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Prognostic factors for treatment failure of imiquimod treatment in basal cell carcinoma – an observational study

To the Editor,

Imiquimod 5% cream is the most effective non-invasive treatment for superficial and nodular basal cell carcinoma (sBCC and nBCC). In two randomized controlled trials (RCTs), including patients with low risk sBCC and nBCC, treatment with imiquimod 5% cream for 6-12 weeks resulted in a probability of tumour-free survival around 80% after 5 years of follow-up.[1,2] Little is known about factors that may influence the response to imiquimod treatment. Previous studies have shown that a less severe skin reaction and male sex are

Table 1 Percentage with treatment failure according to the level of prognostic factors

	Number of patients	Treatment failure, n (%)
Clinical patient and tumour characteristics	**n = 262**	
Age (years), median (IQR)	63.5 (55-70)	
<64 years	132	15 (11.4%)
≥64 years	130	26 (20.0%)
Female, n (%)	131	13 (9.9%)
Male, n (%)	131	28 (21.4%)
Location		
Head and neck, n (%)	45	8 (17.8%)
Lower extremities, n (%)	39	14 (35.9%)
Upper extremities, n (%)	35	3 (8.6%)
Trunk, n (%)	143	16 (11.2%)
Largest tumour diameter (mm), median (IQR)*	9.0 (7.0-13.0)	
≤9.0mm	139	25 (18.0%)
>9.0mm	122	16 (13.1%)

Table 1 *Continued*

	Number of patients	Treatment failure, n (%)
Treatment-related characteristics†	**n = 262**	
Skin reaction		
None	21	7 (33.3%)
Mild/moderate	135	27 (20.0%)
Severe	103	6 (5.8%)
Missing	3	1 (33.3%)
Compliance		
30 days	183	32 (17.5%)
<30 days	65	7 (10.8%)
Missing	14	2 (14.3%)
Histologic tumour characteristics	**n = 136**	
Tumor thickness (mm), median (IQR)‡	0.50 (0.31-1.00)	
≤0.5 mm	69	8 (11.6%)
>0.5 mm	65	9 (13.8%)
Epidermal aspect		
Normal	100	13 (13.0%)
Atrophic	29	2 (6.9%)
Hyperplastic	4	1 (25.0%)
Missing§	3	1 (33.3%)
Ulceration		
Absent	110	11 (10.0%)
Present	26	6 (23.1%)
Parakeratosis		
Absent	62	5 (8.1%)
Present	74	12 (16.2%)
Erosion		
Absent	77	7 (9.1%)
Present	59	10 (16.9%)
Infiltrate		
None	14	2 (14.3%)
Mild	58	9 (15.5%)
Moderate	39	3 (7.7%)
Severe	25	3 (12.0%)
Amount of plasma cells		
Not pronounced	112	13 (11.6%)
Pronounced	10	2 (20.0%)
Missing^	14	2 (14.3%)
Amount of blood vessels		
Not pronounced	73	6 (8.2%)
Pronounced	63	11 (17.5%)
Solar elastosis		
None	12	3 (25.0%)
Mild	53	6 (11.3%)
Severe	71	8 (11.3%)

BCC, basal cell carcinoma; SD, standard deviation; IQR, interquartile range.
*Information on tumour diameter was missing in one patient.
†Based on patient diaries.
‡Measured from the stratum granulosum, or base of overlying ulceration, to the deepest tumour nest with a 0.01-mm precise ocular micrometer.
§Epidermal aspect could not be assessed in three BCCs due to coarse ulcerations (n = 2) and poor quality of the biopsy (n = 1).
^Plasma cells could only be assessed in biopsies where inflammation was present.

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Table 2 Odds ratio with 95% confidence interval for treatment failure according to patient, tumour, treatment and histological characteristics. Mixed logistic effects models were used

		OR	95% CI	*P*-value
Multivariable model of patient and tumour characteristics	**Patient and tumour characteristics**			
	Sex			
	Female	1.00		
	Male	2.77	1.29-5.94	*0.009*
	Age per year*	1.02	0.99-1.06	0.205
	Largest tumour diameter (mm)**	1.02	0.96-1.07	0.565
	Location			
	Head and neck	1.00		
	Upper extremities	0.49	0.12-2.09	0.337
	Trunk	0.61	0.23-1.64	0.327
	Lower extremities	3.02	1.03-8.82	*0.044*
Multivariable model of treatment characteristics	**Treatment characteristics**			
	Skin reaction			
	Severe	1.00		
	Mild/moderate	4.82	1.76-13.21	*0.002*
	None	9.10	2.38-34.82	*0.001*
	Compliance per day increase***	1.00	0.89-1.13	0.968
Separate univariable models of all histological factors	**Histologic characteristics**			
	Tumour thickness (mm)****	0.94	0.42-2.13	0.881
	Epidermal aspect			
	Normal	1.00		
	Atrophic	0.50	0.11-2.34	0.375
	Hyperplastic	2.23	0.22-23.09	0.501
	Parakeratosis			
	Absent	1.00		
	Present	2.21	0.74-6.65	0.160
	Ulceration			
	Absent	1.00		
	Present	2.70	0.89-8.15	0.078
	Erosion			
	Absent	1.00		
	Present	2.04	0.73-5.73	0.176
	Infiltrate			
	None	1.00		
	Mild	1.10	0.21-5.78	0.909
	Moderate	0.50	0.07-3.36	0.476
	Severe	0.82	0.12-5.59	0.838
	Amount of plasma cells			
	Not pronounced	1.00		
	Pronounced	1.90	0.36-9.95	0.445
	Amount of blood vessels			
	Not pronounced	1.00		
	Pronounced	2.36	0.82-6.81	0.112
	Solar elastosis			
	None	1.00		
	Mild	0.38	0.08-1.82	0.227
	Severe	0.38	0.09-1.71	0.207

OR, odds ratio, 95% CI = 95% confidence interval. OR >1 and OR<1 indicate increased and decreased risk of treatment failure, respectively, where categories with OR=1 were used as the reference category.
*The odds ratio for age represents increase in risk per year.
**The odds ratio for largest tumour diameter represents increase in risk per increase in mm.
***The odds ratio for compliance represents increase in risk per day increase of compliance.
****The odds ratio for tumour thickness represents increase in risk per 0.1mm increase. $P < 0.05$ is considered statistically significant.
Italic values indicate statistically significant *P*-values ($P < 0.05$).

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associated with treatment failure to imiquimod.[3–5] In the current study, we aimed to confirm previous findings and to identify new histologic factors associated with risk of failure after imiquimod treatment.

Data were derived from 189 sBCC and 73 nBCC patients who participated in two RCTs on the efficacy of imiquimod.[6,7] In both trials, imiquimod was applied once daily, five days a week, for 6 weeks. Treatment failure was evaluated by an investigator at 12-month post treatment and had to be histologically confirmed. Candidate prognostic factors were categorized into three groups: 1) patient and tumour characteristics, 2) factors related to treatment and 3) histological characteristics. To evaluate the association between prognostic factors and 1-year treatment failure, odds ratios (ORs) with 95% confidence intervals (95% CIs) were calculated. Mixed-effects logistic regression analyses were used to account for the pooling of data from two studies. Multivariable models were used for mutual adjustment of factors in the factors in the first two groups, but for the large group of histologic factors, only univariable models were used.

In total, 262 patients were included, 189 patients from the sBCC trial[7] and 73 patients from the nBCC trial.[6] Histologic characteristics were available in a subgroup of 136 patients (Table 1). Treatment failure ≤1 year after treatment occurred in 41/262 (15.6%) BCCs. The risk of treatment failure was significantly higher for males (OR 2.77, $P = 0.009$) compared to females and for tumours on the lower extremities compared to tumours in the head and neck area (OR 3.02, $P = 0.044$). Compared to patients with severe skin reaction, the OR with mild/moderate skin reaction was 4.75 ($P = 0.002$) and increased to 8.28 ($P = 0.002$) for patients without any skin reaction. The OR for tumour thickness of 0.94 per 0.1 mm increase in thickness was not significant ($P = 0.881$) (Table 2). Four nBCCs invaded beyond the dermis and reached into the subcutis, all achieved treatment success (data not shown). Factors that may affect permeability of the skin (hyperplastic epidermal aspect and parakeratosis) showed an OR of 2.23 ($P = 0.501$) and 2.21 ($P = 0.160$) for treatment failure, respectively. The OR for presence of ulceration was 2.70 ($P = 0.078$).

In this study, we confirmed that male sex, location on the lower extremities and a less severe/absent skin reaction were significantly associated with an increased risk of treatment failure following imiquimod cream in nBCC and sBCC. The results indicate that risk of treatment failure is not increased in thick tumours and tumours with a high amount of tumour infiltration. Presence of ulceration, parakeratosis and a hyperplastic epidermal aspect were associated with slightly increased ORs. These results might suggest that less permeability of the skin could play a role in the risk of treatment failure as well as the presence of ulceration, a well-known risk factor in melanoma. However, due to small numbers of patients with treatment failure, the power of this study to detect small but relevant associations was small, and results need to be validated in larger data sets.

Conflict of interest

None declared.

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Data availability statement

Data are available upon reasonable request.

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