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Topical Imiquimod for Lentigo Maligna: Survival Analysis of 103 Cases With 17 Years Follow-up

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ABSTRACT

Topical imiquimod 5% cream has been investigated as off-label primary or adjuvant treatment for melanoma in situ, lentigo maligna type (LM). Herein, we present the largest known case series of lentigo maligna treated with topical imiquimod, with up to 17 years of follow-up, and include a recurrence-free survival analysis. In this case series, 103 lesions were retrospectively evaluated for treatment response and recurrence following a course of topical imiquimod with or without tazarotene gel 0.1% pretreatment between January 1, 2002 and March 31, 2019, and prospectively followed through November 15, 2019. Over median follow-up of 5.1 years (mean = 6.2 years, S = 5.2 years, range, 0.08–17.1 years), including 29.1% LM with >10 years follow-up, we observed a response rate of 97.1% (100/103), with 8 local recurrences (8/100, 8.0%) developing at mean 2.9 years (SD: 2.7 years). Local recurrence was significantly associated with a history of failed excision (P= 0.001), <60 applications of imiquimod (P= 0.04) and partial clinical clearance (P= 0.0003). Recurrence-free survival analysis demonstrated significant risk-stratification for low and high-risk groups (P= 0.0001). Long term risk for recurrence showed significant differences among low- and high-risk cases, with low-risk cases demonstrating favorable long-term outcomes, comparable to conventional and staged surgery. Our observed low recurrence in a large case series with long-term follow-up suggests the efficacy of topical 5% imiquimod for LM and emphasizes the need for randomized control trials comparing imiquimod with, or as an adjunct to, surgical treatment.

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INTRODUCTION

Topical imiquimod 5% cream has been investigated as off-label primary or adjuvant treatment for melanoma in situ, lentigo maligna (LM) type, although long-term follow-up data are lacking.[1] Herein, we present a novel survival analysis based on a case series of 103 LM type (n = 81) or atypical intradermal melanocytic proliferation lesions (consistent with early/evolving LM) (n = 22), who were treated with topical imiquimod and followed up to 17 years thereafter. We report recurrence free survival (RFS) following primary (nonsurgical) or adjuvant treatment (after excision with narrow histologic margins [<1 mm] or histologically positive margins without visible pigmentation) between January 1, 2002 and March 31, 2019 and followed through November 15, 2019.

Treatment protocol was based on evolving best practices; patients were offered surgical resection as first-line therapy or off-label topical imiquimod 5% cream as second-line therapy. Patients were instructed to apply imiquimod five times weekly (weekdays) for 12 weeks with or without pre-treatment using two weeks of daily tazarotene 0.1% gel in order to elicit an appropriate inflammatory response, including erythema and scale.

There were 51 females and 52 males, with average age of 69.9 years (S = 10.4 years, range, 38–92 years). Additional case information is available in Table 1. Primary treatment occurred in 71 cases (68.9%) while 32 cases (31.3%) used imiquimod for adjuvant therapy after surgical resection with margins positive or narrowly excised for LM. Median follow-up was 5.1 years (mean = 6.2 years, S = 5.2 years, range, 0.08–17.1 years); 47 cases (45.6%) had >5 years follow-up, and 30 (29.1%) had >10 years. Lesions were assessed histologically, with post-treatment biopsy one month after completion of treatment when possible (64% of cases), and clinically, including Wood's lamp for residual pigmentation. Suspected recurrences were re-biopsied at the time of clinical suspicion.

The survival analysis assigned one point each to eight risk factors; age >65 years old, history of invasive melanoma at site of treatment, previous failed excision, no pre-treatment with

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TABLE 1.

Study Characteristics and Risk Factors				
	All Cases (n = 103)*	**Disease-free (n = 92)**	**Recurrence Cases (n = 8)**	**p-value ****
Gender, No. (%)				
Male	52 (50.5%)	49 (53.2%)	3 (37.5%)	0.390
Female	51 (49.5%)	43 (46.7%)	5 (62.5%)	0.390
Age, y, mean (SD, range)	69.9 (10.4, 38 - 92)	69.8 (10.4, 38 - 88)	72.5 (12.5, 48-92)	0.481
Greatest dimension of clinical lesion, cm, mean (SD, range)	1.3 (1.9, 0.2 - 12.0)	1.6 (1.6, 0.2 - 10.0)	2.8 (4.1, 0.4 - 12.0)	0.132
Pathologic diagnosis, No. (%)				
Atypical intradermal melanocytic proliferation concerning for LM	22 (21.4%)	20 (21.7%)	1 (12.5%)	0.535
Melanoma in Situ, Lentigo Maligna	81 (78.4%)	72 (78.3%)	7 (87.5%)	0.535
Breslow depth in invasive cases, mm, mean (SD, range)	1.0 (1.0, 0.2 - 3.1)	1.0 (1.0, 0.2 - 3.1)	NA	
Body Site, No. (%)				
Head/Neck	95 (92.2%)	84 (91.3%)	8 (100%)	0.384
Torso	4 (3.9%)	4 (4.3%)	0 (0%)	0.549
Extremities	4 (3.9%)	4 (4.3%)	0 (0%)	0.549
Use of imiquimod, No. (%)				
Primary	71 (68.9%)	62 (67.4%)	7 (87.5%)	0.238
Adjuvant - excision	32 (31.1%)	30 (32.6%)	1 (12.5%)	0.238
Risk Factors for recurrence:				
Age ≥65	73 (70.9%)	66 (71.7%)	7 (87.5%)	0.337
Invasive component prior to excision	11 (10.7%)	9 (9.8%)	2 (25%)	0.187
History of Failed Excsion(s)	8 (7.8%)	5 (5.4%)	3 (37.5%)	0.001
Total applications <60	53 (51.5%)	46 (50.0%)	7 (87.5%)	0.041
# applications <5/week	34 (33.0%)	29 (31.5%)	5 (62.5%)	0.077
<12 weeks of imiquimod	31 (30.0%)	28 (30.4%)	3 (37.5%)	0.682
No tazarotene	34 (33.0%)	30 (32.6%)	4 (50.0%)	0.317
Partial clinical clearance	8 (7.8%)	5 (5.4%)	3 (37.5%)	<0.001
Partial histological clearance ***	4 (3.9%)	4 (4.3%)	0 (0%)	0.465

*There were three non-responders who were excluded from the survival analysis, 92 disease-free cases, and eight recurrences. **_P_-values compare the disease-free cases and recurrences. ***Histological clearance was not included in the model due to missing data in 1/3 of cases.

tazarotene, <60 total applications of imiquimod, <5 applications per week, <12 weeks of treatment, and partial clinical clearance. The sum of a case's risk factors was considered high-risk (>4 risk factors), intermediate (4 risk factors) or low risk (<3 risk factors). Variables of interest were based on previously published literature[1,2] or epidemiological data.[3] An invasive melanoma component and previously failed surgical excision were considered proxies for more aggressive pre-existing disease or undetected sites of invasive disease following excision.[4] History of prior unsuccessful complete excision included patients who required multiple surgeries or developed recurrence years after an initial excision with negative margins. Since the reliability of histologic and clinical confirmation of clearance of LM has been debated,[5] both were considered. Ultimately, histological clearance was not included in the survival analysis due to a lack of recurrences among partial histological responders in our series, as well as biopsy-confirmation in only 64% of cases due to patient preference. RFS was defined as time from end of treatment to the first recorded date of local recurrence. RFS was estimated using Kaplan-Meier plots. Log-rank tests were performed for the comprehensive risk profile. Schoenfeld residuals were used to test the proportional-hazards assumption. As fewer than 10 local recurrences were observed, Cox Proportional Hazards regression was not performed.[6,7]

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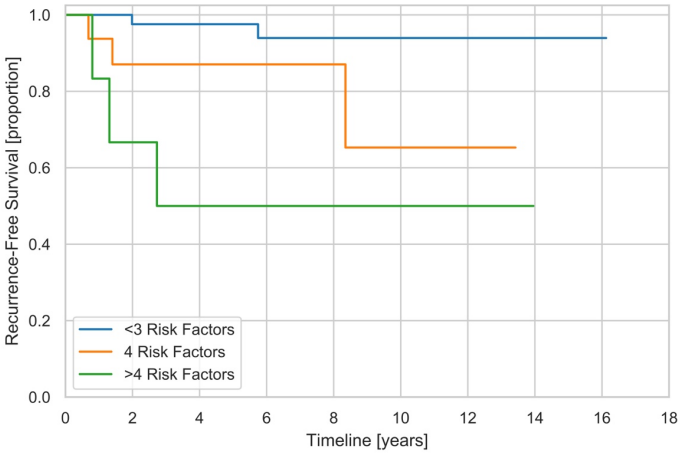
FIGURE 1. Recurrence-free survival among cases with lentigo maligna or atypical intradermal melanocytic proliferation receiving topical imiquimod.



Based on the presence/absence of eight risk factors, cases were stratified into high-risk (>4 risk factors present), intermediate (4 risk factors), or low risk (<3 risk factors) categories. The p-value comparing high vs. low-risk groups was *P*= 0.0001. Risk factors included: age >65 years old, history of invasive melanoma at site of treatment, previous failed excision, no pre-treatment with tazarotene, <60 total applications of imiquimod, <5 applications per week, <12 weeks of treatment, and partial clinical clearance.

Of 103 lesions, there were three non-responders (overall treatment response: 97.1%). Among responders (n= 100), eight local recurrences (8.0%) developed at mean 2.9 years (*S* = 2.7 years, range, 0.7–8.4 years), comprising a mean annual incidence rate of 1.29 recurrences per 100 person-years based on 621 person-years of follow-up time. The recurrence rate for primary treatment (7/69, 10.1%) was not significantly different from the rate for adjuvant treatment (1/31, 3.2%) (*P*=0.238). Variables significantly associated with recurrence in our series included a history of failed excision (*P*=0.001), <60 applications (*P*=0.04) and partial clinical clearance (*P*= 0.0003) [Table 1]. RFS between the lowest risk category and the highest risk category was significantly different (*P*=0.0001) with the low risk category demonstrating RFS 95%, compared to 50% in the high-risk group (Figure 1) at 16 years post-treatment.

Our study benefitted from long-term direction by the senior author (M.S.C.), with a relatively uniform treatment protocol in a large cohort with median follow-up of 5.1 years, including assessment by the same dermatologist or a designate familiar with the protocol. Limitations include a retrospective study design, including missing information such as post-treatment biopsy in 36% of cases, and limitations in published data which prevent weighting the model's risk factors to represent their contribution to risk of recurrence. Despite the latter challenge, the stratification in our model is highly significant, with RFS in the low-risk group comparable to rates of recurrence with margin-controlled surgical techniques.[8] While not a predictive model, this risk stratification may help clinicians frame the pre/post-treatment profile of their cases treated with topical imiquimod.

DISCLOSURES

The authors have no relevant conflicts.

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