Imiquimod to Treat Different Cancers of the Epidermis

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BACKGROUND. **Topical immunomodulatory therapy with imiquimod has been recently used for the treatment of actinic keratoses, intraepithelial carcinoma, and small basal cell carcinoma (BCC) besides the licensed indication of extragenital warts (condyloma).**

METHODS. **We treated several patients with particular epidermal neoplasias such as squamous cell cancer (SCC) and basal cell cancer of sclerodermiform type three times per week for 4 to 12 weeks.**

RESULTS. **We report several novel aspects of the treatment of epidermal cancers with self-applied, nonpainful, immunomodulatory therapy. First, we treated—for the first time—two immunosuppressed renal transplant patients for invasive SCC with imiquimod. Interestingly, systemic immunosuppression did not adversely affect the response to therapy. Second, one patient with the high-risk and aggressive growth pattern of basal cell cancer (sclerodermiform histology) was cured from his disease at a particular location in the face, suggesting sufficient penetration despite scarring. No recurrence was detected in another patient who suffered from 29 BCCs until almost 2-years follow-up. Third, the treatment of actinic keratoses in the face is substantially shorter (in the order of 4 to 6 weeks) as opposed to other skin cancers. Immunomodulatory treatment with imiquimod led to the demarcation of in situ actinic keratosis lesions that could not be identified using the dermatologist's experience, probably because of the existence of exclusive alterations on the molecular level.**

CONCLUSION. **Several novel aspects of immunomodulatory treatment with imiquimod and new indications such as selected cases of sclerodermiform BCC and SCC have been described. The texture of the skin at various different body locations may explain the varying sensitivities to imiquimod when facial skin is compared with skin on the extremities.**

J. EKLIND, MD, J. MASCHKE, MD, P. LIDBRINK, MD, AND U. TARTLER, MD, HAVE INDICATED NO SIGNIFICANT INTEREST WITH COMMERCIAL SUPPORTERS. U. R. HENGGE, MD, HAS RECEIVED SPEAKER'S HONORARIA FROM 3M IN THE PAST.

FREQUENT CANCERS of the epidermis include basal cell carcinoma (BCC) and actinic keratoses that may progress to in situ carcinoma (Bowen's disease) and invasive squamous cell cancer (SCC). Although BCC is the most common malignant skin lesion,[1] it may destroy the neighboring tissue but generally does not metastasize. The guidelines for care of BCC recommend surgical excision and microscopic control of the tumor borders, electrodesiccation and curettage, or where appropriate, nonsurgical methods.[2,3] Surgery can be cumbersome for particular locations or when many lesions are present. Therefore, alternative treatments such as radiotherapy, photodynamic therapy, or 5-fluorouracil represent additional options, especially for hard to operate lesions. However, the therapeutic modalities such as cryotherapy, photodynamic therapy, or radiation therapy are associated with tissue destruction and/or substantial patients discomfort.

Based on the recent success of topical immunomodulatory therapy with imiquimod for actinic keratoses,[4] intraepithelial carcinoma,[5,6] small BCCs,[7–10] and Gorlin–Golz syndrome, we treated several patients with different epidermal neoplasias with self-applied 5% imiquimod cream three times per week overnight for 8 hours.

Imiquimod belongs to a new class of topical immune response modifiers. It has been licensed for condylomata acuminata and has also shown efficacy in the treatment of other viral lesions such as common warts, mollusca, and genital herpes.[11,12] Its mechanism of action in humans is not completely understood but involves the stimulation of the cellular immune system and the induction of several cytokines such as interferon-α, tumor necrosis factor-α, and interleukin-12 from monocytes and macrophages after binding to Toll-like receptor-7.[13,14] It has been speculated that through the induction of interferon-α imiquimod could enhance antigen presentation by increasing the expression of mature histocompatibility class I and thus, together with interleukin-12, augment the development of a Th1-type immune response. In addition, the

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maturation and migration of Langerhans cells may contribute to an improved antigen processing and presentation.[15]

We report several remarkable cases of epidermal neoplasias that were treated with topical imiquimod 5% cream achieving complete clinical and histologic clearance.

Case Report 1

An otherwise healthy 72-year-old white male patient had suffered from multiple superficial BCCs since 1965. His sister and uncle also had multiple superficial BCC. He lacked signs of Gorlin–Goltz syndrome. He had no immune defect nor received immunosuppressive treatment. In the last 5 years, he has undergone two to three surgical excisions every year. Subsequently, he developed a syringe and operation phobia. Because the patient refused any further surgical procedure, he was referred from the Department of Plastic Surgery in December 1999. Besides the BCC of multifocal growth pattern on the left eyebrow, he also had 28 clinically visible lesions on the trunk (Figure 1). Imiquimod treatment was applied to all 29 lesions three times a week by a nurse. After four applications, the patient complained itching and redness, and some lesions became excoriated. The treatment was halted for 1 week. Subsequently, therapy was resumed two times per week for a total of 16 weeks. At week 8, most of the lesions became significantly smaller, and some were ulcerated. At week 16, all treated areas were still slightly erythematous (Figure 1). At this point, the patient accepted four punch biopsies, all of which were free of BCC. Clinical follow-up at 5, 8, 12, and 22 months showed no signs of recurrence at the treated lesions.

We also treated (three times a week for a total of 3 weeks) three histologically confirmed actinic keratoses on his scalp in May 2001 until he developed hemorrhagic crusts and hyperkeratoses; at this point, treatment was stopped. One year later, his scalp remained free of actinic keratoses.

Case Report 2

A 65-year-old patient with terminal kidney insufficiency and renal transplantation presented with an invasive SCC on the right temple of 3-years duration. The lesion was 4×3 cm in size (Figure 2). On palpation, several papules and some induration were noted. Histology showed hemorrhagic debris overlying an ulcerated skin. Dyskeratotic keratinocytes and atypical mitoses were seen in the epidermis at the borders of the ulcer. Proliferations of tumor cells invaded the dermis and were surrounded by a lymphohistiocytic inflammatory infiltrate (Figure 2).

Because of persistent chronic kidney insufficiency (kreatinin 10 mg/dL) after the failure of a kidney graft and a prostate carcinoma that had metastasized to the seventh right rib, treatment with imiquimod was begun three times per week.

After 3 weeks of treatment, the lesion showed initial signs of regression at the borders, whereas an erythema persisted in the center (Figure 2). The patient reported no side effects except for some scaling. Treatment was terminated at week 12. At week 16, the patient presented with a scar at the initial site of the lesion (Figure 2), whereas no evidence for SCC was present in the obtained biopsy at the 6-month follow-up visit.

Case Report 3

A 39-year-old male patient who had received a kidney transplant 12 years ago developed a 5-mm crusted nodule on the sternum adjacent to the scar from prior excision of a SCC (Figure 3) while he was receiving long-term immunosuppressive therapy with tacrolimus and prednisolone. Five weeks after the initiation of treatment, the lesion became much larger, crusted, and surrounded by an inflammatory erythema. At this point, treatment was reduced to two times per week. At week 12, the lesion had entirely cleared, and the erythema gradually subsided within the following month. The patient remains free of cancer 8 months after completion of therapy.

Case Report 4

A 69-year-old gentleman with extensive traveling in Sub-Saharan Africa suffered from several yellowish hypertrophic actinic keratoses on the forehead and the scalp (Figure 4). Histologic control of a shave biopsy revealed a hyperkeratotic actinic keratosis (KIN3, that is, keratinocyte intraepidermal neoplasia grade 3) with single-cell atypia in the upper epidermis (Figure 4). After initiation of imiquimod treatment three times a week, several lesions on the left temple became erythematous at week 4. Interestingly, new lesions in addition to the clinically diagnosed actinic keratoses became visible after imiquimod treatment. At week 12, 15 lesions with marked erythema, and some erosions were present. After termination of treatment, all lesions disappeared within 4 weeks (Figure 4). A control punch biopsy was obtained at week 16 that showed no evidence of epidermal neoplasia besides some increased lymphohistiocytic inflammation (Figure 4). Within 9 months of follow-up, no new lesions developed.

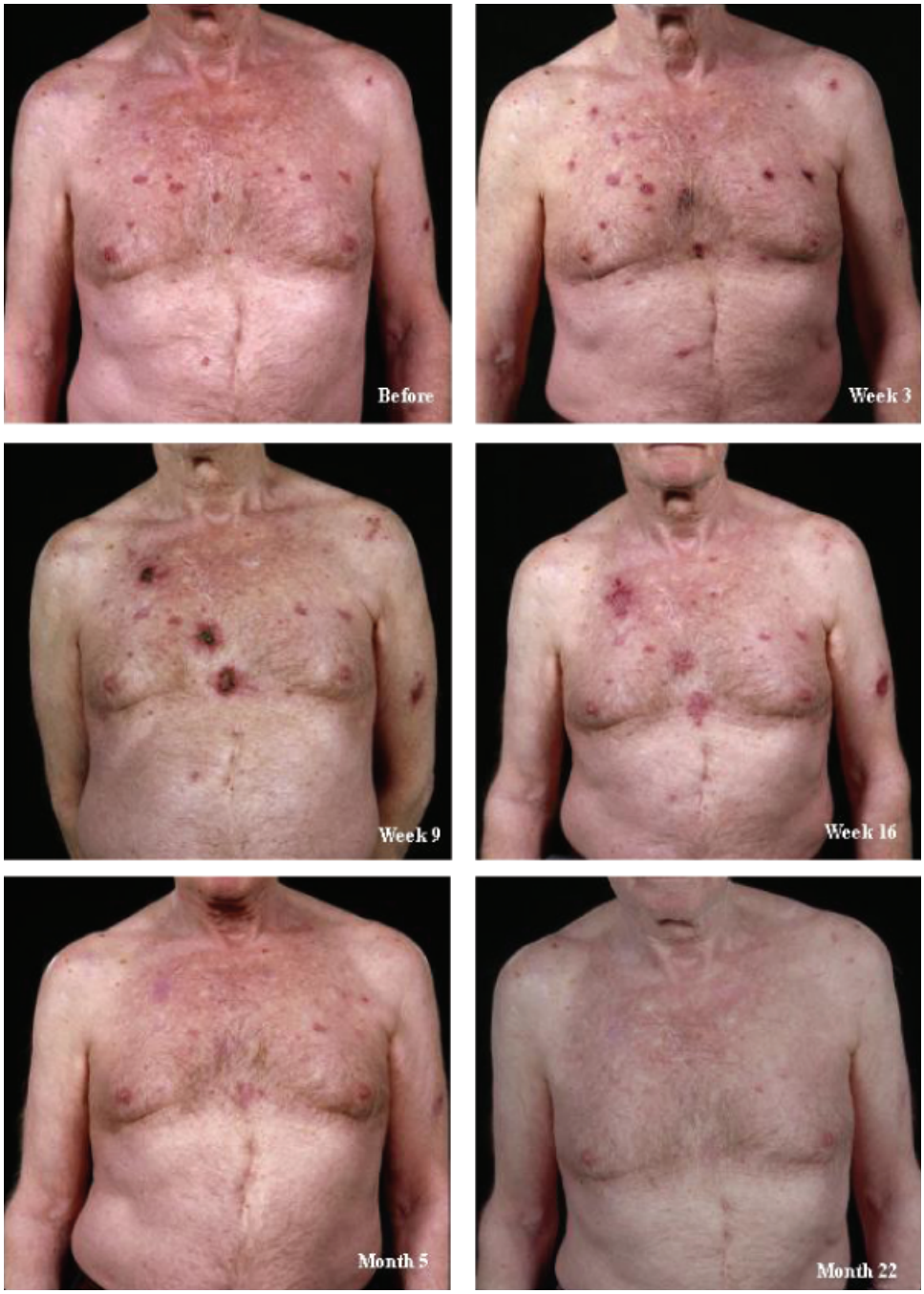

Figure 1. Multiple erythematous BCCs up to 3 cm were present on the trunk. Three weeks after initiation of treatment the lesions became redder, and some became crusted. At 9 weeks, some lesions, such as the two intermammary lesions, became intensely inflamed and heavily crusted and were 5 cm in size. These two lesions were initially very small (see before treatment). At the end of treatment (week 16), an erythema was evident at the former lesion site that gradually subsided (month 5). At 6 weeks after treatment, the BCC lesions healed with minimal scaring. At the most recent follow-up visit (month 22), no evidence of BCC was detected. Please also note multiple scars from prior surgery and cryotherapy.

Case Report 5

A 50-year-old gentleman suffered from a sclerodermiform BCC (Figure 5). He denied any surgical procedure and was started on imiquimod treatment. After treatment, the lesion became inflamed and larger than initially diagnosed because it extended to an area behind the ear. Treatment was stopped at week 16 when the lesion had completely disappeared, and a scar was detected at the former lesion site. Nine months after completion of treatment, the patient had no new lesions (Figure 5). A biopsy taken from the preauricular lesion revealed scar tissue (Figure 6).

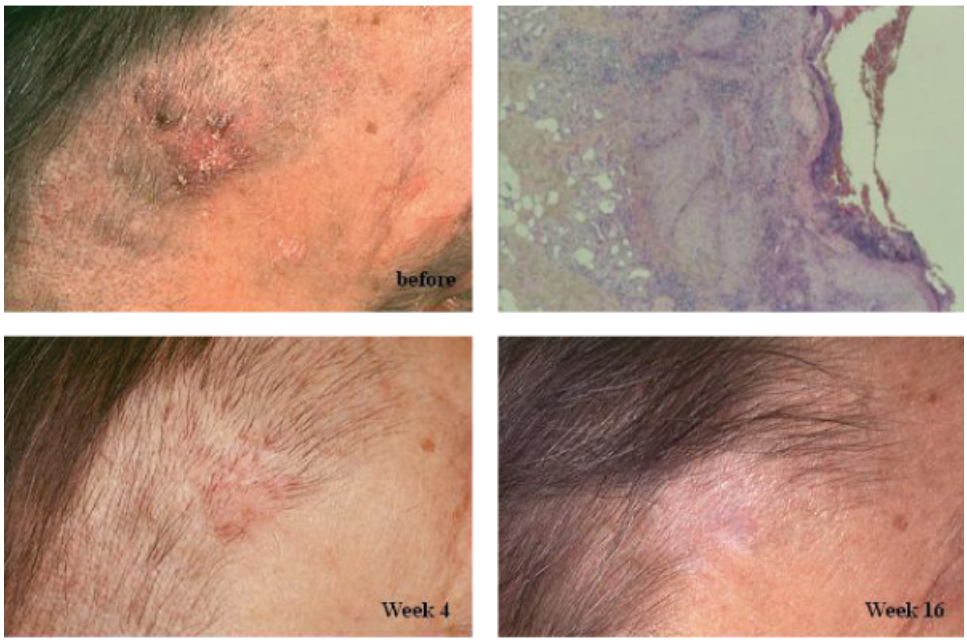

Figure 2. Erythematous, hyperkeratotic plaque on the right temporal aspect on the hair rim of 3-year duration (before). The histology showed hemorrhagic debris overlying an ulcer. Dyskeratotic keratinocytes and atypical mitoses were seen at the borders of the epidermis. Proliferations of tumor cells invaded the dermis and were surrounded by a lymphohistiocytic inflammatory infiltrate (second from top). At week 4, initial regression can be appreciated at the borders, while the central erythema persisted (week 4). At week 16, a white scar is seen at the lesion site (week 16).

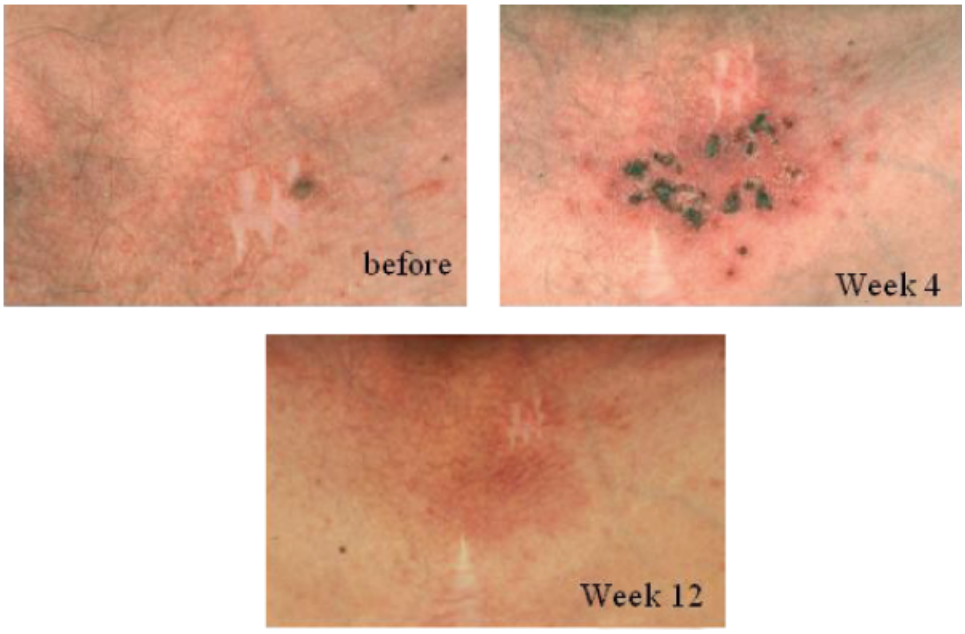

Figure 3. A 5-mm crusted nodule recurred on the sternum adjacent to the scar from prior excision of a SCC (before). At 4 weeks after the initiation of treatment, the lesion became much larger and crusted and was surrounded by an inflammatory erythema at the lower side of the initial lesion (4 weeks). At this point, treatment was reduced to two times per week. At week 12, the lesion had entirely cleared (12 weeks).

Discussion

We present the successful treatment of invasive SCCs in two immunosuppressed patients with severe kidney impairment using a topical immune response modifier. Although several studies have shown the usefulness of topical imiquimod for the treatment of BCC[7,8] in situ carcinoma (Morbus Bowen)[5,9] and actinic keratosis,[4] these are the first cases of SCC successfully treated with imiquimod.

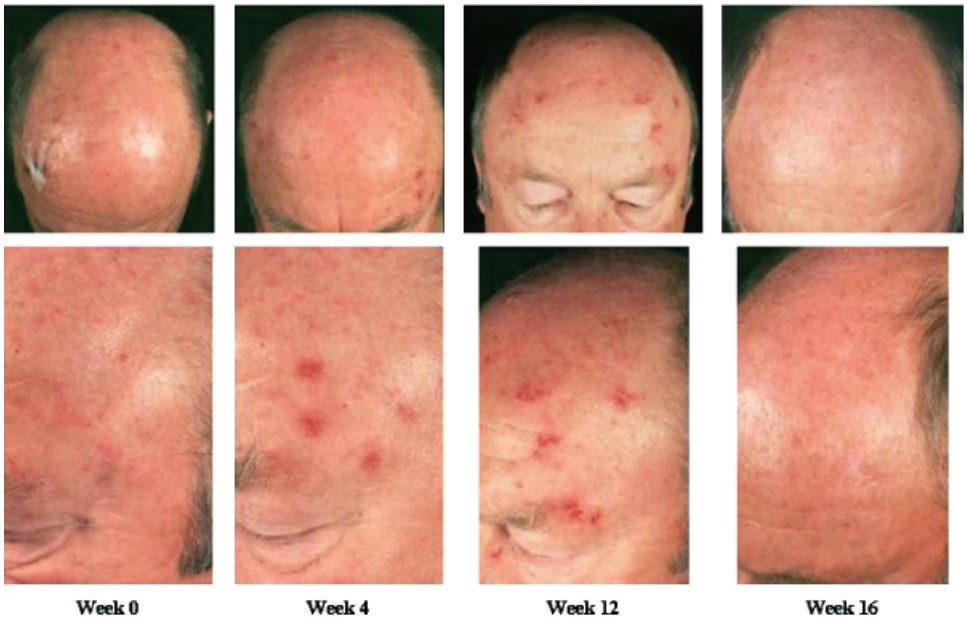

Figure 4. Several confluent actinic keratoses can be appreciated on the forehead. One invasive SCC was excised on the right temple (see tape strips on the right forehead). A close-up of the left temple with one clinically identifiable actinic keratosis next to the eyebrow is depicted in the lower row. At week 4, some lesions had become erythematous (second column from the left). Interestingly, imiquimod treatment highlighted (demarcated) additional lesions that were not clinically identified (second column from the left). At week 12, multiple lesions were present with erythema and excoriations (third column from the left). At week 16 (4 weeks after termination of treatment), no evidence of actinic keratoses was present on the forehead and the left temple (forth column from the left).

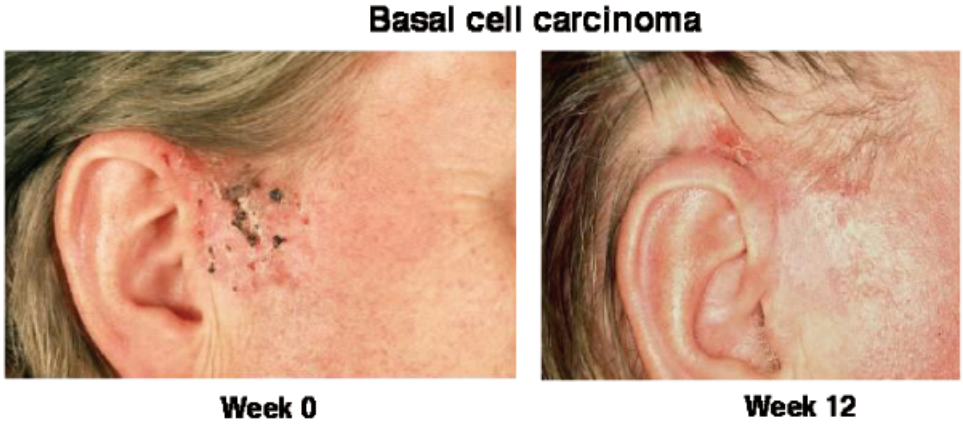

Figure 5. A large sclerodermiform, ulcerated BCC was treated on the right temple. With treatment, the lesion became inflamed and larger than initially diagnosed because it extended to an area behind the ear. Treatment was stopped at week 16 when the lesion had completely disappeared. At this point, a scar was detected at the former lesion site. At 9 months after completion of treatment, the patient had no new lesion.

We also report the first case of high-risk and aggressive growth pattern BCC (sclerodermiform type and localization in the face) that was successfully treated with topical imiquimod. From our earlier experience in treating cutaneous and genital warts, it appears that actinically damaged skin is more susceptible to the effects of topical imiquimod treatment.[11] In addition, the texture of the skin at various different body locations may explain the varying sensitivity to imiquimod when facial skin is compared with the skin on the extremities. The success in treating sclerodermiform BCC suggests a degree of penetration of imiquimod that was sufficient to clear the lesion. The reported cases are remarkable for the number of independent BCC lesions that responded similarly well (case 1) and the sclerodermiform growth pattern (case 5). In addition, the immunomodulatory treatment led to the demarcation of in situ actinic keratosis lesions

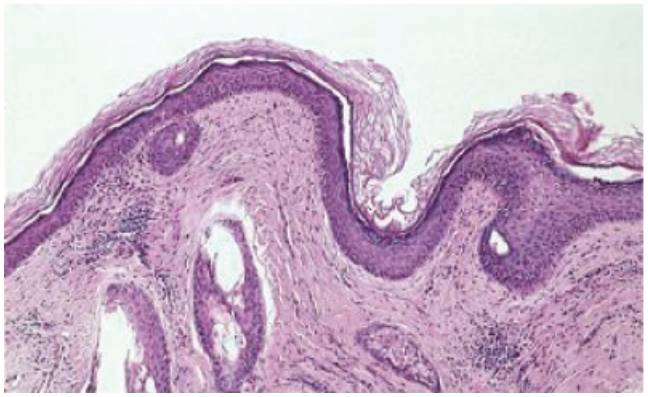

Figure 6. The posttherapy biopsy revealed scar tissue and was free of tumor cells.

that could not be identified using the dermatologist's experience (case 4), probably because of the exclusive existence of molecular alterations.

A side effect that is not usually observed in the treatment of viral lesions was superficial scaring, although hair growth was not affected. However, the cosmetic appearance (avoidance of surgical scars) and the ability to treat multiple lesions at the same time are additional advantages of nonsurgical immunomodulatory therapy.

Beutner et al.[16] reported the clinical efficacy of 5% imiquimod cream in the treatment of solitary BCC of the superficial and nodular type. More recently, a phase II, dose–response, open-label trial conducted in Australia enrolling 99 patients revealed an almost 90% histologic clearance of BCCs of the superficial type after 6 weeks of treatment.[8] The largest BCC lesion (affecting the entire forearm) to date has been successfully treated by Chen et al.[17] Kagy and Amonette[18] also reported the successful treatment of multiple BCCs of the superficial type in a patient with basal cell naevus syndrome. Recently, Hannuksela-Svahn et al.[19] reported the clinical and histologic regression in the majority of scalp BCCs of the nodular type. A phase II trial assessing the response of superficial and nodular BCCs to imiquimod has analyzed the influence of occlusion with three times per week dosing. Histologic cure was achieved in 87% and 76% of superficial and nodular BCCs, respectively.[20] A recent study by Geisse et al.[10] demonstrated that the daily application achieved a 87% cure as opposed to 52% when applied three times per week.

Because BCC and SCC are not regularly associated with human papillomavirus,[21,22] a cell-mediated immune response against a cancerous lesion can be postulated. In that regard, the latest finding of overexpressed patched and p53 gene alterations in sporadic BCC and SCC antigen-1 and antigen-2 that belong to the high molecular weight serine protease inhibitors (serpin) superfamily can potentially function as a mutated protein to be presented upon topical immunostimulatory therapy.[23,24] Usually, SCC antigen-1 and SCC antigen-2 are coexpressed in the suprabasal layers of stratified squamous epithelium of the tongue, tonsil, esophagus, uterine cervix, and vagina. However, they have recently been detected in SCCs of the lung and head and neck, where they were coexpressed in moderately and well-differentiated tumors.[25]

Although several groups have documented the successful clinical response and histologic regression in the majority of superficial and nodular-type BCCs,[7,8] we report the first cases of invasive SCC successfully treated with topical imiquimod 5% cream. This report also shows that topical immunomodulatory treatment for epidermal neoplasias is possible and effective in immunocompromised organ transplant, pointing to the intact quality of the skin-derived immune system in this conditions. A potential adverse effect with regard to the transplanted organ is highly unlikely, as the immunostimulation induced by imiquimod occurs locally in the skin, and second the potency of the systemic immunosuppressive medication is several orders of magnitude greater then the stimulatory effect of imiquimod. However, the treatment should be reserved for selected patients and be based on past history of skin cancer, immune status, age, compliance, and performance status.

Although the potential for nonsurgical, patient-administered treatment of cutaneous malignancies in selected patients is great, extreme care should be executed in clinical and histologic follow-up. Furthermore, carefully designed studies are necessary to establish the usefulness of topical immunomodulatory therapy for SCC, multiple BCCs, and BCCs with more aggressive growth patterns and particularly locations such as the face. Moreover, comparative trials should establish the cost-effectiveness of nonsurgical compared with surgical therapy. However, an ideal treatment regimen for BCC and SCC should minimize the cutaneous side effects and maximize the efficacy and has not yet been defined.

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Commentary

Dermatologic surgeons are in the process of determining various uses of imiquimod for the treatment of skin cancer. Previous trials have provided data for the efficacy of imiquimod in superficial BCC and Bowen's disease. This article extends the use to aggressive tumors such as morpheaform BCCs and invasive SCCs in transplant patients on immunosuppressive therapy. These authors report clearance of aggressive tumors with as few applications as two to three times a week, whereas previous trials have indicated that three times a week would clear only approximately 50% of the less aggressive superficial BCCs. We should proceed cautiously and await further trials to know the potential benefit of topical agents on aggressive tumors and their safety profile, especially in patients with transplanted organs who are on immunosuppressive medication.

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