

Treatment of superficial basal cell carcinoma with ingenol mebutate gel, 0.05%

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Background: Basal cell carcinoma (BCC) is the most common cancer in Caucasians. Surgical approaches are the most widely used and effective treatment strategies for well-defined BCC. However, for patients with low-risk, superficial BCCs (sBCCs), medical therapy may be a treatment option. In this small case series, we describe our experience in using topical treatment with ingenol mebutate gel, 0.05%, for patients who refused surgical treatment for sBCC.

Methods: We conducted a retrospective chart review of seven patients from our community dermatology practice for whom sBCC was treated with ingenol mebutate. The chart review extracted information on demography, dermatologic history, and prior treatment for actinic keratosis or skin cancer. Summary of the treatment outcome with ingenol mebutate included the size and location of the sBCCs, description of administration, local skin reactions, adverse events, and efficacy.

Results: Histopathologic analysis of a shave biopsy sample of suspicious lesions on the trunk confirmed nine sBCCs: a single sBCC in five patients and two well-separated lesions in each of the other two patients. Patients were treated at 10 to 14 days after shave biopsy; biopsy sites were not required to be fully healed. Lesions were either occluded using a standard adhesive bandage (n=6) or not occluded (n=3). All patients experienced local skin reactions that began on day 1 or 2 of treatment, peaked on days 2 to 7, and were largely resolved at 2 weeks. All sBCCs were clinically resolved on short-term follow-up at 2 to 4 weeks. Repeat biopsy of six lesion sites in four patients at 3 or 4 months confirmed histologic clearance. There were no clinically suspicious lesions in any patients at subsequent follow-up evaluations at 3-month intervals. The longest follow-up to date has been 14 months.

Conclusion: Ingenol mebutate gel, 0.05%, was efficacious and well tolerated for the treatment of biopsy-confirmed sBCCs on the trunk in seven patients.

Keywords: superficial basal cell carcinoma, ingenol mebutate, nonsurgical treatment, local skin reaction

Introduction

Basal cell carcinoma (BCC) is the most common cancer in Caucasians and is the leading cancer in the United States.¹ Its exact incidence is difficult to determine because it is not reported to national registries.^{2,3} However, analysis of US government claims databases for nonmelanoma skin cancer (NMSC), which includes BCC and squamous cell carcinoma, demonstrates dramatic increases in the total number of procedures for NMSCs and in the number of persons treated since 2002.^{2,3} Prospective cohort studies have also confirmed a steady increase in the age-adjusted rates of BCC in both males and females.⁴ Although NMSC generally occurs in people over 50 years of age, significant

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increases in BCC have been noted in young people under the age of 40, particularly females,⁵ in whom the use of indoor tanning devices has been implicated.⁶ BCCs are commonly slow-growing tumors that rarely metastasize. Nonetheless, they can be locally invasive and result in considerable cosmetic, functional, and economic burdens.^{1,7}

Surgical excision with predetermined margins is one of the most widely used and effective treatment strategies for well-defined BCCs; Mohs micrographic surgery is generally applied to higher-risk tumors and those in cosmetically sensitive areas.^{7,8} For superficial BCCs (sBCCs) of small size on the trunk or limbs, electrodesiccation and curettage (EDC) is an acceptable option of treatment.⁷⁻¹⁰

For those sBCCs deemed to be at low risk for recurrence, medical therapy with topical treatments or photodynamic therapy is a treatment option in appropriately selected patients.^{7,10} Some patients may be poor candidates for surgery, and others may prefer nonsurgical and nondestructive methods of treatment to reduce the risk of scarring.⁸ Although surgical methods remain the gold standard, medical modalities are valid, nonsurgical treatment options when appropriate.^{7,10}

Ingenol mebutate gel, 0.05%, applied once daily for 2 consecutive days, is approved for the treatment of actinic keratosis in affected areas of 25 cm² on the trunk and extremities.¹¹ Ingenol mebutate gel is not indicated for treatment of sBCC; however, its safety and efficacy for treating histologically confirmed sBCC were reported from a Phase IIa study, evaluating two applications of ingenol mebutate at concentrations of up to 0.05% in a small number of patients.¹² In the treatment arm in which patients received the 0.05% strength administered for 2 consecutive days, five of the eight patients (63%) achieved histologic clearance at day 85, as compared with none of the five patients in the vehicle group ($P < 0.031$).¹²

The small case series presented here describes our experience in using ingenol mebutate gel, 0.05%, for sBCC in patients who refused surgical treatment.

Methods

We conducted a retrospective chart review of seven patients from our community dermatology practice for whom sBCC was treated with ingenol mebutate gel, 0.05%. The chart review extracted information on demography, patient's dermatologic history, and prior treatment for actinic keratosis or skin cancer. Analysis of the treatment outcome with ingenol mebutate included the size and location of the sBCCs, description of administration, clinical assessment of local skin reactions (LSRs), adverse events, efficacy, and results of follow-up from

clinic visits at 3-month intervals. All patients provided informed consent verbally for treatment and participation in this study. Ethical approval was not sought since the study did not take place in a hospital or academic setting and because this was a retrospective chart review study.

Results

Description of patients

The seven patients (three men, four women; age range 47 to 75 years) presented with primary lesions that were suspicious for BCC (Table 1). Histopathologic analysis of a shave biopsy sample confirmed nine low-risk sBCCs: a single sBCC in each of five patients and two well-separated lesions in each of two patients. All lesions occurred on the trunk and were located on the back ($n=5$), chest ($n=2$), or shoulder ($n=2$). Lesion size ranged from 0.6 to 3.5 cm, with six of nine lesions being ≤ 1.0 cm in diameter. When treatment options were discussed, each of these patients indicated a desire to avoid scarring that results from EDC and surgical excision. Upon discussion of topical treatments, they elected treatment with ingenol mebutate because of the shorter regimen. Patients were treated from May 2014 to August 2015 at 10 to 14 days after shave biopsy confirmation of sBCC; biopsy sites were not required to be fully healed. Ingenol mebutate gel, 0.05%, was applied to cover the lesion plus a 0.5 cm margin. Lesions were either occluded using a standard adhesive bandage (six lesions in four patients) or not occluded (three lesions in three patients). As treatment of sBCC with ingenol mebutate is off-label, these alternatives were included to observe whether occlusion had any impact on the LSRs, tolerability, or resolution of the sBCC. A 3.5 cm lesion (patient 4) was treated for 2 days, two lesions (patient 7) were treated for 4 days, and all other lesions were treated for 7 days. A maximum of one treatment kit with two tubes of medication was used. The variation in the number of treatment days resulted from the practical utilization of a single treatment kit that contained two tubes of ingenol mebutate gel, 0.05%. The patient applied the medication once daily as instructed until the tubes were empty. We also noted whether the number of treatment days had an effect on LSR severity and tolerability.

Treatment results

All patients experienced LSRs that began on day 1 or 2 of treatment, peaked on days 2 to 7, and largely resolved at 2 weeks (Figure 1). The most common LSRs were erythema, flaking/scaling, and crusting, which were assessed as mild. Neither occlusion nor the number of treatment days appeared to affect LSR severity. Patients reported mild itching ($n=4$), mild burning/discomfort ($n=3$), and

Table 1 Summary of ingenol mebutate gel, 0.05%, treatment of sBCC in seven patients

	Dermatologic history	sBCC characteristics	Treatment course	LSRs	Clearance assessments
Patient 1 male, age 52 years	None	1.0 cm, R upper back 1.5 cm, middle upper back	2 sBCCs treated in June 2014 for 7 d with occlusion	Mild erythema and crusting Mild discomfort and pruritus LSRs began on d 2, peaked on d 5, and were resolved at 2 wk Residual erythema at 2 mo	Lesions cleared at 2 wk Biopsy at 3 mo confirmed histologic clearance No recurrence at last follow-up at 4 mo
Patient 2 female, age 47 years	None	0.6 cm, L upper chest	sBCC treated in February 2015 for 7 d without occlusion	Mild erythema, flaking/scaling, and crusting Mild pruritus LSRs began on d 2, peaked on d 3, and were resolved at 2 wk LSRs treated with moisturizers	Lesion cleared at 1 mo No recurrence at last follow-up at 2 mo
Patient 3 male, age 58 years	Eleven sBCCs on separate sites of the shoulders, back, and forearm from 2005 through 2014; all were surgically treated >10-year history of AK treated with cryosurgery and diclofenac	1.0 cm, L anterior chest	sBCC treated in June 2014 for 7 d with occlusion	Mild erythema and flaking/scaling Mild burning and pruritus LSRs began on d 1, peaked on d 4, and were resolved at 2 wk Residual erythema at 2 wk	Lesion cleared at 2 wk Biopsy at 3 mo confirmed histologic clearance No recurrence at last follow-up at 14 mo
Patient 4 male, age 65 years	2-year history of AK treated with cryosurgery	3.5 cm, R anterior shoulder	sBCC treated in May 2014 for 2 d without occlusion	Mild erythema and flaking/scaling Mild discomfort and pruritus Moderate burning LSRs began on d 1, peaked on d 2, and were resolved at 2 wk Mild erythema at 3 wk LSRs treated with moisturizers	Lesion cleared at 3 wk Biopsy at 3 mo confirmed histologic clearance No recurrence at last follow-up at 10 mo
Patient 5 female, age 65 years	Malignant melanoma on R forearm; treated with excision AK, prior treatment unavailable	1.0 cm, L posterior shoulder	sBCC treated in March 2015 for 7 d with occlusion	Mild erythema, flaking/scaling, and crusting LSRs began on d 1, peaked on d 2, and were resolved at 2 wk	Lesion cleared at 2 wk No recurrence at last follow-up at 3 mo
Patient 6 female, age 75 years	None	1.0 cm, middle back	sBCC treated in February 2015 for 7 d without occlusion	Mild erythema and flaking/scaling LSRs began on d 1, peaked on d 2, and were resolved at 2 wk	Lesion cleared at 2 wk No recurrence at last follow-up at 5 mo
Patient 7 female, age 52 years	Nodular BCCs on R arm and chest treated with excision in 2014 No AK	1.0 cm, L upper back 2.0 cm, L lower back	sBCC treated in August 2015 for 4 d with occlusion	Mild erythema and flaking/scaling LSRs were resolved at 2 wk	No recurrence at last follow-up at 4 mo Biopsy at 4 mo confirmed histologic clearance

Abbreviations: d, day/s; wk, weeks; mo, month/s; R, right; L, left; AK, actinic keratosis; LSRs, local skin reactions; sBCC, superficial basal cell carcinoma.



Figure 1 Course of treatment with 7 days of ingenol mebutate gel, 0.05%.

Notes: (A) Patient 2, before treatment; the biopsy site is visible. Mild local skin reactions (LSRs) are noted at day 10 after the start of 7 days of ingenol mebutate treatment. At 1 month after treatment, LSRs are resolved; hypopigmentation is noted at the site of the diagnostic biopsy. (B) Patient 5, before treatment; the incompletely healed biopsy site is visible. Mild LSRs are noted at day 12 after the start of 7 days of ingenol mebutate treatment. At 3 months after treatment, erythema is noted at the biopsy site.

moderate burning (n=1). LSRs were treated in two patients with moisturizers.

All sBCCs were clinically resolved on short-term follow-up at 2 to 4 weeks. Residual mild erythema was present at 2 to 8 weeks in three patients. Repeat biopsy of six of the nine lesion sites at 3 or 4 months (in four of the seven patients) was performed and confirmed histologic clearance in all biopsy samples. None of the patients experienced scarring due to topical treatment at the treatment site. There were no clinically suspicious lesions in any patient on subsequent follow-up evaluations at 3-month intervals. The longest follow-up to date has been 14 months. All patients reported that the medicine was well tolerated.

In contrast to these seven described patients who experienced short-term clearance of sBCC after ingenol mebutate treatment, one patient in our clinic experienced clinical recurrence a few months after an sBCC was treated with ingenol

mebutate (not occluded) and subsequently was treated with traditional surgical methods.

Discussion

BCC is the most common cancer in the US, and the incidence continues to rise. The goal of primary treatment is cure of the tumor, with maximal preservation of function and cosmesis. Surgical approaches offer the most effective treatment, although patients who have low-risk sBCCs may be treated with topical treatments, albeit at a lower cure rate. Nonsurgical treatments include topical treatments (fluorouracil and imiquimod), photodynamic therapy, and cryotherapy.¹³

The seven patients described here had histologically confirmed sBCC on the trunk. They had declined both surgical treatment and destruction with EDC, electing, instead, treatment with ingenol mebutate gel, 0.05%, to minimize scarring and the total treatment time. Ingenol mebutate gel is generally administered for a few days, in contrast to topical treatments

with fluorouracil¹⁴ or imiquimod,¹⁵ which are administered for several weeks. Although all of these agents produce LSRs, the prolonged LSRs and the adverse cosmetic effects associated with the longer treatment durations of fluorouracil and imiquimod may compromise tolerability and adherence.¹⁶

All seven patients experienced a local inflammatory response upon treatment that included erythema, flaking/scaling, and crusting. In all patients, it was assessed as mild and generally resolved within 2 weeks. The one exception was erythema, which persisted in three patients for 2 to 8 weeks. More severe, but also self-limiting, LSRs were described in a case report of 2-day treatment with ingenol mebutate gel, 0.05%, for a 4 cm sBCC on the back.¹⁷

None of our seven patients had scarring, beyond that from the shave biopsy, which could be assessed as related to topical treatment. However, scarring at 3-month follow-up has been reported in a patient who was treated for superficial and micronodular BCC with ingenol mebutate gel, 0.05%, beginning at 1 day after curettage of the lesion.¹⁸

The findings from our case studies indicate that ingenol mebutate gel, 0.05%, was well tolerated for the treatment of biopsy-confirmed sBCC on the trunk. All patients experienced short-term clinical remission and continue to be monitored for recurrence at 3-month intervals.

Limitations

This is a small case series of seven patients in a community dermatology setting who were assessed over a relatively short-term follow-up. Confirmation of the safety and efficacy of ingenol mebutate for the treatment of sBCC requires evaluation in a larger number of patients and evaluation of recurrence rates from studies with at least 5 years follow-up, in order for the recurrence rates to be considered valid.⁷ Further, while it was appropriate to consider ingenol mebutate gel, 0.05%, for these patients, all patients should be individually evaluated to determine the most appropriate treatment for their particular sBCC.

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Disclosure

The author reports no conflicts of interest in this work.

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