ORIGINAL ARTICLE

# Prognostic markers in lentigo maligna patients treated with imiquimod cream: A long-term follow-up study

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***Background:*** More data are needed to define factors that predict long-term success after imiquimod therapy for lentigo maligna (LM).

***Objective:*** We sought to determine the demographic, clinical, and histologic prognostic markers of relapse-free survival in patients with LM who were treated with imiquimod.

***Methods:*** This was a single-arm, open-label, nonrandomized, prospective study.

***Results:*** Eighty-nine patients with histologically confirmed LM and a median follow-up time of 4.8 years after imiquimod treatment were included in our study. Sixteen patients (18%) relapsed. Statistically significant indicators of an increased risk of local recurrence included: the total number of melanocytes, the number of basal and suprabasal melanocytes and the number of pagetoid spreading melanocytes.

***Limitations:*** Our study was a single-center, nonrandomized study.

***Conclusion:*** An assessment of different melanocyte fractions in the diagnostic baseline biopsy specimen may help to predict the response of LM to imiquimod therapy. (J Am Acad Dermatol http://dx.doi.org/10.1016/j.jaad.2015.08.031.)

***Key words:*** efficacy; follow-up; imiquimod; lentigo maligna; prognostic marker; recurrence; topical immunomodulators.

## INTRODUCTION

Lentigo maligna (LM), a melanoma in situ on chronically sun-damaged skin, primarily affects elderly patients and has a strong predilection for the head and neck region.[1,2] Several therapeutic modalities have been used in the treatment of LM, such as surgery, cryotherapy,[3,4] and radiotherapy.[5-7] Surgical excision with safety margins (typically 5 mm) is the treatment of choice.

Imiquimod is a topical immune response modifier that has been recently suggested as a valuable alternative treatment to surgery in patients with LM, especially in cases with larger lesions located on the face in elderly and comorbid patients[1,8-16] when surgery is not indicated or cannot be performed. It has also been proposed as a neo- or postadjuvant treatment option to operative procedures.[9,12-14] Recurrence of LM or lentigo maligna melanoma (LMM) after treatment with imiquimod has also been observed in some patients.[17]

The aim of our study was to evaluate the response of LM to nonsurgical treatment with imiquimod cream 5% in a cohort of patients with long-term follow-up. In addition, the role of demographic, clinical, and histologic features for the long-term efficacy of imiquimod treatment in patients with LM was assessed.

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## METHODS

### Patients, treatments, and assessments

Between 2003 and 2013, 89 patients (55 women and 34 men) with histologically confirmed LM were enrolled in the study. The patients were instructed to apply imiquimod cream 5% (Aldara; 3M Pharma, Rueschlikon, Switzerland), with or without occlusion, to cover the macroscopically pigmented area, as described elsewhere,[16] once or twice daily, until a weeping erosion developed. All patients underwent regular clinical follow-ups at the Department of Dermatology of the University Hospital of Bern, Switzerland.

The following patient data were analyzed: age at the beginning of the therapy, sex and Fitzpatrick skin phototype, side effects and clinical response during therapy, size and location of the lesion, occurrence of relapse, time from the beginning of the therapy to relapse, date of the last clinical follow-up, death, and other skin malignancies.

**CAPSULE SUMMARY**

- Different therapeutic modalities (eg, surgery, radiotherapy, and imiquimod) have been used in the treatment of lentigo maligna.
- Imiquimod is associated with a recurrence rate of about 18%, with a higher recurrence rate being associated with an increased number of melanocytes.
- Imiquimod may be an acceptable nonsurgical option after assessing melanocyte fractions in the diagnostic baseline biopsy specimen.

### Histologic evaluation

Punch biopsy and excisional biopsy specimens were obtained and fixed in formalin and embedded in paraffin using routine techniques. The diagnosis of LM was made by ≥2 Board-certified dermatopathologists by analyzing hematoxylin–eosin-stained slides and immunohistochemical staining for melan-A antigen. The total number of melanocytes, the number of basal and suprabasal melanocytes, and the number of pagetoid spreading melanocytes (ie, melanocytes above the basal and suprabasal layers of the epidermis) were assessed on melan-A–stained tissue sections using conventional light microscopy with an integrated millimeter scale. All of the parameters are indicated as cells/positive events per millimeter of epidermis. Because the epidermis in these primarily elderly individuals with sun-damaged skin was always thin, counting cells linearly along the length of the epidermis and indicating cells/events per millimeter of epidermis was more reliable than counting cells/events per square millimeter. In addition, the maximal epidermal depth of the melanocytes was estimated—this was usually the maximal depth of the melanocytes along the hair follicle. Similar to tumor thickness (according to Breslow), the distance between the stratum granulosum and the deepest melanocyte was measured. The maximal extent of noninvasive melanocytes was called epidermal tumor thickness.

### Study design

This investigator-initiated, open-label, nonrandomized, prospective study was approved by the local Research Ethics Committee of the University of Bern. Informed consent was obtained from all patients. All clinical investigations were conducted according to the principles of the Declaration of Helsinki.

### Statistical analysis

Descriptive statistics were computed for the patients' demographic and clinical characteristics. Time to relapse was calculated from the beginning of therapy to relapse. If the patients were lost to follow-up or died before relapse, they were censored at the time of the last visit. All *P* values related to the 2-sided test with an alfa level of 0.05, and R software (version 2.13.0; www.r-project.org) was used for computations. The confidence interval (CI) of the hazard ratios (HRs) for the Cox regression and survival function (for time to event variables) were calculated based on the cumulative hazard and pointwise log (survival). Otherwise, the methods used to conduct tests (*P* values) and CIs are specified separately. The 2-sided exact Wilcoxon signed rank test was also used, whereas patients who were censored (ie, lost to follow-up or death) were not included in this analysis.

## RESULTS

Patient and tumor characteristics are shown in Table I. Eighty-nine patients (55 women and 34 men) with a median age of 72.5 years (range, 38.6-93.8 years) were included in the study. Only 5 of 89 LMs were located outside the face (ie, either on the arm, neck, or shoulders). No LM was found on the trunk or lower extremities. The treatment-induced local inflammatory reaction was generally well tolerated, but 1 patient had to discontinue treatment after 63 days because of a generalized pruritic macular papular rash. Other side effects, including hypopigmentation, persistent erythema and telangiectasia at the treatment site, malaise,