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Office-based treatment of basal cell carcinoma with immunocryosurgery: feasibility and efficacy

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Abstract

Introduction: Minimally invasive, non-surgical, office-based modalities are a welcome alternative to surgery for basal cell carcinoma (BCC). This study evaluates the treatment of BCC with immunocryosurgery (cryosurgery during topical imiquimod) in a dermatology office setting.
Methods: Response of BCC to immunocryosurgery (daily imiquimod for 5 weeks and a liquid N2 cryosurgery session at the end of the 2nd week) was evaluated according to treatment feasibility, tumor clearance, and relapse.
Results: Twenty-four patients with a total of 36 BCC (four relapses after cryosurgery or surgery) were recruited and all finished treatment (follow-up: 2–24 months). One month after the end of treatment, 30/36 sites were clinically cured. In five cases, a repeat cryosurgery at this time led to clinical cure (one patient refused cryosurgery; overall cure rate: 97.2%). Two relapses occurred after 12 and 14 months follow-up, which were successfully treated with immunosurgery and cryosurgery, respectively. Adverse effects included hypopigmentation, redness persisting for up to 3 months after treatment, superficial scarring that improved with time, and worry during treatment because of skin irritation (resolved with a phone discussion in all cases).
Conclusion: Immunocryosurgery is a feasible and efficacious procedure that can be performed at a dermatology office for the treatment of primary and relapsed BCC.

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Introduction

Basal cell carcinoma (BCC) represents approximately 6.5% of all diagnoses at outpatient dermatology offices in Albania (1). The high incidence of BCC in this country reflects the past excessive and unprotected sun exposure of the population because most people lived and worked in rural areas before 1990 (2). An effective, minimally invasive, non-surgical, office-based treatment modality for BCC would be a welcome alternative to surgery, especially for elderly multimorbid patients (3). Furthermore, in order to contain the treatment costs it is necessary to evaluate the feasibility of any proposed modalities for BCC for their applicability in the office-based setting (4, 5). Recently, immunocryosurgery (i.e. cryosurgery during ongoing treatment with topical imiquimod) was introduced for the treatment of BCC with very promising therapeutic results not only for small tumors, but even for larger, relatively "difficult-to-treat" cases, including tumor relapses after surgery (6–10). Meanwhile, the effectiveness of this method to treat BCC was confirmed in a prospective clinical trial (NCT01212562) that included 119 tumors with maximum diameter ≤ 2 cm (11). To date, all studies on the use of immunocryosurgery to treat BCC were performed in a clinical setting and the applicability of this minimally invasive modality under office-based conditions has been not evaluated yet. The aim of this study was to report the therapeutic and cosmetic outcome of the treatment of BCC with immunocryosurgery in an office-based setting.

Material and Methods

From October 2010 to November 2012, patients diagnosed with BCC were recruited for treatment with immunocryosurgery; that is, cryosurgery during ongoing daily topical imiquimod application (12). The tumors were treated according to a slightly modified protocol adapted from Gaitanis et al. (8, 11). Patients applied 5% imiquimod cream once daily, as a thin layer on the tumor and about 0.5 cm onto the rim of the surrounding skin. Two weeks after the onset of imiquimod application, cryosurgery was performed (open spray, liquid N2, two cycles of 20 sec each) on the inflammatory skin area and a 0.5 to 1 cm rim around the clinical margins of the tumor (8, 9, 11). The freezing time (20 seconds) refers to the duration of active cryogen spraying after the target tissue was completely frozen. Imiquimod application was continued without any interruption; that is, from the evening of the cryosurgery day and every evening thereafter for 3 more weeks (= "end of treatment" and "start of follow-up period"). Scheduled follow-up visits were at 1 month after the end of the treatment and every 3 months thereafter. Based on past experience, the persistence of erosion 1 month after the end of the treatment cycle was interpreted as evidence for persisting tumor remnants (8, 9, 11). For such cases, an additional cryosurgery session at this time without prior imiquimod treatment was considered.

Treatment outcome was evaluated for feasibility and effectiveness according to the following parameters (8, 9, 11): (a) "Feasibility" (i.e., the proportion of patients that terminated the treatment according to the protocol). In addition, adverse treatment effects including treatment-associated complaints and treatment-induced conditions were recorded; (b) Tumor "clearance rate" (i.e., the proportion of BCC that cleared 1 month after the end of treatment). Subsequent treatment outcomes were designated as (i) "complete response" (CR) when the treated area was clinically free of tumor remnants, and (ii) "non-response" (NR) otherwise; and (c) Tumor "relapse rate" (i.e., the rate of treated tumors that recurred contiguous to or within 1 cm of the treatment scar). During the follow-up visits, the cosmetic outcome of the treated skin area was evaluated by the physician and the patient, according to a subjective scale: excellent, good, acceptable, and unacceptable.

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This evaluation considers the results of the last follow-up examination through January 2013.

Results

Patients and tumor characteristics

Twenty-four patients (16 men and 8 women; mean age: 62.6 years, range: 45–85 years) with a total of 36 BCC were enrolled (Table 1). All tumors were located on the head and neck region; 33/36 of them in the face. Most tumors were primary BCC; however, four relapses after previous cryosurgery and one after surgery were also included. In seven patients, multiple (up to four) synchronous tumors were treated in parallel (Table 1). The follow-up period ranged from 2 to 24 months (median: 7.5 months).

Feasibility of immunocryosurgery

All 24 patients finished treatment at all 36 sites. Major complaints during treatment were discomfort, oozing, and pruritus, which peaked the week following cryosurgery. The cosmetic outcome was generally considered good to excellent by the attending physician (Fig. 1 and 2). The results were rated "good" in 21/36 evaluable tumor sites and "excellent" in 13/36. Principal adverse effects were hypopigmentation largely restricted to the area of the healed tumor (eight cases; cf. Fig. 1e), local redness that persisted for up to 3 months after treatment (20 cases; cf. Fig. 2e), and some degree of superficial scarring that improved with time (17 cases; cf. Figs. 1e–f). All 24 patients were satisfied with the cosmetic outcome and expressed their preference for this therapeutic modality again in the future in the case of a tumor relapse. During treatment, 12 patients expressed concern because of escalating irritation at the treatment site. Phone discussion of the predictability of this adverse effect resolved anxiety in all cases.

Efficacy of immunocryosurgery: tumor control ("clearance")

One month after the end of treatment, 30/36 sites were clinically free of tumor remnants (complete responders, CR). In six cases, residual tumor was suspected during clinical examination. In five of these cases (Tumors 2, 4, 15, 17, 21A; Table 1), a repeat cryosurgery session at a 1-month follow-up examination (without imiquimod pretreatment) led to CR. One patient (tumor 7B) refused repeated cryosurgery and decided to await the final outcome of the treatment and probably treat a relapse in the future. Taken together, in 35/36 tumors (97.2%) clinical clearance was achieved through immunocryosurgery.

Table 1 | Patients treated with immunocryosyrgery; once-daily imiquimod on the tumor for a total of 5 weeks and a session of liquid N2 tumor cryosurgery at the end of the 2nd week of imiquimod treatment (open spray, two cycles of 20 s).

Patients	Sex	Age [years]	Tumor	Tumor diameter [mm]	Repeat cryosurgery at week 4 after end of imiquimod#	Follow-up [months]	Relapse
01	Male	68	1A	15		24	No
			1B	12		24	No
			1C	7		24	No
02	Female	63	2	4	Yes	18	Yes
03	Male	71	3A	11		18	No
			3B	9		18	No
04	Female	49	4	25	Yes	16	Yes
05	Male	71	5	59		14	No
06	Male	52	6	7		14	No
07	Male	57	7A	22		15	No
			7B	8	Denied	15	ND*
08	Male	85	8	8		12	No
09	Male	60	9A	13		12	No
			9B	9		12	No
10	Male	69	10	12		11	No
11	Female	60	11	6		11	No
12	Male	50	12	9		10	No
13	Female	69	13	7		8	No
14	Female	48	14	12		7	No
15	Male	51	15	18	Yes	7	No
16	Female	73	16	11		7	No
17	Male	66	17	15	Yes	4	No
18	Male	74	18A	5		3	No
			18B	10		3	No
			18C	8		3	No
			18D	19		3	No
19	Male	50	19	30		2	No
20	Female	62	20	6		7	No
21	Male	59	21A	18	Yes	3	No
			21B	18		3	No
			21C	8		3	No
			21D	7		3	No
22	Male	59	22	36		2	No
23	Female	69	23A	43		4	No
			23B	34		4	No
24	Male	68	24	27		5	No

#Repeat cryosurgery was offered to patients at week 4 after the end of treatment only for six tumors with clinical signs of remnant tissue (partial responders). One patient (#7) refused repetition of cryosurgery.
*ND: Outcome not yet definable.

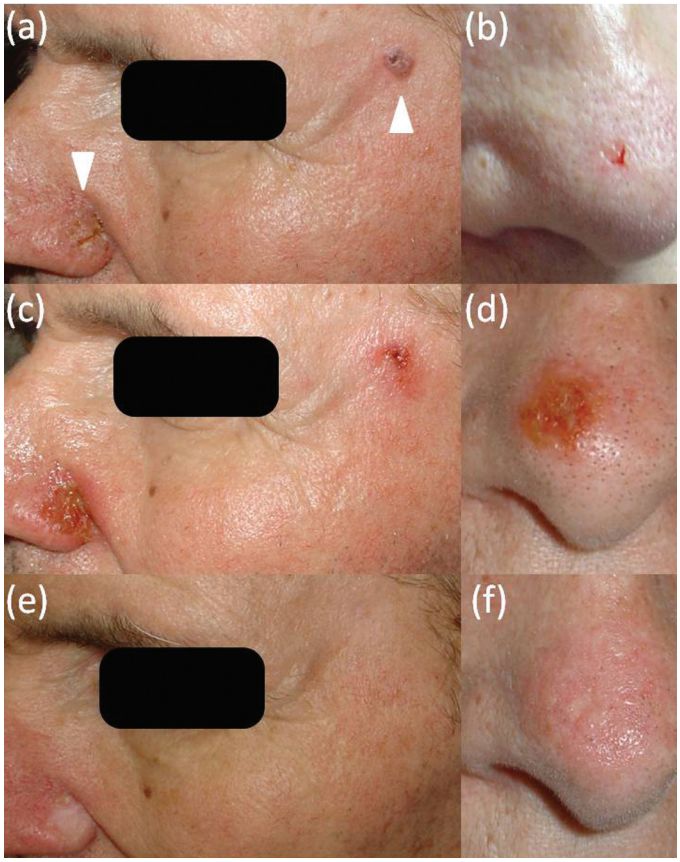

Figure 1 | Treatment of basal cell carcinomas with immunocryosurgery. Patient 03 (Table 1): panels (a), (c), and (e), and Patient 02 (Table 1): panels (b), (d), and (f). Panels (a) and (b): tumors before treatment. Panels (c) and (d): after 2 weeks of topical imiquimod once daily, just before treatment with cryosurgery. Panels (e) and (f): 16 and 10 months after the end of treatment.

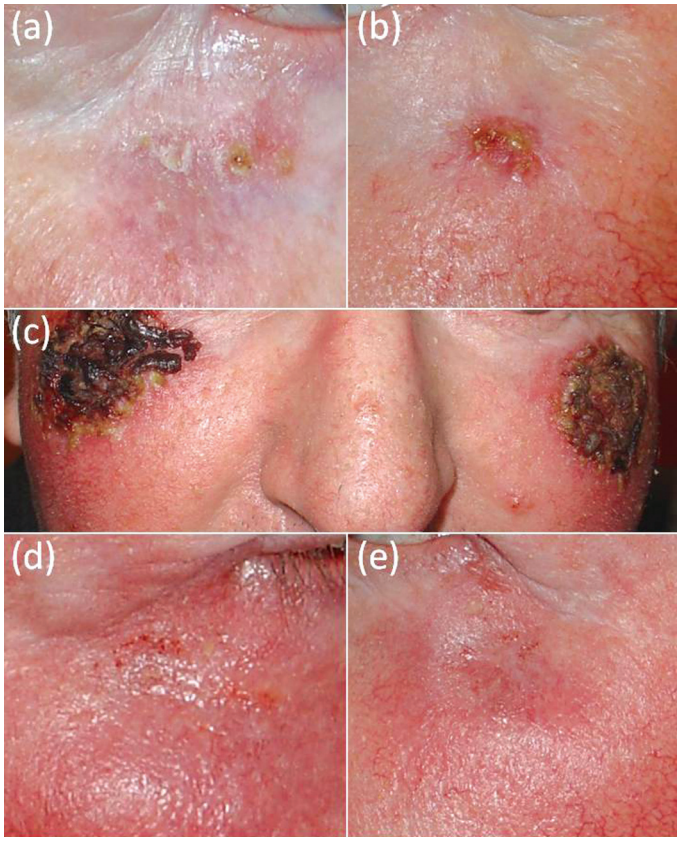

Figure 2 | Treatment in parallel of two basal cell carcinomas in the same patient (Patient 01, Table 1) with immunocryosurgery. Panels (a) and (b): Before treatment. Panel (c): At the end of the 5-week immunocryosurgery treatment cycle. Panels (d) and (e): Outcome 4 months after the end of treatment.

Efficacy of immunocryosurgery: tumor relapse

33/35 CR tumors were relapse-free at 2 to 24 months after treatment. Two relapses occurred during follow-up (Tumors 2 and 4; Table 1). Remission was induced again for Tumor 2 with a second cycle of immunocryosurgery and for Tumor 4 with cryosurgery monotherapy.

Discussion

A number of surgical and non-surgical treatment modalities are currently available for BCC (12). The goal of the treatment is to eradicate the tumor with minimal disability and deformity for the patient (12). Each of the standard therapeutic methods (surgery, cryosurgery, curettage and electrodessiccation, topical 5-fluouracil, topical imiquimod, and radiotherapy) is effective enough to be proposed for at least some selected patients (13–15). The majority of neoplasms, especially of smaller primary tumors, can be successfully treated in an office-based setting (4). However, in face of the increasing BCC incidence in Caucasians worldwide, it is imperative to develop new cost-effective and office-feasible treatment strategies for all clinical forms of BCC (16). The combination of cryosurgery and imiquimod within the framework of the current immunocryosurgery protocol substantially improves the effectiveness of the individual modalities (17). The timing of cryosurgery (i.e., during and not before imiquimod treatment) is crucial for the efficacy of the proposed modality (9). As detailed elsewhere, the combination of imiquimod-induced immunomodulation of the tumor basin and cryoablation may mutually potentiate the pro-apoptotic, anti-angiogenic, and pro-inflammatory effects of each modality, leading to their effective synergism in tumor eradication (6, 9, 11).

To the best of our knowledge, this is the first report that evaluates immunocryosurgery in an office-based setting. By including tumor relapses and tumors with diameters > 20 mm in this case series, our results indicate that this combination modality clearly expands the potential of office-based dermatologists without access to surgery facilities to treat relatively advanced BCCs. In a minority of BCC cases, the standard 5-week immunocryosurgery treatment cycle does not suffice for complete clearance of the tumor. For these patients, an additional session of mild cryosurgery 1 month after the end of the 5-week immunocryosurgery treatment cycle, as presently performed in five cases, or a repeat cycle of immunocryosurgery, may accomplish tumor clearance (7, 10, 11). Future randomized studies should focus on optimization of the treatment strategy for BCCs that failed to clear after standard immunocryosurgery.

Major patient complaints during treatment included discomfort, oozing, and pruritus at the site of treatment that peaked the week following cryosurgery, in addition to concerns about treatment-associated local skin inflammation. Despite thorough counseling prior to initiating treatment, some patients perceived this predictable reaction as worsening of their condition. However, in all cases reassurance during a telephone call resolved all inquires and enhanced overall treatment compliance. The main drawback of this study is the relatively small number of cases included and a rather short follow-up period. However, our results can be coupled with the effectiveness of immunocryosurgery for BCCs in the clinical setting and thus we are justified in projecting that treatment efficacy could also be equivalently high; that is, about 95% (8, 9, 11).

In conclusion, our results indicate that immunocryosurgery, originally developed for treating skin neoplasms in a clinic-based setting, can also be optimized for and adapted to use as a treatment modality for BCC in an office-based setting. It offers the office-based dermatologist a simple, but versatile, and highly effective therapeutic method for at least small to medium-sized tumors.

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