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Brief Report

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Prognostic Factors for Treatment Failure of Photodynamic Therapy and 5-Fluorouracil in Bowen's Disease

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Clinical trial · Dermato-oncology · Dermatopathology · Drug reaction · Nonmelanoma skin cancer · Photodynamic therapy · Skin cancer

Abstract
Introduction: Little is known about prognostic factors that may influence the response to non-invasive treatments of patients with Bowen's disease. The aim of this study was to identify patient and lesion characteristics that are associated with a higher risk of treatment failure after 5-fluorouracil and photodynamic therapy in Bowen's disease. The hypothesis that the thickness of the Bowen's lesion and extension along the hair follicle is associated with the risk of treatment failure after noninvasive treatment was also explored. ***Methods:*** Data were derived from a non-inferiority randomized trial in which 169 patients were treated with 5% 5-fluorouracil cream twice daily for 4 weeks or 2 sessions of methylaminolevulinate photodynamic therapy with 1-week interval. All patients had histologically confirmed Bowen's disease of 4–40 mm. The initial 3 mm biopsy specimens were re-examined to measure the maximum histological lesion thickness and extension along the hair follicle. To evaluate the association between potential risk factors for treatment failure at 1-year follow-up, univariate and multivariate logistic regression analyses were used to calculate odds ratios (ORs) with 95% confidence intervals and *p* values. ***Results:*** Histological lesion thickness was not significantly associated with treatment failure (OR: 0.84, $p = 0.806$), nor was involvement of the hair follicle (OR: 1.12, $p = 0.813$). Lesion diameter was the only risk factor that was significantly associated with 1-year risk of treatment failure (OR = 1.08 per mm increase, $p = 0.021$). When using the median value of 10 mm as cut-off point, the risk of treatment failure was 23.4% for lesions >10 mm compared to 10.3% for lesions ≤10 mm (OR: 2.66, $p = 0.028$). ***Conclusions:*** Only clinical lesion diameter was identified as a prognostic factor for response to non-invasive therapy in Bowen's disease.

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Introduction

Bowen's disease, also known as squamous cell carcinoma in situ, is often treated noninvasively. In a recent randomized controlled trial (RCT), including patients with histologically confirmed Bowen's disease of 4–40 mm, the proportion of patients with sustained clearance after 1 year was 85.7% with 5-fluorouracil cream and 82.1% with methylaminolevulinate photodynamic therapy (MAL-PDT) [1]. Despite high effectiveness, a proportion of patients still had treatment failure and little is known about factors that can help predict the response to non-invasive treatments of Bowen's disease. In other keratinocyte carcinomas histologic characteristics are known to impact treatment outcome [2–5]. Previous studies have suggested that thickness is a predictor for response because noninvasive treatments may not be able to fully penetrate thicker lesions [6, 7]. Furthermore, in Bowen's disease, the dysplasia sometimes reaches deep into the epidermis extending along hair follicles. We hypothesized that both histological thickness and extension along the hair follicle might increase the risk of treatment failure after noninvasive treatment of Bowen's disease. In this study, we aimed to identify patient and lesion characteristics that are associated with a higher risk of treatment failure after 5-fluorouracil and PDT in Bowen's disease. We specifically looked at histological lesion thickness and extension along the hair follicle and explored other potential histological features.

Methods

Study Design and Population

Data were derived from patients who had participated in a multicenter non-inferiority RCT [1]. Only patients randomly assigned to 5% 5-fluorouracil cream twice daily for 4 weeks or 2 sessions of MAL-PDT with a 1-week interval were included. All patients had histologically confirmed Bowen's disease of 4–40 mm and histological specimens of the lesions were available for re-examination. Treatment outcome was evaluated at 3 and 12 months after treatment. Any clinical indication of recurrence was confirmed histologically with a 3 mm punch biopsy. The trial was approved by the Medical Ethical Committee of Maastricht University Medical Center (METC19-009). All patients provided informed consent. Further details on the design and the results from this trial have previously been published [1].

Potential Risk Factors for Treatment Failure

Data on several risk factors, such as sex, age, Fitzpatrick skin type, lesion location, and maximum lesion diameter were already available from the RCT. For histological measurement of lesion thickness and extension along the hair follicle, the histopathological slides of the initial 3 mm diagnostic biopsy specimens were examined by an independent dermatopathologist, blinded to treatment assignment. Three pathologists were involved, and each examined part of the lesions after extensive briefing and guided by a uniform step-by-step protocol on how to perform the histological measurements. Maximum lesion thickness was measured from the start of the stratum granulosum to the deepest part where epidermal keratinocytic dysplasia was located. In case of ulceration or erosion, thickness was measured from the level of the adjacent epidermis. Furthermore, it was noted whether extension along a hair follicle was present and the thickness of the stratum corneum was also measured.

At MUMC+, VieCuri Medical Center, and Zuyderland Medical Center, additional data were collected on cellular atypia, solar elastosis, presence or absence of inflammation and apoptosis, mitotic figures, and height of these mitotic figures. Solar elastosis and cellular atypia were categorized into three levels: mild, moderate, or severe. The height of mitotic figures was defined as the highest location within the epidermis where a mitotic figure was found. Therefore, the epidermis was divided into three equal sections from the dermal site to the skin surface. All measurements were performed with a Zeiss microscope in millimeters (mm) with a 0.1-mm precise ocular micrometer with ×10 magnification and an objective with ×10 magnification.

Statistical Analysis

Continuous variables are presented as mean with standard deviation or median with range. Categorical variables are presented as numbers and percentages. Differences in baseline characteristics between patients with treatment failure and patients with treatment success were tested for significance using the *t* test for independent samples or the Mann-Whitney U test for continuous variables, and the χ^2 test or Fisher exact for categorical variables.

To evaluate the association between potential prognostic factors and risk of treatment failure at 1-year follow-up, univariate and multivariate logistic regression analyses were used to calculate odds ratios (ORs)

Table 1. Patient and lesion characteristics according to treatment outcome

Characteristics	Total (n = 161)	Treatment failure (n = 25), n (%)	Treatment success (n = 136), n (%)	p value
Sex, n (%)				0.439
Female	105	18 (17.1)	87 (82.9)	
Male	56	7 (12.5)	49 (87.5)	
Age				
Median (range)	76 (51–92)	77 (63–85)	76 (51–92)	0.153
≤76 years	86	11 (12.8)	75 (87.2)	0.306
>76 years	75	14 (18.7)	61 (81.3)	
Fitzpatrick skin type, n (%)				
I	34	8 (23.5)	26 (76.5)	Reference
II	125	17 (13.6)	108 (86.4)	0.159
III	2	0 (0.0)	2 (100.0)	0.766
Treatment, n (%)				0.306
MAL-PDT[a]	75	14 (18.7)	61 (81.3)	
5-FU[b]	86	11 (12.8)	75 (87.2)	
Lesion location, n (%)				
Head or neck	48	9 (18.8)	39 (81.2)	0.579
Trunk	33	4 (12.1)	29 (87.9)	0.347
				0.690
Extremities	80	12 (15.0)	68 (85.0)	Reference
Lesion diameter, mm				
Median (range)	10 (4–32)	12 (6–32)	10 (4–30)	**0.021**
≤10 mm	97	10 (10.3)	87 (89.7)	**0.028**
>10 mm	64	15 (23.4)	49 (76.6)	
Histological lesion thickness, mm				
Median (range)	0.33 (0.02–1.53)	0.31 (0.10–1.50)	0.34 (0.02–1.53)	0.808
Quartiles				
0–0.23	42	8 (19.0)	34 (81.0)	Reference
0.24–0.33	39	7 (17.9)	32 (82.1)	0.899
0.34–0.50	41	4 (9.8)	37 (90.2)	0.236
>0.50	39	6 (15.4)	33 (84.6)	0.664
Hair follicle involvement, n (%)				0.813
Yes	42	7 (16.7)	35 (83.3)	
No	119	18 (15.1)	101 (84.9)	
Histological thickness of stratum corneum, mm				0.752
Median (range)	0.11 (0–2.32)	0.14 (0–0.62)	0.11 (0–2.32)	
Additional histologic characteristics[a]	Total (n = 111)	Treatment failure (n = 17), n (%)	Treatment success (n = 94), n (%)	p value
Cellular atypia				
Mild	7	0 (0.0)	7 (100.0)	Reference
Moderate	82	14 (17.1)	68 (82.9)	0.414
Severe	22	3 (13.6)	19 (86.4)	0.515
Solar elastosis				
Mild	26	4 (15.4)	22 (84.6)	Reference
Moderate	65	11 (16.9)	54 (83.1)	0.858
Severe	20	2 (10.0)	18 (90.0)	0.590
Inflammation				0.446
Yes	92	13 (14.1)	79 (85.9)	
No	19	4 (21.1)	15 (78.9)	

Table 1 (continued)

Additional histologic characteristics[a]	Total (n = 111)	Treatment failure (n = 17), n (%)	Treatment success (n = 94), n (%)	p value
Apoptosis				0.430
Yes	103	15 (14.6)	88 (85.4)	
No	8	2 (25.0)	6 (75.0)	
Mitotic figures				0.546
Yes	100	16 (16.0)	84 (84.0)	
No	11	1 (9.1)	10 (90.9)	
Height of mitotic figures[b]				
1/3	19	4 (21.1)	15 (78.9)	Reference
2/3	49	8 (16.3)	41 (83.7)	0.646
3/3	32	3 (9.4)	29 (90.6)	0.242

[a]Measured at Maastricht University Medical Center, VieCuri, and Zuyderland Medical Center. [b]If mitotic figures were observed.

with 95% confidence intervals (95% CIs) and p values. A p value of 0.05 or lower was considered statistically significant. All statistical analyses were performed with IBM SPSS Statistics, Version 25.0 (IBM Corp., Armonk, NY, USA).

Results

Study Population

From May 2020 to January 2021, 90 patients were treated with 5-fluorouracil and 79 with MAL-PDT. A total of 8 patients were lost to follow-up; 3 patients did not attend the follow-up visits, 1 moved, and 4 died. Of the remaining 161 patients (86 treated with 5-fluorouracil and 75 with MAL-PDT), 25 patients (15.5%) had treatment failure and 136 (84.5%) had treatment success at 12-months. The distribution of patient and lesion characteristics in both groups is shown in Table 1.

Potential Prognostic Factors for Treatment Failure

Table 2 shows the ORs for treatment failure with 95% CI from univariate and multivariate logistic regression models according to patient and lesion characteristics. Histological lesion thickness as continuous variable was not significantly associated with risk of treatment failure (OR: 0.84 per mm increase, p = 0.806) nor was the involvement of hair follicle (yes vs. no) (OR: 1.12, p = 0.813). An additional analysis was performed, wherein patients were categorized into quartiles according to lesion thickness. No trend toward a higher risk of treatment failure at thicker lesions was observed. No other histologic features were of significant prognostic value (Tables 1, 2).

Lesion diameter was the only risk factor that was significantly associated with a 1-year risk of treatment failure (OR: 1.08 per mm increase, p = 0.021). Lesions were also categorized into size groups, where the median value of 10 mm was chosen as cut-off value. The risk of treatment failure was 23.4% for lesions >10 mm compared to 10.3% for lesions ≤10 mm (OR: 2.66, p = 0.028).

The independent effect of lesion size, histological lesion thickness and involvement of hair follicle was evaluated using a multivariate logistic regression model. After adjustment, the association with lesion size remained significant with an OR of 1.08 per mm increase (p = 0.022) (Table 2).

Discussion

The results of this study show that lesion size was significantly associated with an increased risk of treatment failure in Bowen's disease treated with MAL-PDT or 5-fluorouracil cream. The results do not support the hypothesis that histological lesion thickness and hair follicle involvement are useful predictors of treatment response.

In this study, a large prognostic difference between lesions sized ≤10 mm and lesions >10 mm was found. While patients with a small lesion have a probability of success of 90%, this decreases to 77% for larger lesions. This information can be important for patients who want to be involved in shared decision-making: knowing how

Table 2. Odds ratios for treatment failure with 95% CI and *p* values according to patient and lesion characteristics

Patient characteristics	Univariate logistic regression			Multivariate logistic regression		
	odds ratio	95% CI	*p* value	odds ratio	95% CI	*p* value
Sex, female versus male	1.45	0.57–3.71	0.439			
Age, years	1.05	0.98–1.11	0.154			
Fitzpatrick skin type						
I	Reference					
II	0.51	0.20–1.31	0.164			
III	0.62	0.03–14.30	0.766			
Treatment, PDT versus 5-FU	1.57	0.66–3.69	0.307			
Lesion location						
Head or neck	1.31	0.51–3.38	0.579			
Trunk	0.78	0.23–2.62	0.690			
Extremities	Reference					
Lesion diameter (continuous)	1.08	1.01–1.16	**0.021**	1.08	1.01–1.16	**0.022**
>10 mm versus ≤10 mm	2.66	1.11–6.38	**0.028**			
Histological lesion thickness (continuous)	0.84	0.20–3.45	0.806	0.99	0.25–4.02	0.994
>0.33 mm versus ≤0.33	0.63	0.26–1.50	0.294			
Quartiles						
0–0.23	Reference					
0.24–0.33	0.93	0.30–2.86	0.899			
0.34–0.50	0.46	0.13–1.67	0.236			
>0.50	0.77	0.24–2.47	0.664			
Hair follicle involvement, yes versus no	1.12	0.43–2.91	0.813	1.03	0.39–2.73	0.959
Histological thickness of stratum corneum	0.78	0.17–3.54	0.751			

often they can expect to need retreatment after treatment with 5-fluorouracil and MAL-PDT allows the setting of realistic expectations. More so, it could lead to personalized treatment strategies where larger lesions may require a different treatment strategy, such as longer duration or more frequent treatments or maybe surgery.

We tried to find explanations for the finding that an increased lesion diameter is associated with treatment failure. Tumor specific explanations might be that larger lesions exist longer and therefore exhibit more aggressive growth by accumulation of different genetic mutations and also presence of more malignant cells automatically increases the chance of non-responding cells [8, 9]. Furthermore, pharmacokinetics may play a role, as for larger lesions, the relative amount of the cream applied might be lower and application might be less evenly distributed compared to smaller lesions. Moreover, in smaller lesions the applied cream might also reach the lesion through the healthy surrounding skin and not only through the affected, often hyperkeratotic lesion. To overcome this problem, a longer application period or repeated treatment rounds could be a solution.

In squamous cell carcinoma and melanoma, lesion thickness is a known risk factor for local recurrence and metastasis, defined as the depth of invasion beyond the epidermis [3–5, 8]. Consequently, lesion thickness is measured by pathologists and reported to clinicians for accurate tumor staging. However, as Bowen's disease is not an invasive tumor, the extent is per definition limited to the epidermis, and our results showed that the thickness of the affected epidermis was not associated with treatment failure. Even extension along the hair follicle was not found to be of prognostic value. It is therefore not necessary to include the measurement of lesion thickness in routine histological examination of Bowen's disease.

This study has some limitations. First, given the sample size in the groups with and without treatment failure (25 vs. 136), there was limited power of 62% to detect a medium Cohen's effect size of 0.5 (two-sided alpha = 5%). Second, measurements on 3 mm biopsies

may not be representative for the entire lesion. Other diagnostic techniques such as optical coherence tomography might be more suitable to provide a comprehensive view of the entire lesion. Optical coherence tomography or other non-invasive imaging tools with high resolution may be helpful in detection of additional tumor characteristics with possible prognostic value in the near future. In conclusion, the results show that only lesion size was significantly associated with an increased risk of treatment failure following 5-fluorouracil cream and MAL-PDT in Bowen's disease.

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Statement of Ethics

Written informed consent was obtained for participation in this study. Reviewed and approved by Maastricht University Medical Center Ethics Committee (#142052); approval #19-009 ClinicalTrials.gov number: NCT03909646.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Conceptualization: Ahmady, Mosterd, and Kelleners-Smeets. Formal Analysis and visualization: Ahmady. Investigation: Ahmady, Abdul-Hamid, van Marion, and Demeyere. Methodology: Ahmady and Nelemans. Project administration: Ahmady and Mosterd. Resources: Abdul-Hamid, van Marion, and Demeyere. Supervision: Mosterd, Nelemans, and Kelleners-Smeets. Validation: Nelemans. Writing – original draft: Ahmady, Mosterd, and Nelemans.

Data Availability Statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from the corresponding author (S.A.) upon reasonable request.

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