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Treatment of lentigo maligna with topical imiquimod

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Summary A published case report and anecdotal experience suggested that topical imiquimod is an effective treatment for stage 0 melanoma (lentigo maligna). To gauge the efficacy of this therapy, we undertook a trial of topical imiquimod in 30 subjects with histologically confirmed lentigo maligna. Thirty subjects with lentigo maligna were recruited for an open-labelled efficacy trial with daily topical application of imiquimod 5% cream for 3 months. Study subjects were enrolled from the Dermatology service of the University of Oklahoma, the Oklahoma City Veteran's Administration Hospital Dermatology service and from referrals for the study from other practitioners. In order to determine an initial response rate, a four-quadrant biopsy was carried out on all patients 1 month after cessation of treatment, targeting the most clinically and dermatoscopically suspicious areas. Of 28 evaluable subjects who have completed the 3-month treatment phase, 26 (93%) were complete responders and two were treatment failures at the time of the 4-quadrant biopsy. Over 80% of the 28 subjects that completed treatment have been followed for more than 1 year with no relapses. The results of this study demonstrate that topical imiquimod produces a high complete response rate in lentigo maligna when applied daily for 3 months.

Key words: imiquimod, lentigo maligna, stage 0 melanoma, topical therapy

Introduction

Lentigo maligna (LM) is an increasing problem as the population ages and increasing numbers of people achieve high total ultraviolet (UV) exposures early in life from intentional sun exposure and tanning-bed use. Anecdotal cases of lentigo maligna treated with imiquimod, an immune response modifier (IRM), as well as at least one report in the literature, suggested to us that imiquimod might be a useful therapy for stage 0 melanoma (lentigo maligna).[1]

Patients and methods

In order to gauge the efficacy and safety of imiquimod for topical treatment of LM, institutional review board approval was obtained for an open-label trial of imiquimod 5% cream. Thirty subjects were enrolled from the patient populations of the University of Oklahoma Dermatology Clinic, and the Oklahoma City Veteran's Hospital Dermatology Clinic. Patients referred from community dermatologists were also included. Patients were at least 18 years of age and had a diagnosis of lentigo maligna, with a minimum 2 cm^2 of tumour left to treat after biopsy. The diagnosis was established on the basis of clinical and dermatoscopic findings consistent with stage 0 melanoma, and supported by histology confirmed by the study pathologist (N.C.). Individuals suspected of having stage 1 melanoma were excluded. The characteristics of the subjects and lesions are given in Tables 1 and 2.

Patients were enrolled after histological confirmation of the diagnosis. Prior to treatment, the tumours were photographed and traced on transparent plastic templates that included outlines of other landmarks so that the affected areas could be located accurately following treatment. At the enrolment visit, patients were instructed in the application of the topical imiquimod cream. Patients subsequently visited the clinic on weeks 1, 4, 8, 12, 16, 24 and 52. Patients were instructed to apply the cream at least 2 cm beyond the suspected margin of the tumour and to attempt to continue daily applications to the site unless treatment

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Table 1. Subject characteristics

		Age (years)	
Gender ($n = 30$)	Number of subjects	Mean	Range
Men	25	69	43–91
Women	5	60	42–91

Table 2. Lesion characteristics

		Area (cm^2)		
Location	Number of subjects	Mean	Median	Range
Head	26*	4·0	1·7	0·5–24·8
Upper extremity	3	6·7	1·4	1·0–17·5
Thorax	1	N/A	N/A	N/A
Lower extremity	0	N/A	N/A	
All Locations	30	4·2	1·7	0·5–24·8

*Two lesions that were nonresponders were located on the head/face.

became intolerable. The goal was for each subject to treat daily for 12 weeks, unless rest periods were required due to intolerable irritation or impending ulceration. Each application by the patient was entered in a treatment diary, so that the actual number of treatments used could be determined accurately.

Treatment was discontinued at week 12, and at week 16 a minimum of four 2-mm punch biopsies were taken in the previously affected area. The precise locations of these biopsies were determined by ascertaining the areas most suspicious for persistent tumour using both dermatoscopic and clinical criteria. If no pigmented or suspicious areas could be detected, a minimum of four biopsies were taken in each of four arbitrarily defined quadrants.

Results

Thirty subjects were enrolled in the study. Of these, one patient was withdrawn after the first month because a random biopsy to monitor therapy suggested invasion (stage 1). Although the tumour appeared to be responding, by protocol he was withdrawn, and the tumour was surgically removed.

At present, 28 patients have completed the 12-week treatment phase. Of these 28 assessable patients, two were treatment failures, with persistent tumour visually and on biopsy at week 16. The remaining 26 patients were complete responders at week 16 (defined as complete absence of tumour by clinical and histological criteria) (Fig. 1). This corresponds to an initial complete response rate of 93% (26/28). Over 80% of this cohort has now been followed for at least 12 months, and no relapses have been observed. No visible erythema was ever noted in or around the tumour site in the two patients who failed to respond. These were both treated with surgical excision.

Side-effects

Approximately one-third of the patients required rest periods or reduced application frequency after the first month to avoid intolerable irritation or ulceration of the treatment area. Beyond mild to moderate irritation in the treatment area (seen in all subjects except the treatment failures), side-effects observed in this study were of three general types: secondary infections, severe local reactions and cytokine-release syndromes.

Secondary infections considered significant enough to merit topical antibiotic treatment were seen in four patients. A fifth patient warranted treatment with systemic antibiotics combined with topical antibiotics. The presence of secondary infection was judged clinically by the presence of honey-coloured crusts and/or purulence, combined with a recent corresponding increase in surrounding erythema, swelling and tenderness. The three secondary infections observed in this study cleared after topical and/or systemic antibiotics combined with a 7-day rest period. Treatment was restarted in all cases.

While all responding patients had variable amounts of irritation at the treatment site, 10 reported severe local skin reactions (SLRs). Six of the patients reporting SLRs required rest periods ranging from 2 to 14 days. Four of these patients stopped treatment early, including one who discontinued treatment because of a cytokine-release reaction.

Cytokine-release syndrome is occasionally seen with topical IRM therapy, and is presumably due to release of sufficient quantities of interferon or other cytokines to induce systemic symptoms similar to those associated with the systemic use of interferon (headache, gastrointestinal upset, malaise, fever). The risk of this may increase as the area treated and the degree of inflammation triggered by the IRM increases. Two patients in this study were considered to have this side-effect, one severe enough to discontinue therapy prematurely (due to chills, malaise, stomach upset and headache), and another who had mild application-associated headaches that did not prevent completion of the protocol. Although the more severely affected of these two individuals discontinued treatment after only 8 days, both patients had complete responses.

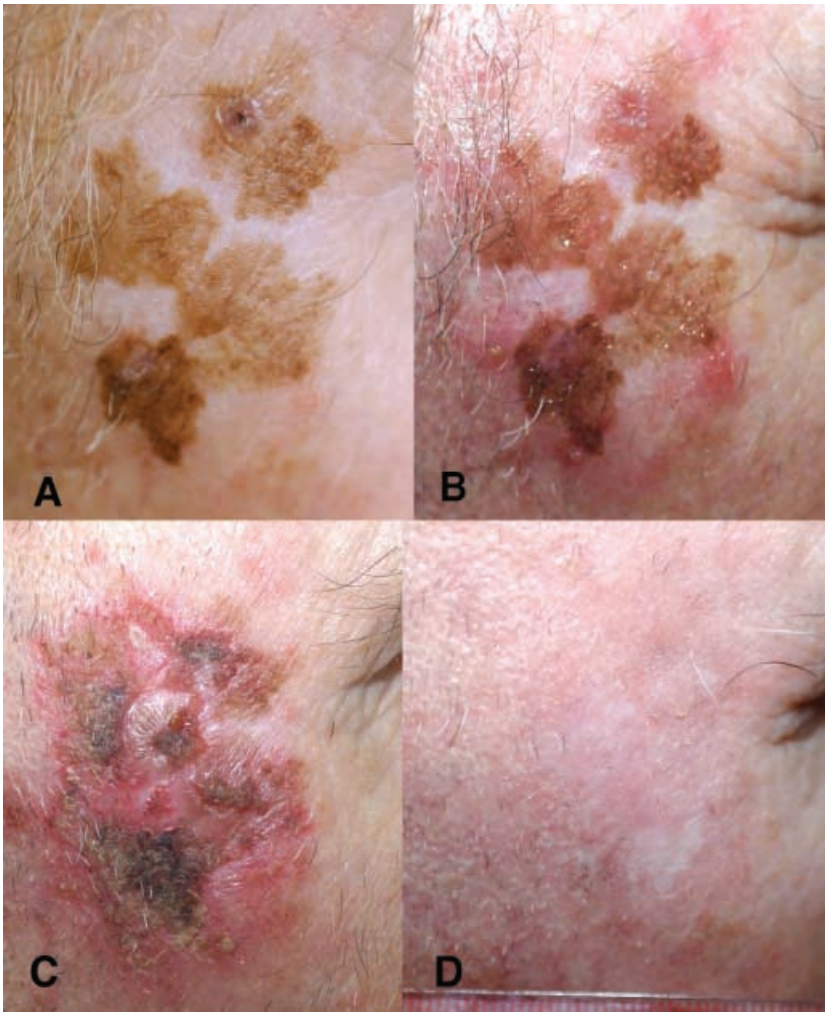

Figure 1. Subject response to imiquimod at: (A) week 0; (B) week 1; (C) week 4; and (D) week 16.

Discussion

Lentigo maligna is several times more common than invasive melanoma. In one recent study, half of the melanomas diagnosed arose from lentigo maligna.[2] Analyses performed in previous decades suggested that this was principally a disease of the elderly who might die of old age before the tumour became lethal. Lentigo maligna today is increasingly a disease of middle age and even younger adults, which can include individuals in their 30s, especially sunseekers or avid tanners. In the present study, almost half the patients were under the age of 70, and four of them were under 50. In younger adults, successful treatment is more important to avoid a fatal outcome, as a greater percentage of these individuals will live long enough for the tumour to progress and become life-threatening.

It appears that a high percentage of individuals who respond to this form of therapy achieve complete responses (all who reacted with inflammation in this study). It is not clear why two subjects in the present study failed to respond. Because LM has the potential to spread rapidly and/or progress to an invasive melanoma, patients with this tumour are generally highly motivated. Poor compliance as a cause of treatment failure therefore seemed unlikely in this group.

Imidazoquinolines, such as imiquimod, work through activation of the NF-κb and the Jnk signal transduction pathways via Toll-like receptors (TLRs).[3] It is possible that the two nonresponders had an absence or a structural variation in their TLRs, which prevented a drug response. It is also possible that there was another defect somewhere in this signal-transduction pathway.

Our experience has been that all areas of tumour need to be treated to obtain a complete local response. This clinical observation is consistent with the notion that a primary mechanism of action of tumour clearance of topically applied imiquimod is through activation of innate immune mechanisms such as natural killer cells and activated macrophages.

Surgery for LM has a relatively high failure rate with larger lesions, due to technical difficulties in determining clear margins.[4] Cure rates for large LMs may prove to be higher for topical imiquimod treatment than for standard surgical treatments, primarily due to technical difficulties with surgical margins. It is feasible to treat for several centimetres beyond the visible margins of tumours with imiquimod cream, which should yield higher cure rates. Thus, topical imiquimod may prove to be the treatment of choice for very large tumours, in poor surgical candidates, or in the young to avoid surgical scars.

Topical IRMs, such as imiquimod, provide a nonsurgical alternative and may also prove useful as an adjunct to traditional surgical methods. Surgery will probably remain the treatment of choice for lesions that are easily resectable, particularly as this approach may lend itself more easily to accurate pathological staging of the tumour.

This pilot study demonstrates that topical imiquimod is a highly effective therapy for LM, although additional studies should be carried out to confirm these results. This is a treatment that should be carried out by specialists, as diagnostic expertise with pigmented lesions is necessary to avoid inadvertent treatment of more advanced tumours, as well as to adequately monitor treatment responses.

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