Imiquimod 5% cream as primary or adjuvant therapy for melanoma in situ, lentigo maligna type

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Background: Surgical resection of lentigo maligna (LM) is complicated by noncontiguous, subclinical extension and actinic melanocytic hyperplasia in sun-damaged skin of older individuals.

Objective: We sought to determine the long-term effectiveness of imiquimod as primary or adjuvant therapy for LM.

Methods: Patients were retrospectively identified from January 1, 2003, to December 31, 2013, with LM, early/evolving LM, and LM melanoma who had used topical imiquimod 5% cream for either primary therapy after diagnostic biopsy, or adjuvant therapy after narrow-margin surgical resection or complete clinical but not histologic resection of LM. Follow-up occurred through December 31, 2014.

Results: In all, 63 cases were identified in 61 patients, mean (SD) age 71.1 (12.4) years; 58 were analyzed for local recurrence. Imiquimod was used as primary therapy in 22 of 63 (34.9%) and adjuvant therapy in 41 of 63 (65.1%) for mean duration of 11.7 (range 2-60) weeks. Fifty cases (86.2%) demonstrated clinical clearance at mean (SD) follow-up of 42.1 (27.4) months: 72.7% primary and 94.4% adjuvant at 39.7 (23.9) and 43.1 (28.9) months, respectively.

Limitations: Retrospective cohort study and lack of standardized imiquimod application are limitations.

Conclusion: Imiquimod cream appears to be a viable option for primary or adjuvant treatment of LM in older patients who are poor surgical candidates. (J Am Acad Dermatol 2015;72:1047-53.)

Key words: adjuvant therapy; imiquimod; inflammatory response; lentigo maligna; lentigo maligna melanoma; melanoma; melanoma in situ; primary therapy.

Lentigo maligna (LM) is an increasingly common melanoma in situ (MIS) subtype on chronically sun-exposed skin in elderly individuals. The risk of progression of LM to its invasive counterpart, LM melanoma (LMM) has been estimated at 5% to 50%,[1,2] although no prospective analysis of untreated LM has been conducted, and the risk may be as low as 2% to 5%.[1]

Surgery is the mainstay of treatment for MIS and in most cases is curative. Surgical margins of 5 mm were recommended for MIS by the National Institutes of Health Consensus Development Conference on Diagnosis and Treatment of Early Melanoma in 1992, although not based on any randomized trials.[2] Certain MIS subtypes (eg, LM and acral lentiginous)

Abbreviations used:

AAD:	American Academy of Dermatology
LM:	lentigo maligna
LMM:	lentigo maligna melanoma
MIS:	melanoma in situ
NCCN:	National Comprehensive Cancer Network
VAPAHCS:	Veterans Affairs Palo Alto Health Care System
WLE:	wide local excision

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demonstrate subclinical extension and noncontiguous "skip" areas, making the use of histologically controlled margins through Mohs micrographic surgery or staged excision potentially more effective compared with conventional wide local excision (WLE).[3-5] However, surgical intervention for LM may not be feasible for patients with significant comorbidities or large lesions on cosmetically sensitive areas. An additional factor complicating histologic assessment and surgical clearance is actinic melanocytic hyperplasia, which is common in chronically sun-damaged skin and may be difficult to differentiate from true LM.[6]

CAPSULE SUMMARY

- Lentigo maligna incidence is increasing in older individuals who may be poor candidates for surgical resection.
- In our series, the long-term clearance rate was 86.2% when using 5% imiquimod cream for primary or adjuvant therapy of lentigo maligna.
- Imiquimod field treatment is an option for lentigo maligna but requires close follow-up and careful patient discussion.

Recent studies have supported the use of 5% imiquimod cream as a treatment option for LM, with cure rates ranging from 53% to 100%,[7-10] although published data are limited by variable designs (primary or adjuvant), application regimens (ranging from daily or more for 4 weeks to 22 months), treatment margins (0-2 cm around the clinical lesion), and short-term patient follow-up (mean 18 months).

To date, no randomized, prospective trials comparing the use of imiquimod with conventional or Mohs micrographic surgery have been conducted for MIS, and its use for LM has not been approved by the Food and Drug Administration. Despite this, both the National Comprehensive Cancer Network (NCCN) and American Academy of Dermatology (AAD) melanoma practice guidelines recognize the potential benefits of topical imiquimod cream in situations where complete surgical resection of LM is not possible.[11,12]

Limited data have been published on the effectiveness of imiquimod as primary therapy after diagnostic biopsy of LM, in which a clinical residual lesion is evident, versus as adjuvant therapy after surgical resection, in which histologic transection is present without clinical correlate, or when histologic margins are considered "narrow." Robust inflammation at imiquimod-treated sites has been reported as a possible prognostic factor of improved response for LM.[10,13] Our study aimed to determine the long-term effectiveness of imiquimod as primary or adjuvant treatment of LM and to examine the differences and potential significance of the inflammatory reaction in a retrospectively identified cohort of patients.

METHODS

Patients given a diagnosis of LM, early/evolving LM, and LMM were retrospectively identified from January 1, 2003, to December 31, 2013, in the Veterans Affairs Palo Alto Health Care System (VAPAHCS) Pathology Service database and Stanford Cancer Institute Research Database, who had undergone treatment with topical imiquimod 5% cream as either primary therapy of LM after diagnostic biopsy, or as adjuvant therapy after narrow-margin surgical resection or complete clinical, but not histologic, resection. Primary therapy was defined as use of imiquimod after partial biopsy, which confirmed peripherally transected LM in the setting of a clinical residual lesion. Adjuvant therapy was defined as the use of imiquimod after at least 1 prior WLE that showed persistent histologic involvement of LM at the peripheral margin without clinical residual tumor, or narrowly excised LM (generally <1 mm from the specimen edge). Cases of atypical intraepidermal melanocytic proliferations in which the diagnosis of early or "evolving" LM were included, as were cases of LMM in which the focal microinvasive or deeper invasive component was excised histologically and the MIS component (eg, LM) was transected at the peripheral margin. Data collected included patient age, sex, clinical prebiopsy size of LM/LMM, histopathology of the biopsy/excision, frequency and duration of imiquimod treatment, inflammatory response elicited (brisk, as defined by erythema, scale, and/or erosion), local recurrence (defined as clinical and/or histologic clearance), and progression to invasive or metastatic melanoma. Exclusion criteria included use of imiquimod as a neoadjuvant modality to reduce the size of LM before surgery, less than 10 weeks of clinical follow-up after discontinuation of imiquimod, and situations in which use of imiquimod could not be confirmed.

The precise regimen of imiquimod was tailored to each patient's inflammatory response and compliance with the medication, with more frequent application commonly used to elicit appropriate inflammation. Concurrent use of topical retinoids was evident in 1 case. All patients had close scheduled follow-up, although some did not

comply; most cases were documented with clinical photographs before, during, and after treatment. Clinical outcome was assessed through December 31, 2014. The study was approved by Stanford University and VAPAHCS institutional review boards.

RESULTS

Patients

In all, 63 cases of biopsy-proven LM/early LM or LMM were identified in 61 patients, mean (SD) age 71.1 (12.4) years, in whom imiquimod was used for primary or adjuvant treatment. Most patients were treated at VAPAHCS (63.9%) vs Stanford (36.1%), and the majority were male (76.7%). Mean diameter of the initial clinical lesion was 15 (range 4-40) mm; 18 of 63 (29.0%) were diagnosed as atypical intraepidermal melanocytic proliferation favoring early LM, 29 of 63 (46.0%) were diagnosed as LM, and 16 of 63 (25.4%) were diagnosed as LMM. The majority of lesions (47/63, 74.6%) were located on the head and neck. Other anatomic locations are presented in Table I. Of the 16 LMMs, mean (SD) Breslow thickness was 1.17 (1.52) mm.

Imiquimod treatment

Imiquimod was typically prescribed 3 times (n = 33/63, 52%) to 5 times (n = 20/63, 32%) per week for a planned course of 12 weeks and included a margin of 2 cm around and overlying the clinical lesion or WLE scar, depending on patient tolerance and response. Titration to a more frequent dose (daily, n = 10/63, 16%) was used to elicit an inflammatory response. Mean duration of imiquimod use was 11.7 (range 2-60) weeks. Mean clinical follow-up from diagnostic biopsy was 52.2 (range 6-111) months and 42.1 (range 2-106) months from discontinuation of imiquimod.

Imiquimod was used as a primary therapy in 22 of 63 (34.9%) cases and an adjuvant therapy in 41 of 63 (65.1%) cases. Most cases in the adjuvant group (25/36, 69.4%) had scattered increased atypical junctional melanocytes extending to the peripheral margin or what was deemed true histologic transection of LM. The remainder (11/36, 30.6%) had undergone WLE showing narrowly excised LM. Thirteen patients underwent 2 or more excisions before adjuvant imiquimod treatment. The most common reason cited for use of imiquimod was poor surgical candidacy for primary or additional WLE as a result of advanced age, large size and/or location of lesion, significant medical comorbid conditions, and/or patient or family preference to avoid surgery.

Table I. Patient characteristics and use of imiquimod cream

	61 patients, n = 63
Gender, No. (%)	
Male	47 (77)
Female	14 (23)
Site, No. (%)	
Stanford	22 (36)
VAPAHCS	39 (64)
Mean age, y (SD)	71 (12)
Greatest dimension of clinical lesion, mm, mean (SD)	15 (10)
Pathologic diagnosis, No. (%)	
Atypical intraepidermal melanocytic proliferation, favor early lentigo maligna	18 (29)
Lentigo maligna	29 (46)
Lentigo maligna melanoma	16 (26)
Body site, No. (%)	
Scalp	8 (12)
Forehead/temple/eyebrow/eyelid	8 (12)
Preauricular/cheek	12 (19)
Nose	4 (6)
Lip/chin/jawline/submentum	5 (8)
Neck	4 (6)
Ear	5 (8)
Face, NOS	1 (2)
Arm	5 (8)
Hand	0 (11)
Trunk	7 (11)
Leg	3 (5)
Foot	1 (2)
Breslow depth, mm, mean (SD)	1.17 (1.52)
Mean length of imiquimod use, wk	11.1
Mean length of clinical follow-up from diagnosis, mo	52.1
Mean length of clinical follow-up after imiquimod, mo	42.1
Inflammatory response, No. (%)	
Positive	48 (76)
Negative	9 (14)
Unspecified	6 (10)
Use of imiquimod, No. (%)	
Primary	21 (33)
Adjuvant	42 (67)
Prior intervention before imiquimod use, No. (%)	
None	19 (30)
Excision (1)	32 (51)
Excision (2)	10 (16)
Excision (≥3)	2 (3)
Posttreatment biopsies or excisions, No. (%) [n = 58]	
Yes	15 (26)
No	43 (74)

NOS, Not otherwise specified; *VAPAHCS*, Veterans Affairs Palo Alto Health Care System; *SD*, standard deviation.

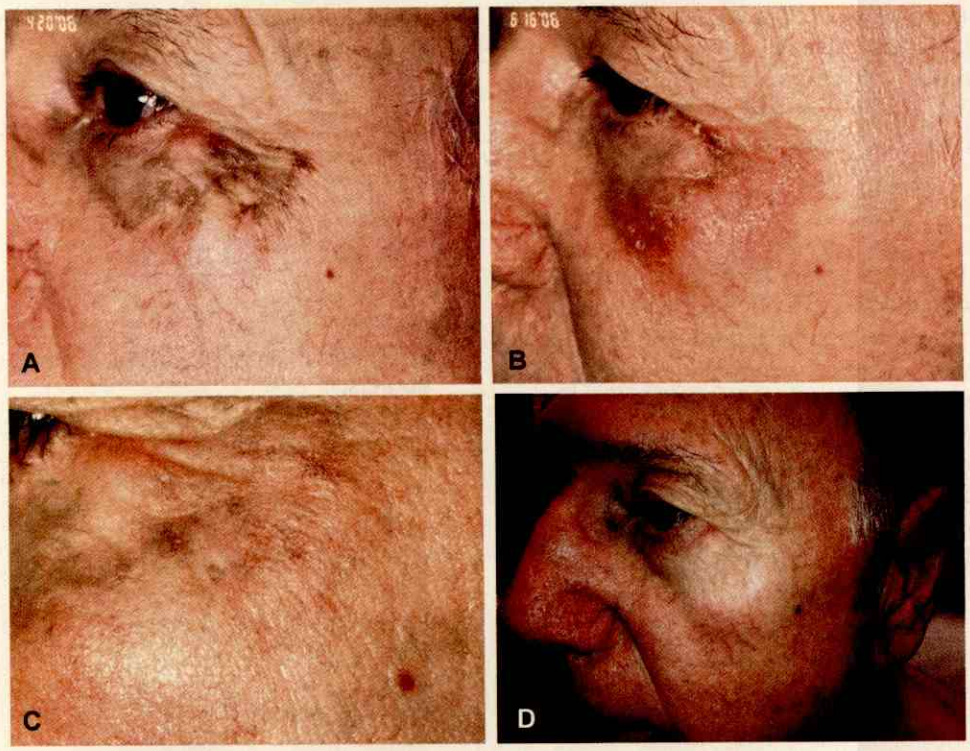

Fig 1. Clinical images of a patient treated primarily with imiquimod for lentigo maligna. **A**, At baseline. **B**, At 3-month follow-up, with brisk inflammatory reaction. **C**, At 5-month follow-up after cessation of imiquimod, with scouting biopsy specimen demonstrating only post-inflammatory pigment deposition. **D**, At 8- year follow-up, remaining clinically free of disease.

Response to treatment

In all, 58 cases of LM/LMM were analyzed for overall response and local recurrence; 5 with LMM were excluded from analysis in the adjuvant therapy outcome group because of development of metastasis, 2 of whom had completely resected melanoma (including the LM component) and 3 of whom were treated with adjuvant imiquimod for histologic transection of LM at the peripheral margin (after prior WLE with standard clinical margins for invasive melanoma). Overall, 50 of 58 cases (86.2%) demonstrated clinical clearance, with a mean (SD) follow-up of 42.1 (27.4) months. Of the 22 primary cases, 16 (72.7%) demonstrated clearance at mean follow-up of 39.7 (range 8-95) months. Of the 36 adjuvant cases, 34 (94.4%) demonstrated clearance at mean follow-up of 43.1 (range 4-106) months. Posttreatment biopsy or complete excision was performed in 15 of 58 (25.9%) of cases and demonstrated histologic clearance in 7 of 15 (46.7%) and residual LM in 8 of 15 (53.3%). Residual LM in 5 of 8 patients was treated with WLE, and 3 of 8 patients underwent a second course of imiquimod with documented clinical clearance thereafter.

Eighteen of 22 (81.8%) primary treatment cases demonstrated a brisk inflammatory response (Fig 1), 3 had no inflammatory response, and 1 response was unspecified. Only 2 of the 18 inflammatory responders failed to show clinical or histologic clearance as opposed to 4 of 4 nonspecified or unspecified responders. Both responders' courses were incomplete and complicated by loss of follow-up; 1 progressed to thin LMM (0.5 mm) that was subsequently excised. Of the 36 adjuvant cases, 26 (72.2%) demonstrated a brisk inflammatory response, 5 had no inflammatory response, and 5 were not specified. All 5 cases with no inflammatory response remained clinically or histologically clear, whereas 4 (80%) with an unspecified response remained clinically or histologically clear. Of the 26 inflammatory responders, only 1 (with underlying autoimmune disease) lacked clinical or histologic clearance after treatment, as did 1 of 10 nonspecified or unspecified responders. Outcomes are summarized in the flow chart depicted in Fig 2.

Correlation of response/recurrence with inflammatory reaction

There was a statistically significant association ($P < .01$) between imiquimod-induced inflammation and clinical or histologic clearance in primary but not adjuvant cases. Nine of 34 adjuvant cases that remained clinically clear over a mean (SD) follow-up period of 40.2 (30.3) months failed to

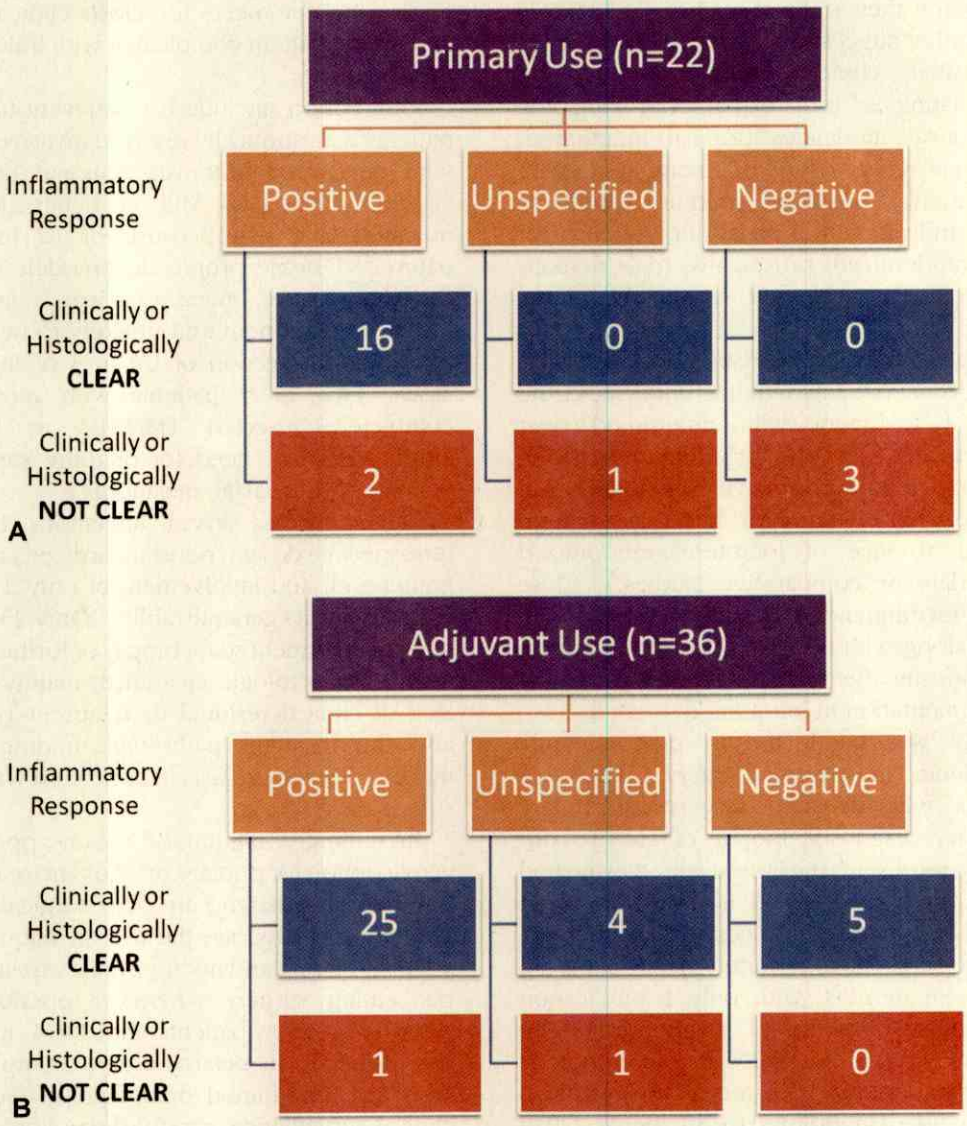

Fig 2. Outcomes flowchart for imiquimod according to inflammatory response. Patient outcomes depicted for imiquimod use as a primary treatment (**A**) and as an adjuvant therapy (**B**), based on presence or absence of inflammatory response.

display clinical evidence of inflammation during the treatment period. Conversely, 1 of 2 adjuvant cases that failed to completely clear on imiquimod demonstrated an ongoing inflammatory response while on therapy.

DISCUSSION

The incidence of LM and LMM subtypes of melanoma is increasing in the United States, particularly in older, fair-complexioned individuals.[14-16] In an institutional analysis of the VAPAHCS Tumor Registry data from 2003 through 2013, LM accounted for 75.5% (237/314) of subtyped MIS cases and LMM for 46.2% (147/318) of invasive melanomas. Management of LM is complicated by its typical location on the head and neck in older individuals, in whom surgical options may be limited, and histologic difficulty in differentiating actinic melanocytic hyperplasia in chronically sun-damaged skin from true LM. Up to 25% of melanocytes in sun-damaged skin of fair-skinned adults are estimated to be morphologically atypical by middle age, with clinically normal-appearing or mottled, hyperpigmented, overlying skin.[6]

Both the NCCN and AAD clinical practice guidelines for melanoma advocate WLE for MIS, including the LM subtype, but recognize the potential benefits of topical imiquimod therapy for surgically unresectable LM. The NCCN guidelines recommend consideration of imiquimod or

radiation therapy after "optimal surgery."[12] The AAD guidelines further suggest that when surgery for LM is not possible, clinical observation may be acceptable, citing a lack of superior outcome with nonsurgical modalities (topical imiquimod, radiation therapy, cryosurgery) compared with observation alone.[11] However, imiquimod remains an off-label indication for melanoma because of the lack of randomized, prospective trials demonstrating its efficacy compared with conventional surgery.[7,13,17-20]

A thorough discussion of risks and benefits is necessary so that patients/families understand the limitations of treatment with imiquimod over standard surgical resection, including the risk of missing or undertreating invasive melanoma, local recurrence caused by lack of histologic margin control, and absence of long-term randomized controlled trials or comparative studies.[11] Close follow-up is recommended in patients treated with imiquimod, along with a low threshold to perform "scouting" biopsies after treatment and biopsy of any recurrent pigmentation in imiquimod- treated sites.

Our study was conducted in predominantly elderly patients in whom surgery had been optimized or who declined surgery as primary treatment after diagnostic biopsy of LM. To our knowledge, it represents the largest cohort evaluated for the efficacy of imiquimod in LM, with mean follow-up of 42.1 months after cessation of therapy. Previous case series have reported mean follow-up of less than 36 months, with only 1 publication reporting longer follow-up of 49 months.[13] The overall clearance rate of 86.2% in our cohort is similar to prior reports. In a recent review of 46 reports on the use of imiquimod for MIS or LM, 220 of 264 (82%) patients demonstrated clinical or histologic clearance.[20]

The degree of inflammation with imiquimod has been correlated with long-term clearance but depends on the clinical setting in which the agent is used. If a large clinical residual LM is evident after diagnostic biopsy, the likelihood of significant inflammatory response is high, compared with its use in the adjuvant setting, in which histologic transection of LM after attempted excision, or what may only be actinic melanocytic hyperplasia, results in little to no inflammation. In our study, a positive inflammatory response was similarly high in both the primary (81.8%) and adjuvant (72.2%) settings and associated with long-term clearance (72.7% and 94.4%, respectively). We observed 3 treatment nonresponders (1 adjuvant and 2 primary users) who developed an inflammatory reaction but later failed to clear LM or progressed to LMM, reinforcing the need for close clinical follow-up and strong patient compliance with imiquimod field treatment.

Our cohort included 5 adjuvant-use cases in patients with surgically resected invasive melanoma, who developed in-transit, regional nodal and/or visceral metastasis. MIS is believed to confer no metastatic risk because of its intraepithelial nature.[21] Disease progression models support that development of metastasis was related to the invasive component and unlikely to be affected by histologic transection of LM in 3 of the metastatic cases. Two of 5 patients with metastasis had completely resected LM/LMM at the outset, emphasizing the need for ongoing surveillance in patients with invasive melanoma.

Our study has several limitations, including its retrospective design, nonstandardized application of imiquimod, and involvement of only 2 institutions, which limits its generalizablilty. Only 25.9% of cases had posttreatment scout biopsy or further excision to assess for histologic clearance, mainly because of lack of clinical residual or recurrent pigmentation and the frequent pathologic finding of actinic melanocytic hyperplasia in our cohort with extensive sun damage.

In summary, imiquimod cream appears to be a viable option for primary or adjuvant treatment of LM in older patients who are poor surgical candidates. We typically advocate the use of imiquimod in the adjuvant setting and not for primary treatment of LM, performing surgery whenever possible. Caution must be taken in patients with LMM, in whom the risk of metastasis persists despite complete surgical resection. Imiquimod field therapy requires close clinical surveillance, careful discussion, and patient compliance with treatment and follow-up. A multicenter, randomized controlled prospective trial should be performed to determine the long-term efficacy of topical imiquimod compared with or as an adjunct to surgical resection of LM.

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