobiologic therapies and single/multi-agent chemotherapy have all shown clinical efficacy although duration of response is often short-lived.[4,11,12]

Multivariate prognostic models developed for systemic nodal lymphomas, such as the follicular lymphoma international prognostic index (FLIPi),[13–15] provide accurate prediction of survival and progression risk. More recently, a prognostic index for systemic peripheral T-cell lymphoma unspecified (PTCL-U) was proposed but is inappropriate for cutaneous lymphomas.[16]

Previous reports of small cohorts of MF/SS patients have highlighted striking prognostic heterogeneity, which is partly dependent on age and clinical stage.[9,17–28] Another report has suggested an alternative scoring system for skin involvement with prognostic implications.[29]

We recently reported actuarial survival data from a cohort of 1502 MF/SS patients.[3] Our multivariate data validated the revised staging proposal for MF/SS and identified new prognostic factors.[3] We have now developed a cutaneous lymphoma international prognostic index (CLIPi) based on predictive factors identified by this multivariate analysis of 1502 patients and subsequent validation in a large US cohort.

2. Methods

2.1. Study subjects

From 1980, details of all patients referred to our multidisciplinary cutaneous lymphoma clinic were entered onto a cutaneous lymphoma database (ICARSIS) which supports a Research Tissue Bank (NRES: 07/H10712/106). Our derivation set was based on our recently published 1502 cohort of MF/SS patients[3] and the validation set was based on 1221 patients from the MD Anderson collected from 1982 to 2009.[30] As our risk score aimed to predict survival up to 10 years, patients were censored at 10 years after diagnosis or on 1st June 2009 whichever was sooner. Further, patients in the derivation dataset had longer follow up than those in the validation set. Censoring all surviving patients at 10 years gave comparable datasets. A multivariate stepwise regression analysis incorporating the recent proposed staging criteria and diverse clinico-pathologic factors, identified significant predictors of overall/disease specific survival (OS/DSS) and risk of disease progression (RDP) at diagnosis.[3] This analysis established that advanced skin (T) stage, presence in peripheral blood of the tumour clone without Sezary cells (B0b), raised LDH and folliculotropic MF were independent predictors of poor survival and increased RDP. Large cell transformation (LCT) and tumour distribution were independent predictors of increased RDP only and N, M and B stages, age, male gender and poikilodermatous MF were only significant for survival.[3] All variables were analysed as potential prognostic factors including other clinical variants. All demographic and clinical data from both the derivation and validation datasets are shown in Supplementary Table 1. Notable differences between the derivation and validation sets included female:male ratio (1:1 ratio in the validation set compared to a higher male:female ratio in the derivation set), higher rates of clinico-pathologic variants such as folliculotropic and poikilodermatous variants in the derivation set, a lower proportion of patients with an elevated LDH in the validation set possibly reflecting a bias in the derivation set due to recording of LDH primarily on advanced disease patients. No patients were classified as Nx in the validation set as all patients with palpable nodes underwent a fine needle aspirate (FNA) assessment of nodes in contrast to the derivation set where only patients with bulky palpable nodes underwent an excision or core biopsy to define the extent of nodal involvement. The proportion of patients with blood involvement was higher in the validation set (based on flow) compared to the derivation set where blood involvement was defined on the basis of lymphocyte morphology.