Chapter 2
Topical Therapies for Nonmelanoma Skin Cancers

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As the incidence of nonmelanoma skin cancer (NMSC) continues to rise, topical therapies may be used with increasing frequency. Topical therapies are currently being utilized, both on- and off-label, as primary or adjunctive means of treating NMSC. Surgical therapies, such as Mohs micrographic surgery (MMS), remain the mainstay for tumor removal; however, topical therapy can provide an alternative treatment modality for some skin cancer patients and serve as a useful adjunct to surgery. Topical therapies may also increase overall NMSC treatment efficacy in the management of subclinical lesions and identify asymmetrical growth. In some patients, such as those with multiple NMSCs or those with high surgical risk, topical therapy may be used to avoid surgery or minimize its extent. In instances where biopsy sites are equivocal, topical therapy may also facilitate tumor identification prior to surgical intervention. In some patients who have issues with scarring in general, topical therapies may be preferable to other methods of treatment for NMSC.

The most commonly employed topical therapies include imiquimod, 5-fluorouracil (5-FU), ingenol mebutate (IGM), and diclofenac. Each agent has a different pharmacologic action and may be used in various clinical settings. Photodynamic therapy (PDT), with a variety of compounds and energy sources, has also been used for the treatment of AKs and NMSC, but this topic will be discussed in (Chap. 4). Drawing from their own experience with each topical therapy for NMSCs, the present authors will provide tips to optimize treatment outcome. Particular attention is paid to US Federal Drug Administration (FDA)-approved treatment modalities and select off-label indications. Experimental and/or non-FDA-approved therapies are also briefly mentioned in this chapter for their potential future significance.

Imiquimod

Mechanism of Action

Imiquimod is a type of imidazoquinolone, a class of immuno-enhancing drugs that mobilize several cytokines having antiviral and tumoricidal properties [1]. This cytokine recruitment occurs due to a highly intricate process involving the innate and adaptive immune response through cell surface receptors named toll-like receptors (TLR), located on macrophages, Langerhans cells (LC), and dendritic cells. Imiquimod agonizes TLR-7 and TLR-8, thus activating NF-kB and the formation of cytokines that stimulate both innate and acquired immune response pathways modulating subsequent antitumor activity [2–6].

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Side Effect Profile

Side effects of imiquimod may be local and/or systemic in nature. Common local reactions include erythema, erosion, pain, and ulceration in severe cases [7] (Fig. 2.1). Dyschromia, namely, hyperpigmentation and hypopigmentation, due to postinflammatory changes is not uncommon, although usually mild. Vitiligo-like hypopigmentation has been reported on several occasions [7–11]. Rare reactions have been reported including drug-induced pemphigus of the vulva and aphthous ulcers, presumably mediated by various proinflammatory cytokines such as IFN-α and TNF-α [12–15]. Acute urinary retention and eruptive epidermoid cysts are nonimmunologic effects of imiquimod therapy [16, 17]. Since imiquimod is an immunostimulant of TH_1 cell-mediated immunity, exacerbation of preexisting conditions that are mediated by this part of the immune system may potentially occur. Multiple studies reporting a worsening of psoriasis following imiquimod application have been noted [18–20]. Moreover, exacerbations of atopic dermatitis and HLAB-27 spondyloarthropathy have also been observed after imiquimod therapy [21, 22]. Systemic symptoms have also been reported with the use of imiquimod. These likely occur when proinflammatory cytokines enter the systemic circulation, but it could also be the result of an individual hypersensitivity response to these cytokines. Albeit uncommon, systemic signs and/or symptoms are often likened to a "flu-like" illness, including malaise, fatigue, anorexia, weight loss, diarrhea, postural hypotension, and elevated erythrocyte sedimentation rate [23]. These systemic symptoms typically resolve quickly upon discontinuation of imiquimod therapy. Imiquimod is pregnancy category C, and its use during pregnancy should be avoided [24].

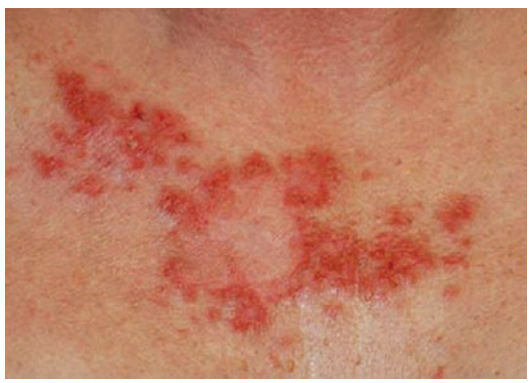

Fig. 2.1 An acceptable reaction after imiquimod use. Note the subclinical areas represented by the satellite erythematous regions

5-Fluorouracil

Mechanism of Action

5-FU is a structural analog of thymine that competes for enzymes with normal metabolites such as uracil [6]. It is eventually incorporated into ribonucleic acid (RNA) and inhibits deoxyribonucleic acid (DNA) formation by covalent bonding that blocks thymidylate synthetase [6]. This ultimately results in cell death since protein synthesis is halted. No immunomodulatory mechanisms have been identified. Nevertheless, it has been postulated that the intense inflammation caused by 5-FU contributes to tumor regression or that the release of antigens, by destroyed tumor cells, may contribute to an immunologic response [6].

Side Effect Profile

Like imiquimod, 5-FU may cause intense erythema, erosions, and ulceration depending on the dose and schedule (0.5–5%). However, the 5-FU reaction most likely depends on the destruction of proliferating cells in NMSCs and sun damage and not on the body's innate ability to mount an immune response. True allergic contact dermatitis to 5-FU, like imiquimod, is infrequent and more commonly triggered by a preservative or vehicle compounded within the cream [25, 26].

Systemic responses to topical 5-FU are rare but have been known to occur in patients with variable deficiency of dihydropyrimidine dehydrogenase, an enzyme critical for metabolism [27]. One should carefully consider applications of 5-FU to large body surface areas, since damaged skin could theoretically result in increased absorption with possible systemic effects. 5-FU is pregnancy category X and absolutely contraindicated during pregnancy [24].

Diclofenac

Mechanism of Action

Topical diclofenac is a nonsteroidal anti-inflammatory drug (NSAID) primarily used to treat actinic keratoses. The main effects of NSAIDs occur through the inhibition of cyclo-oxegnase-2 (COX-2), which is overexpressed in several epithelial tumors and catalyzes the synthesis of prostaglandins [28]. In addition to having anti-inflammatory activities, diclofenac may inhibit neoplastic cell proliferation by inducing apoptosis [28]. Apoptotic pathways via bcl-2 and caspase-8 are similar to the ones seen in imiquimod-induced apoptosis [28].

Side Effect Profile

Several reports of allergic contact dermatitis to topical diclofenac have been observed [29, 30]. These eczematous eruptions are likely a result of the diclofenac molecule itself and less the vehicle or preservative. Photoallergy from topical use has also been reported [31]. The importance of clinical surveillance for an allergic reaction is imperative since an eczematous dermatitis may mimic local reactions induced by topical diclofenac. Diclofenac is the only FDA-approved topical chemotherapeutic agent that is pregnancy category B [24].

Ingenol Mebutate

Mechanism of Action

Ingenol mebutate (IGM) is a hydrophobic, macrocyclic diterpene ester extracted from the weed *Euphorbia peplus* with a dual mechanism of action [32, 33]. Several hours following application, IGM causes rapid cellular death followed, within days, by an inflammatory phase capable of clearing residual cells [34]. Cell necrosis is caused by mitochondrial swelling, chemical destruction, and plasma membrane disruption. The inflammatory phase is mediated by protein kinase C catalyzing neutrophil-mediated, antibody-dependent cellular toxicity [32, 35, 36].

Side Effect Profile

Reported side effects from IGM during initial studies include transient erythema, flaking/scaling, crusting, blistering, pustulation, and erosions. Most importantly, scarring was not reported during these comprehensive trials [32, 34]. The most common side effects resolve within 2 weeks for the face and scalp and 4 weeks for the trunk and extremities. IGM has also demonstrated little potential for skin sensitization, photo-irritation, or photoallergy [37]. There are no known drug interactions for IGM, and its metabolites have no effect on cytochrome P450 enzymes [38]. Although systemic absorption has not been demonstrated, IGM is pregnancy category C and not recommended during pregnancy [24].

Topical Therapy for Actinic Keratoses: The Authors' Experience

Monotherapy for Actinic Keratoses

Actinic keratoses are induced by ultraviolet light radiation (UVR) and, in some cases, develop directly into full-blown squamous cell carcinomas (SCCs) [39]. Topical therapies including imiquimod, 5-FU, IGM, and diclofenac may offer some advantages over traditional treatment modalities. Several major trials demonstrating the clinical efficacy of each topical treatment as monotherapy for AKs have been well studied [40–62]. Table 2.1 summarizes the authors' approach for each topical therapy. Figure 2.2 illustrates the concept of field therapy.

Table 2.1 Topical agents for actinic keratoses

5% imiquimod	5-Fluorouracil	Diclofenac	Ingenol mebutate
Apply over a cosmetic unit, such as one cheek or forehead (approx. 25 cm^2) until the skin retains a shiny appearance	Apply 0.5–5% formulation in the same manner as for imiquimod (Fig. 2.2)	Apply 3% gel (similar to imiquimod and 5-FU) twice daily to any part of the body for 90 days	Apply 0.015% gel to face/scalp once daily for 3 days Apply 0.05% gel to trunk/extremities daily for 2 days
Start application 3×/weekly for 4 weeks	Apply twice daily on face/scalp for 3 weeks and up to 4 weeks for trunk/extremities	The side effect profile is more favorable than other topicals, but its efficacy is inferior	Most common local skin reactions are erythema, flaking/scaling, and crusting
If no response after 2 weeks, increase dose to once daily until an acceptable reaction occurs and treat for 4 weeks (Fig. 2.1)	If the reaction becomes brisk, titrate to once daily or every other day	May be used for patients with contraindications to other topical therapies, patient preference, or if unable to follow-up as recommended	Can apply as field therapy but small amounts dispensed make it more practical for individual lesion treatment
After a 4-week treatment, monitor for residual lesions	Keratolytics may be added to penetrate depth of a thick lesion	Contact or irritant dermatitis may be more common and should be monitored	<25 cm^2 recommended treatment area
Repeat treatment if lesions are still persistent after a 4-week rest period posttreatment	Large body surface area application is discouraged due to potential risk of absorption on damaged skin		Short treatment schedule encourages patient compliance
If no response even after daily dosing, treatment should continue through 16 weeks (per package insert)	Topical steroids may be used to calm the treated area since the mechanism does not solely depend on the inflammatory response		No local reaction to medication could mean inactivated product due to poor storage and handling
For hypertrophic lesions, keratolytics or retinoids may be added to aid penetration	Topical anesthetics are not regularly implemented since pain can help to titrate therapy and avoid contact sensitization		Persistent reaction to non-lesional skin could indicate infection
A thorough history and physical is important to screen for cell-mediated preimmunologic conditions to prevent exacerbation	Infection may be assessed in the same manner for imiquimod		
Topical steroids are not used to reduce inflammation since they may inhibit imiquimod's mechanism of action			
The regular use of topical antibiotics is not encouraged unless infection is diagnosed			
Infection may be present if the area feels worse than it appears or if purulence or signs of cellulitis are present			

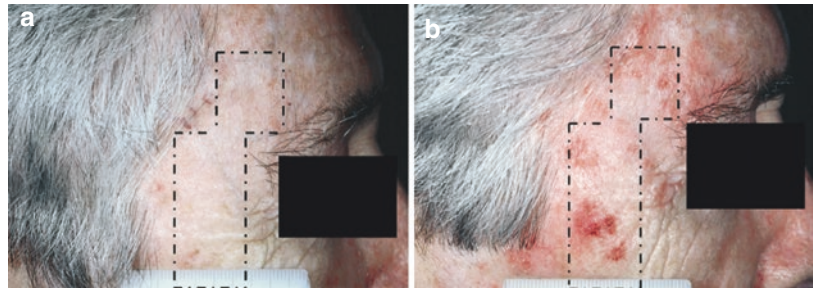

Fig. 2.2 Field therapy depicting the presence of hidden AKs. (**a**) Baseline AK lesion count of 5, (**b**) but after imiquimod therapy commenced, 10 visible lesions appeared in the area treated

Imiquimod Versus 5-Fluorouracil for AKs

One study compared the efficacy of imiquimod (three times per week for 4 weeks), 5% 5-FU (twice daily for 4 weeks), and cryosurgery (20–40 s per lesion) for treating actinic keratosis [63]. Twenty-five patients were randomized to treatment with imiquimod, 5-FU, or cryosurgery and displayed 68%, 96%, and 85% initial clearance, respectively [63]. However, after a 12-month follow-up, a higher rate of recurrence and new lesions were seen in the 5-FU and cryosurgery arms [63]. Furthermore, imiquimod-treated lesions showed greater histologic clearance [63]. In addition, the imiquimod-treated group was judged to have the best cosmetic outcomes [63]. The study concluded that although imiquimod did not clear AK lesions as well as 5-FU or cryosurgery initially, sustained clearance over time was greater.

Another article compared the clinical efficacy between imiquimod (twice weekly for 16 weeks) and topical 5-FU (twice daily for 2–4 weeks) applied as field therapy [64]. Five percent 5-FU was more effective than imiquimod in exposing what were presumed to be subclinical AK lesions, reducing the final count (total AK count declined during the 24-week study by 94% vs. 66%, $p < 0.05$), achieving complete clearance (incidence of 84% vs. 24% by week 24, $p < 0.01$), and attaining clearance rapidly [64]. Tolerability was similar except for erythema, initially significantly higher with 5-FU than imiquimod, then resolved rapidly and was significantly lower than imiquimod by week 16 [64].

A meta-analysis examined ten different studies comparing topical 5-FU and imiquimod with various treatment doses and schedules [65]. Results suggested that imiquimod may have higher efficacy than 5-FU for AK lesions located on the face and scalp (70% for imiquimod vs. 52% for 5-FU) [65]. Interestingly, a study of community observational data found 5-FU reduced the short-term risk of subsequent AKs in a 2-year follow-up period compared to imiquimod, although there was no statistically significant comparative reduction of AK risk during the 5-year follow-up period [66]. Our experience is similar to studies that suggest imiquimod maintains clearance longer than its counterparts for AKs [47, 66].

To date, there are no randomized controlled trials evaluating the risk of subsequent NMSC in patients treated with 5-FU or imiquimod for AKs. Therefore, the authors practice a case-based approach for each patient with AK lesions. In obvious situations, any patient who cannot tolerate one topical medication, for various reasons, may benefit from the other. It is important to obtain a pertinent medical history with respect to cellular immunity. As described before, imiquimod has induced exacerbation of preexisting dermatoses (i.e., psoriasis) and even systemic conditions (i.e., spondyloarthropathy) [18–20]. In these cases, topical 5-FU may be a better option. On the other hand, it has been demonstrated that 5-FU may increase gene mutations, with an unclear implication of the risk of carcinogenesis [47]. Although additional studies are required, the use of imiquimod is encouraged when it is a viable option.

Imiquimod and 5-FU Combination Therapy

Combination therapy involving the use of topical 5-FU and imiquimod has been used successfully

to optimize therapy. Each topical treatment has a different mechanism of action, thereby affecting AK lesions uniquely. Thus, imiquimod and 5-FU may be utilized to complement each other. This is analogous to the use of different chemotherapeutic agents for the treatment of cancer in order to maximize outcomes. In one study, patients applied 5-FU in the morning and imiquimod each night to their lesions daily for 1 week each month over the course of 3 months [67]. The study concluded that this combination was a relatively more rapid and convenient form of therapy compared to each medication alone [67]. Probably the biggest hurdle to this approach is insurance reimbursement since most insurance requires a failed response to one regimen before allowing for a different topical regimen. The authors' approach to combination therapy is described in Table 2.2.

Table 2.2 Combination therapy for actinic keratoses

Combination therapy with imiquimod, 5-FU, and IGM is intended for patients that fail monotherapy or have numerous lesions
Two suggested regimens
1. Separate: Start with a course of imiquimod daily for 1 month immediately followed by a course of 5-FU twice daily for 1 month or IGM once daily for 2 or 3 days
2. Concurrent: Start alternating daily treatment with imiquimod and 5-FU until a sustained inflammatory response for 1 month is observed

5-FU and Calcipotriol Combination Therapy

Calcipotriol, FDA approved for the treatment of psoriasis, has shown to impact the induction of thymic stromal lymphopoietin (TSLP) [68–70]. TSLP, an epithelium-derived cytokine, has been discovered to have potent antitumor effects in skin with barrier dysfunction; this allows for consideration when discussing treatment of skin cancers [70, 71]. In one investigator-blind study, calcipotriol 0.005% ointment was applied as monotherapy to one side of the scalp and face and Ultrabase cream as placebo on the other for 12 weeks [72]. The calcipotriol side showed a statistical improvement in AKs, from baseline, as compared to the placebo side [72]. This antitumor mechanism of calcipotriol was studied in combination with 5-FU, which revealed a synergistic response against AKs via induction of CD4+ T cells [70]. This proposed novel immunotherapeutic regimen was tested in a randomized, double-blinded clinical trial in which 64 patients applied 0.005% calcipotriol ointment plus 5% 5-FU and 67 patients applied Vaseline plus 5% 5-FU twice a day for 4 days [70]. The combination group, 5-FU plus calcipotriol, lead to an 87.8% reduction in AKs as compared to 26.3% in the 5-FU plus Vaseline group ($p < 0.0001$) [70].

Combination Therapy with Cryotherapy

AK lesions may not completely clear with topical treatments alone. Topical therapy may be used in conjunction with cryosurgery and serve to clear residual AK lesions. The opposite technique may be performed as well, by starting with topical therapy first, then destroying remaining lesions with liquid nitrogen. One randomized trial has demonstrated the use of 0.5% 5-FU subsequent to cryotherapy to be more statistically significant than using liquid nitrogen therapy alone for the head and neck [73]. Another open-label study depicted the advantages of applying 0.5% 5-FU prior rather than after cryotherapy, with significant decreases from the baseline number of AK lesions [74]. On a comparable level, the sequential application of topical 3% diclofenac gel for 90 days after cryotherapy has been shown to be more effective in treating AKs than monotherapy with cryotherapy [75]. Similar findings have been reported with IGM in a limited number of patients [76].

Cryotherapy in combination with immunotherapy has also been studied for the treatment of superficial BCC and SCC in situ [77]. After 24 months, recurrence rates of 2% and 0% were observed for superficial BCC ($n = 50$) and SCC in situ ($n = 31$) patients, respectively [77]. The combination of liquid nitrogen followed by imiquimod was more effective than either treatment alone [77]. The authors' approach to combination therapy with cryosurgery is described in Table 2.3.

Table 2.3 Combining topical therapy with cryosurgery for actinic keratoses

Even when failing to clear lesions, topical therapies may highlight lesions to a more confined distribution, facilitating cryosurgery
Two possible regimens: Treat hypertrophic lesions with liquid nitrogen followed 1–2 weeks later with monotherapy with either imiquimod or 5-FU for 1 month, IGM for 2–3 days, or diclofenac for 90 days Treat with initial monotherapy with imiquimod, 5-FU, IGM, or diclofenac followed by liquid nitrogen to residual lesions. (Caveat: If lesions are clinically suspicious or persist after both monotherapy and liquid nitrogen, consider a biopsy to rule out invasive SCC.)

Ingenol Mebutate

At the time of this writing, there are presently no trials comparing the efficacy of IGM to other topical chemotherapeutic modalities. A large multicenter, randomized, and double-blinded study demonstrated 42.2% and 34.1% complete clearance of AKs for face/scalp lesions and trunk/extremity lesions, respectively, utilizing different concentrations if IGM [32]. An additional study demonstrated sustained lesion reduction rates of 87.2% for face/scalp lesions and 86.8% for trunk/extremity lesions after 12 months [32]. IGM is limited in that each package provides enough medicine to treat an area of 25 cm^2 and may provide substantial cost to the patient for multiple treatments or treatment areas. There are no randomized trials evaluating the use of IGM in combination with cryotherapy for the treatment of AKs.

Cost and Treatment Choice for Actinic Keratoses

While the authors focus on the clinically ideal treatment, they realize that cost will always be a limiting factor when treating AKs, and this impacts direct patient care and compliance. A recent review reports that 5-FU and IGM are the most cost-effective topical chemotherapeutic agents for AKs [78]. Yet, the cost of failed therapy must also be evaluated. Since many authors have observed sustained clearance with imiquimod, it may be more economical than 5-FU and/or IGM if repeated treatments are required. Similarly, pharmaceutical companies often provide discount coupons/cards that can help minimize the cost differential, and this should be considered when making cost a central factor in decision-making. Ultimately, the clinical picture, not cost, should guide the decision-making process.

Experimental Topical Therapies

Emerging topical therapies for actinic keratoses include topical retinoids, resiquimod, piroxicam, dobesilate, and betulinic acid [71]. These are either not FDA approved for the treatment of AKs, not widely available, or experimental with only animal subject studies to support them. Perhaps with additional studies, these treatment modalities may impact the treatment of AKs in the future.

Topical Therapy and Nonmelanoma Skin Cancer: The Authors' Experience

Basal Cell Cancer Monotherapy

Imiquimod

Currently, imiquimod 5% is approved by the FDA for the treatment of biopsy-confirmed, primary superficial basal cell carcinomas (BCCs) in immunocompetent adults, with a maximum tumor diameter of 2.0 cm, located on the trunk (excluding anogenital skin), neck, or extremities (excluding hands and feet) [79]. The average clearance rate for superficial BCC using imiquimod, in an aggregate number of lesions (n = 1416), is 79% [80]. Furthermore, when reviewing many studies with imiquimod regimens varying in terms of application frequency and/or duration, cure rates for superficial and nodular BCCs range from 43–94% to 50–65%, respectively [81–94].

Imiquimod, in other treatment settings, may be considered as an off-label application and is not FDA approved. Yet, several studies have shown that lesions larger than 2 cm, above the neck lesions, and nodular BCCs can be effectively treated with imiquimod [82–86, 95–98]. Moreover, multiple trials have established imiquimod's clinical efficacy for superficial and nodular BCCs, and to a lesser degree more aggressive BCC varieties, but for the latter, caution is recommended since there are no randomized control trials in this regard (Figs. 2.3 and 2.4) [82–86, 95–98]. Aggregate data suggest a clearance rate of 65% using imiquimod off-label for the treatment of nodular BCCs ($n = 421$) [80]. As with AK lesions, the authors do not advocate one schedule over another and simply present the data and our experience to help the provider prescribe imiquimod for their patients in the most effective manner.

The package insert states that imiquimod cream should be applied to the lesion including a 1-cm margin five times per week for 6 weeks prior to normal sleeping hours (h) and left on the skin for at least 8 h [79]. In a double-blind, placebo-controlled study looking at 5% imiquimod cream as an adjunct modality to Mohs micrographic surgery for the treatment of basal cell carcinoma, results were similar for patients using imiquimod five times weekly for 4 and 6 weeks [98]. Thus, the package label recommendation is emphasized, and the authors instruct patients to apply imiquimod five times per week for at least 4 weeks, aiming for 6 weeks if patients are able to tolerate the medication and don't have to stop it for any period of time [98]. The package label recommendation is emphasized. See Table 2.4 for the authors' approach to BCC monotherapy.

A question frequently raised by clinicians is how do we assure that tumor has been completely removed after using topical imiquimod or any other topical therapies? In reality, this is no different than knowing if tumor has been removed after any treatment. There is a probability that tumor can recur even after excision, and the prudent and

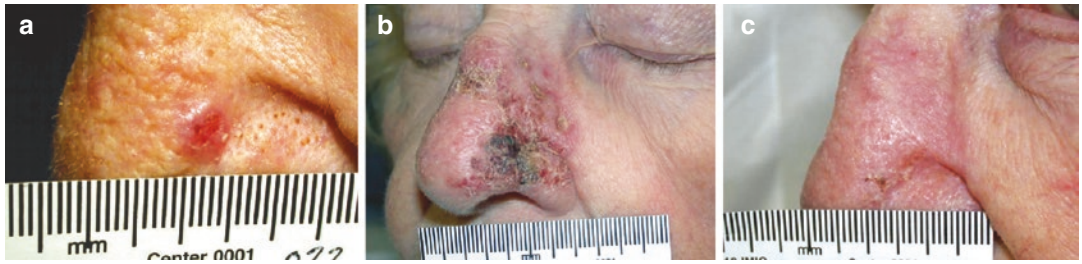

Fig. 2.3 (**a**) A nodular BCC (**b**) treated with imiquimod (**c**) showing complete clinical and histologic devolution. However, we do not treat nodular BCC with imiquimod as monotherapy. We pretreat nodular types with imiquimod prior to surgery, but sometimes clearance may be achieved. We view this as a serendipitous event

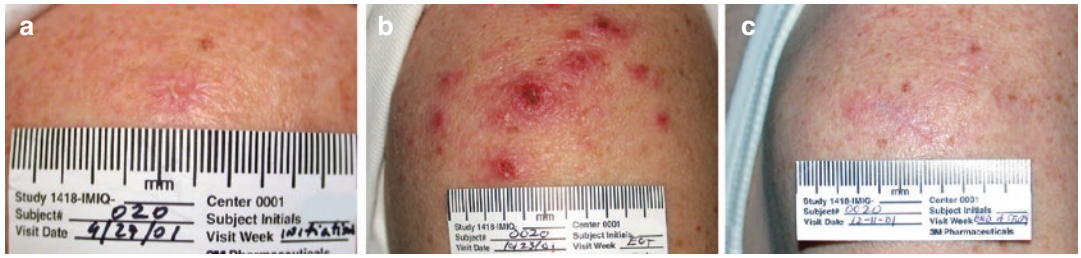

Fig. 2.4 (**a**) Imiquimod treatment for superficial BCC on the left upper arm. (**b**) Note the intense reactionary radius that extends up to the left upper shoulder. Clinically, this is not observed prior to treatment. (**c**) Note that although a biopsy may have appeared to remove the entire superficial BCC on clinical examination, imiquimod may nonetheless incite a robust reaction, which we hypothesize is because of remaining cellular atypia that cannot be detected with the naked eye

Table 2.4 Topical therapies for nonmelanoma skin cancers

	BCC	SCC
5% imiquimod	Apply 5×/weekly on consecutive days for at least 4 weeks, aiming for 6 weeks if tolerable If no response after 2 weeks, daily dosing may be implemented Sometimes twice daily dosing is required to incite a reaction if no reaction with daily dosing at 2 weeks, but caution should be taken, decreasing to daily or 5×/weekly once signs of an initial response ensue If clinical response has occurred but residual tumor is clinically evident, consider further treatment. A 4-week wait period can be allowed to pass before a clinical evaluation for residual tumor since the immunologic response may persist If tumor is still present, we encourage a biopsy or procedural therapy If the clinical assessment is ambiguous, the option is given to the patient to re-biopsy or follow-up after 4 weeks for re-evaluation For BCCs other than superficial types, we do not routinely recommend monotherapy unless a patient is bedridden, terminal, or unable to tolerate a procedure (Fig. 2.3) Warn patients with extensive, adjacent photodamage to expect severe reactions from epidermal field carcinogenesis (Fig. 2.4) For patients concerned about cosmesis, curettage with imiquimod can be recommended for non-high-risk tumors	For SCCs other than superficial in situ types, we do not routinely recommend topical monotherapy unless a patient is bedridden, terminal, unable to tolerate, or refuses a procedure Surgery is the mainstay for treatment for all SCC types, including Bowen's disease, KAs, and superficial or invasive SCCs The main goal of topical therapy is to shrink the tumor prior to surgery or remove confounding adjacent AKs Apply daily dosing from 4 up to 16 weeks planning for a need to extend therapy to 16 weeks since SCCs may take longer to respond The patient should follow up intermittently during the 16 weeks to monitor for clinical improvement or worsening Regular topical use for treating KAs is not encouraged due to conflicting clinical and histopathologic diagnosis
5% 5-fluorouracil	It is FDA approved for superficial BCC regardless of site Evidence-based studies evaluating efficacy and long-term recurrence are lacking Used by authors if there are apparent contraindications to imiquimod and clinically indicated The recommended dose is twice daily for 3–6 weeks up to 10–12 weeks or until erosion occurs, in the amount sufficient to cover the lesion as per package insert	For SCCs other than superficial types, we do not routinely recommend monotherapy unless a patient is bedridden, terminal, or unable to tolerate a procedure The authors typically reserve its use as an adjunct to surgery for all SCC types, including Bowen's disease, KAs, and superficial or invasive SCCs Bowen's disease is the prototypical SCC type. 5-FU may be considered for monotherapy when surgery is not the best option for a patient For Bowen's disease, twice daily dosing for up to 10–12 weeks is recommended Regular topical use to treat KAs is not encouraged due to conflicting clinical and histopathologic diagnosis

traditional course is always to clinically follow the patient for evidence of recurrence. The negative predictive value for imiquimod treatment, defined as the probability of a negative clinical assessment confirmed as being histologically free of tumor, has been reported to be 88.9–93% in various trials [83, 90, 97]. This suggests that most clinicians would be able to determine if a treated superficial BCC has responded appropriately to imiquimod. Longer follow-up periods may be warranted to decrease the amount of false-positive evaluations while observing for evidence of

recurrence. It has been our experience that no perfect follow-up time period exists, and the key is to assure that follow-up occurs based on the histology of the tumor, location, and risk factors for a particular patient.

5-Fluorouracil

If a physician is going to use 5-FU for the treatment of superficial BCCs, then the recommended dose and strength according to the FDA labeling is 5% applied twice daily in an amount sufficient to cover the lesions [99, 100]. Treatment usually is continued for at least 3–10 weeks or until superficial erosion occurs. Therapy may be required for as long as 10–12 weeks before the lesions respond [99]. Refer to Table 2.4 for the authors' approach to the treatment of BCC with 5-FU. An aggregate clearance rate of 92% (n = 144 lesions) has been reported for the treatment of superficial BCC using 5% 5-FU cream twice daily [80]. However, it has been commonly debated as to the actual recurrence rates after this type of therapy.

It is important to note that there can be a wide variability in cure rates due to application methods including utilization of occlusion, once daily or twice daily frequency, or duration of treatment [81]. Although a consideration in superficial BCC, the primary monotherapy use of 5-FU is not commonly recommended for nodular or infiltrative BCCs [101].

Ingenol Mebutate

Although not FDA approved for the treatment of BCCs, IGM has been shown to provide improvement in superficial BCC in a few reports [81]. Histologic clearance was observed in five out of eight (63%) patients after two-day application of IGM gel 0.05% for superficial BCC [102]. The proposed treatment regimen to consider for superficial BCCs is 2–7 consecutive days [81].

Diclofenac

The off-label use of diclofenac to treat superficial BCCs has been reported in some cases [81]. The efficacy of topical application, twice daily for 8 weeks, of diclofenac sodium 3% gel, calcitriol 3 μg/g ointment, and a combination was studied for both superficial and nodular BCCs [103]. Histologic clearance of superficial BCC was observed in 64.3% and 43.8% of patients in the diclofenac monotherapy group vs. the combination therapy, respectively; no statistical improvement was observed for nodular BCCs [103]. The downside of this therapy is suboptimal patient compliance due to several weeks of twice daily application [81].

Squamous Cell Cancer Monotherapy

There is growing evidence that topical agents may serve as noninvasive treatment options for SCC, including Bowen's disease, but neither imiquimod nor 5-FU have an FDA indication for this use. The concern has been that the superficial component may respond, but the deeper invasive components may persist and, yet, not be clinically obvious. Topical treatments may benefit patients with large, superficial bowenoid lesions that may be ill-defined or extend beyond the clinical margin. Likewise, inoperable, invasive SCC may sometimes respond to topical therapy to minimize morbidity or as palliative treatment. A few clinical trials and a host of case reports have demonstrated efficacy for SCC treatment with the use of imiquimod and topical 5-FU. Nevertheless, surgery should be considered the mainstay of treatment for SCC, especially in light of the increased risk of metastasis and perineural invasion with SCC and lack of data to establish removal of deeper invasive components of cutaneous SCC.

Imiquimod

The authors' approach to the treatment of SCC with imiquimod is described in Table 2.4. Our treatment goal is a minimum of 4 weeks and maximum up to 16 weeks, although 20-week regimens have been utilized [100]. The cure rate for SCCis with topical use of imiquimod ranges from 57% to

80% [81, 88, 89, 101]. In this study, complete clinical and histologic clearance was assessed in 80% of patients with SCCis and 71.4% with invasive SCC after daily application of imiquimod 5 days per week for 8–12 weeks [89].

The authors err on the side of caution when treating SCCs with imiquimod, and neither treatment of SCCis or invasive SCC is commonly recommended as primary monotherapy [101]. We reserve imiquimod and other topical treatments for those patients that cannot tolerate, or refuse, surgery or other prescriptions and for adjunctive preparation prior to surgery. Since Bowen's disease may exemplify subclinical extension beyond clinical margins, these lesions tend to be ill-defined. Imiquimod, as well as other topical treatments, may help define the true clinical margins under most circumstances and help reduce the subclinical component, sometimes clearing tumor completely. The authors consider complete clearance as a fortuitous incident, with the main goal of adjunctive therapy being to shrink the tumor before surgery, and thus the extent of surgery. Part of our reasoning for this approach is that we have seen residual SCC with perineural invasion in some patients who appeared to have significant clinical clearance following imiquimod use. New evidence theorizes this may be due to an imiquimod-induced switch from a T_H2 to T_H1 immune response and subsequent reduction in immunosurveillance and tumor editing processes [104]. There is the risk that residual tumor can be left behind, but in our experience with surgery post-imiquimod use, we have not experienced higher recurrence rates nor cases of postsurgical adverse events.

5-Fluorouracil

Topical 5-FU is not FDA indicated for the treatment of SCC but has been used with varying success [105]. This is surprising to many people as they assume that since 5-FU is approved as a therapy for AKs, that by extension, it would be indicated for treatment for SCC. The authors prefer to use topical 5-FU for the treatment of SCC in combination with a surgical modality, as an adjunctive therapy. When surgery is not the best option for the patient, 5-FU has documented high efficacy in an off-label manner against cutaneous SCC in situ, albeit lower cure rates are reported when compared to treatment of superficial BCC as discussed earlier [81, 106].The suggested treatment regimen for SCC in situ is 5% cream applied twice daily for 3–6 weeks, and that can be continued for ≤10–12 weeks if necessary [107]. We find that invasive SCC responds to 5-FU poorly, but 5-FU can still be effective in clearing up confounding collision AK lesions and the SCC in situ component often surrounding invasive SCCs, thus making the subsequent surgery much less burdensome for the patient. Both in morbidity and cost, we are cognizant of the risk that a deeper invasive component can be missed, and thus, it can be utilized to decrease the margin of excision while still taking a conservative excision margin when the anatomy allows. To date, our recurrence rate and lack of significant adverse events support this approach but would welcome randomized controlled trials to assess this approach.

Diclofenac

Diclofenac, although off-label, has been reported to show clearance of SCCis in several cases [81]. In this case series, two patients with Bowen's disease, or SCCis, were successfully treated with twice daily application of 3% diclofenac gel for 80–90 days, and no recurrence was noted for up to 10–12 months both clinically and histologically [108]. In an additional study, five patients with SCCis had histologic clearance at 1 month follow-up after daily application of diclofenac 3% gel for 8 weeks [109]. Although diclofenac can be considered for topical therapy of SCCis, it has not been usually recommended for invasive SCC [81, 109].

Combination Topical Therapy

Topical combination therapy with 5-FU and imiquimod has been used for Bowen's disease in patients who have failed monotherapy with

either treatment [110]. The logic being the same as for systemic chemotherapy regimens where agents can have a synergistic effect because of different mechanisms of action. It may be that the effects of 5-FU are enhanced in the presence of several cytokines induced by imiquimod, producing a synergistic reaction whose mechanisms are not fully understood [110]. It has been our experience that lesions on the extremities and digits have the propensity to be thicker, where topical treatments may find it more difficult to penetrate, and thus may not be as effective.

Topical Therapy as a Surgical Adjunct to NMSC

Preoperative Topical Therapy

The authors prefer to use imiquimod or 5-FU preoperatively to help reduce the size of the surgical defect and thus subsequent repair (Table 2.5). Although MMS may approach cure rates up to 99%, incomplete removal can occur (see Chap. 11 for further details). Imiquimod has also been used as adjuvant treatment following incomplete MMS for large, mixed type BCCs to help clear any residual tumor [111].

The authors investigated the mean reduction in tumor size after using imiquimod prior to MMS [98]. Subjects applied imiquimod five times weekly for 2, 4, or 6 weeks in this double-blind, randomized, placebo-controlled study [98]. The 4- and 6-week treatment groups demonstrated statistically significant reductions in pretreatment versus posttreatment tumor target areas and surgical wound sizes. Yet, they also found cure rates were equal for both the 4- and 6-week treatment groups at approximately 66%. Thus, presurgical adjunctive therapy with imiquimod resulted in elimination of surgery in two-thirds of the patients or a reduction in the extent of surgery in the remaining poor responders (Fig. 2.5).

If there is a contraindication to imiquimod, topical 5-FU may be considered to reduce tumor

Table 2.5 Preoperative topical therapies as surgical adjuncts for NMSCs

5% Imiquimod	5% 5-Fluorouracil
Goal is to facilitate excision by reducing tumor load/size and complete clearance is a fortuitous incident	Goal is to facilitate excision by reducing tumor load/size, and the patient should be aware of this
May be used to clean up actinic and in situ changes adjacent to invasive SCC or BCC, helping to better delineate the neoplasm	Used if there is a contraindication to imiquimod for debulking of tumor
Dosing schedule is similar to treating superficial BCC as monotherapy	May be used to clean up actinic and in situ changes adjacent to invasive SCC or BCC, helping to better delineate the neoplasm
A wait of 2–4 weeks is encouraged before MMS or excision so inflammation may subside, and the excised tissue can be better evaluated histologically	When treating invasive SCC, it is important to confirm the location prior to surgery since the skin lesions may at times appear to have clinically resolved, and post-excision tissue should include some clinically normal skin

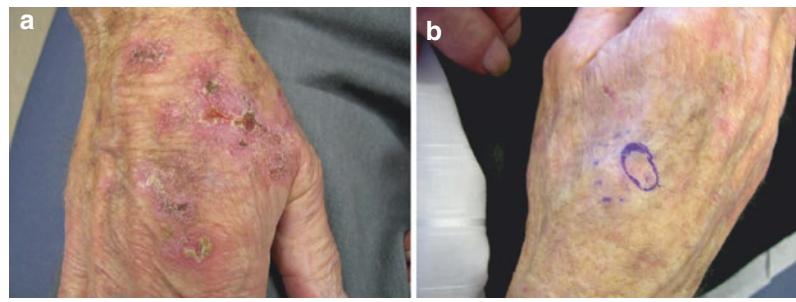

Fig. 2.5 (**a**) A biopsy proven SCC with surrounding actinic damage. After pretreatment with 5-FU, the area was considerably debulked for MMS. (**b**) The circle represents the SCC site

size [112]. Anecdotally, before imiquimod was available, the authors used 5-FU for the preoperative treatment of SCC. The logic behind this is that SCC often occurs in sun-damaged skin with a background and collision of actinic keratoses. The margins of SCC in situ and superficial forms of SCC can be difficult to differentiate from AK in the above described scenario. The authors found that often the entire SCC cleared with 5-FU use, but even when the SCC did not clear, a substantial part of the AK and/or SCC in situ component resolved making the final surgery smaller and easier. It is important to confirm the location of the SCC, when using this approach, so that surgery can be performed in the appropriate area and where more invasive SCC is suspected. The authors emphasize to patients that this is adjunctive therapy, and surgery is recommended to ensure the tumor has been removed appropriately even if the lesion appears clinically removed.

Intraoperative Topical Therapy

It has been reported that 30–47% of NMSCs located on the head and neck that are treated with electrodesiccation and curettage (ED&C) are associated with residual tumor [113–115].

It is the authors' experience that using imiquimod with curettage without electrodesiccation for nodular and/or superficial BCC patients may induce at least equivalent cure rates to curettage and electrodesiccation with better cosmetic results [116]. In this study, 57 nodular and superficial BCCs were curetted without electrodesiccation. Imiquimod 5% cream was then initiated once daily five times per week for 6 weeks. There were three investigators, one of whom started the cream at the time of surgery, one that started 1 week after surgery, and one that waited for reepithelialization before therapy. The patients were evenly divided among all three approaches. At 1-year follow-up, 0 of the 57 BCCs treated had clinical recurrences. Cosmetic results were deemed to be very good to excellent and depicted superior cosmetic outcomes when compared to curettage and electrodesiccation [116]. See Table 2.6 for the authors' approach. Figure 2.6 compares the cosmetic results of curettage with electrodesiccation and curettage with imiquimod cream. Patient satisfaction was much higher postoperatively when adding imiquimod rather than using electrodesiccation alone. The cost of combination therapy is a consideration when choosing the appropriate treatment modality. The

Table 2.6 Intraoperative topical therapies as surgical adjuncts for NMSCs

Curettage followed by imiquimod may facilitate tumor clearance and improve overall cosmesis and cure rate
Curettage without electrodesiccation may serve to improve imiquimod penetration
Curettage without electrodesiccation is performed; then the patient waits for 1 week after curettage and is followed by imiquimod 5×/week y on consecutive days for 4–6 weeks
The patient may return for a clinical evaluation 4 weeks after completing imiquimod to see if more topical therapy is needed
The same rules apply as if it were being used as monotherapy, performing a re-biopsy if the BCC appears to be present, or clinical observation if tumor presence or absence is ambiguous to interpret
This procedure is not recommended for SCCs, since they may portend more aggressive behavior unless the patient is deemed a better candidate for electrodesiccation and curettage

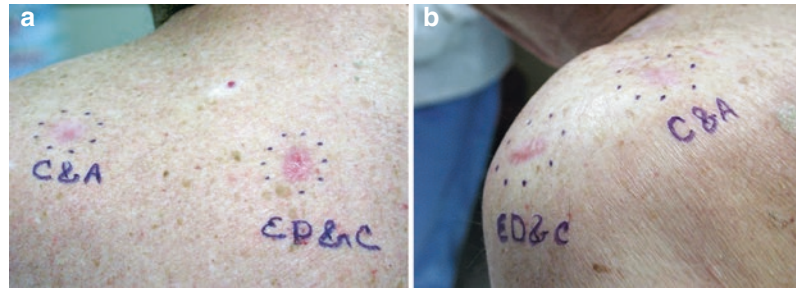

Fig. 2.6 (**a**) Curettage with imiquimod consistently appears to induce pink, flat scars that tend to fade quickly. (**b**) Electrodesiccation and curettage may cause atrophic or hypertrophic cicatrices, depending on a patient's skin type

average cost of curettage and imiquimod cream together may be greater than treatment with excision if patients use each imiquimod packet only once [117]. In practice, most patients apply multiple applications from each individual packet, which substantially decreases the cost of this treatment and, in many cases, can make it less expensive than excision since unused packets can be used to treat multiple lesion [117]. Another consideration is the cost for the procedure and mediation with insurance for coverage. One author's approach is to either bill for the curettage alone or bill for an office visit and not the procedure; since the curettage does not require electrodessication, it does not need to be repeated three times, making it relatively easy to do.

Postoperative Topical Therapy

There is scant data to prove if postoperative use of imiquimod or 5-FU prevents recurrence; however, in theory it would seem logical that use of these topicals may serve to benefit patients with tumors that have a high chance of recurrence. In addition, imiquimod or 5-FU treatment may address discontinuous growth patterns susceptible to recurrence after surgery. It is our opinion that imiquimod may facilitate the clearance of remaining tumor in high-risk lesions successfully due to its unique immunomodulatory mechanism, and we use it in situations where the nature of the tumor is suggestive of a greater risk of recurrence, either because of the host status or presenting nature of the tumor.

Unusual Situations/ Complications/Variations

Problematic Areas

Lips

Diclofenac is an FDA-approved treatment for AK lesions of the lip [57]. Cure rates with 90 days of diclofenac have been shown to be similar when applied to skin after a 30-day follow-up [118]. Furthermore, the tolerability profile of diclofenac would appear to lend itself well, especially when treatment decisions involve cosmetic appearance during and subsequent to therapy [118]. An isolated study also illustrated that topical diclofenac after 6 weeks of therapy may improve this condition with minimal adverse events [119]. Nevertheless, the author's experience is that diclofenac can still result in an occasional robust reaction or allergic contact dermatitis when used on the lips. It is also a slow process, which can affect patient compliance.

Topical 5-FU has been used to treat isolated lip AKs as well as diffuse actinic damage of the lower lip [120]. Although it produced considerable temporary discomfort, final results in one study proved excellent, with recurrences in only 2 of 12 patients [120]. The mean length of therapy was 12 days of topical 5-FU application every other day up to once daily, and patients were clear up to an average of 22 months. Actinic cheilitis has also been treated with imiquimod three times weekly for 4–6 weeks [121]. All 15 patients showed clinical clearing of their actinic damage at 4 weeks after discontinuation of imiquimod. Sixty percent of patients experienced a moderate to marked increased local reaction consisting of increased erythema, induration, erosions, or ulcerations, which in some cases continued through the period of therapy [121]. A recent 6-month follow-up study compared the efficacy of diclofenac, imiquimod, and IGM in 30 patients with actinic cheilitis [122]. Greater clearance of lesions was achieved with imiquimod than IGM or diclofenac (50% vs 40% vs 20%, respectively).

The authors contend that topical therapies have an important role in the treatment of lip AKs and actinic cheilitis. Although topicals may result in uncomfortable side effects during treatment, they may help avoid more aggressive forms of therapy such as carbon dioxide laser ablation. In addition, topical therapies may "biologically image" and discern malignant lesions from more benign varieties, especially in this area at high risk for metastasis. These medications may obviate the need for biop-

Table 2.7 Pearls for topical treatment of lip AKs/actinic cheilitis

5% imiquimod	5-Fluorouracil	Diclofenac
Initially, twice weekly application is employed	5% formulation is used every other day and then increased gradually to daily after a week and, finally, twice daily after 2 weeks as tolerated	Applied every other day and gradually increased to daily as tolerated and stopped when reaction occurs
Careful and slow titration to daily treatment may be required if no evident reaction occurs after 1–2 weeks	Once the patient develops a reaction, it is recommended the patient stay on that regimen or steps down to the prior dosing scheme to prevent a severe dermatitis and possibly subsequent discontinuation	Observation to differentiate response from contact dermatitis is important
If any type of response is experienced, then the patient is highly encouraged to continue with that schedule or the previous schedule	An antiviral agent may be prescribed to prevent a herpes labialis flare, if there is a history of HSV	An antiviral agent may be prescribed to prevent a herpes labialis flare, if there is a history of HSV
An antiviral agent may be prescribed to prevent a herpes labialis flare, if there is a history of HSV	Strong clinical suspicion for a more invasive process is imperative, especially if persistent after several treatment cycles	If no response with diclofenac or other topical medication, treatment is discontinued, and procedural therapy is recommended such as surgical excision or MMS
If lesion is persistent after several treatment cycles, suspect a more invasive process	If after 4 weeks of therapy there is no reaction, the topical agent can be switched to imiquimod or diclofenac	
If after 4 weeks of therapy there is no reaction, the topical agent can be switched to 5-FU or diclofenac	If no response with either medication, treatment is discontinued, and procedural therapy is recommended such as surgical excision or MMS	
If no response with either medication, treatment is discontinued, and procedural therapy is recommended such as surgical excision or MMS	Pretreatment lymph node examination is recommended as nodes can enlarge posttreatment secondary to inflammation	

sies if clinical success ensues after their use. Nevertheless, patients have to be advised that effects such as swelling can persist for unpredictable periods even after discontinuing use of the topical agent, and the reactions to therapy can be robust with any topical treatment. The authors' suggested approach in this regard is described in Table 2.7.

Eyelids

Eyelid BCCs have been treated with success with imiquimod on numerous occasions according to smaller published studies [123–125]. We have treated two patients with eyelid margin lesions that have shown no recurrence at 5 years. However, this is an off-label use and the safety profile would have to be further investigated before we could advocate the regular use of imiquimod for eyelid lesions. Nevertheless, for the patient that refuses surgery or radiotherapy, after a biopsy reveals a clinically removed nodular or superficial BCC, this can be a consideration.

Avoiding the use of 5-FU near the eye, especially the conjunctiva, may be wise since multiple cases of ectropion have been reported [126–128].

Other ocular side effects include a transient keratitis, erythema, and irritation [129]. As a result, we do not promote the use of 5-FU on or near the conjunctival margin, medial, or lateral canthi. The degree of irritation may be exaggerated in these areas, and cicatricial ectropion has been reported [126].

Penis

No randomized trials exist to determine the true value of imiquimod for Bowen's disease of the penis. However, multiple cases treated with imiquimod have been reported with various dose regimens [130–132]. Bowenoid papulosis has been successfully treated with imiquimod, probably a testament to the medication's antiviral properties [133]. In some instances, a penectomy may have been prevented with the use of topical imiquimod for an invasive SCC [134]. Our experience has been that topical imiquimod has been moderately efficacious for SCC in situ lesions of the penis, including erythroplasia of Queyrat and bowenoid papulosis. We find that topical imiquimod, prior or subsequent to surgery, can be considered as an adjunct, although not FDA approved, for SCC in situ of the penis to minimize more invasive procedures that would not allow maximal sparing of tissue. However, patients need to be prepared for possible significant associated discomfort, swelling, and irritation in the area. The authors do not advocate the use of imiquimod for invasive SCC of the penis because of the unknown risk of locoregional spread. Although Schroeder et al. depicted complete resolution of SCC in situ of the penis, a case-by-case assessment should be made before any patient receives imiquimod as the sole treatment for SCC in situ of the penis [135].

Basal Cell Nevus Syndrome

Imiquimod has been used to treat patients with Gorlin's syndrome and/or multiple acquired BCCs with varying degrees of success. The BCCs described in these studies were usually not only superficial but also included nodular and morpheaform types [136–139]. The authors have had success with several patients with a similar presentation, and often some lesions will respond while others do not, so patients need to be advised of this and monitored closely. Nevertheless, our experience is that imiquimod has been useful in decreasing the extent of surgery necessary for these patients, especially if used early when lesions are first clinically noticed to be developing. Patients with this disorder become very adept at identifying these early lesions (Fig. 2.7).

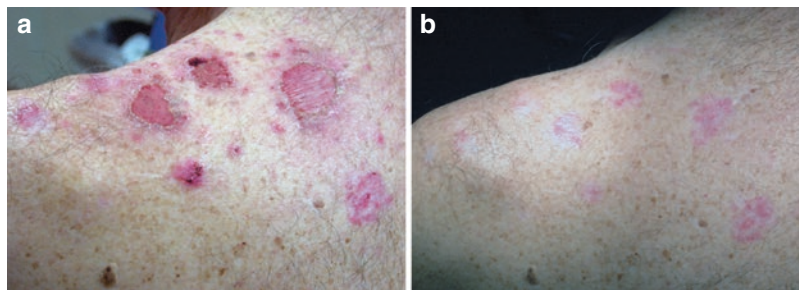

Fig. 2.7 (**a**) Multiple acquired superficial BCCs of the left posterior shoulder. These BCCs resolved after imiquimod 5×/weekly application for 6 weeks. (**b**) The residual pink, flat scar may erroneously cause false-positive readings. We recommend close follow-up and observe for recurrence. These pink areas usually fade with time

Transplant Patients

NMSCs are one of the major causes of morbidity after organ transplantation [140]. This immunosuppressed population chiefly includes organ transplantation recipients but may include any patient that may be undergoing chemotherapy for various reasons (i.e., lymphoma). Of all NMSCs, SCC is the predominant type with a 65- to 100-fold increased incidence in transplant recipients compared to the general population [141]. Therefore, although the exact progression rate of a single actinic keratosis in this patient population is unknown, thorough treatment of these lesions is warranted [142].

A 2018 systematic review of eight randomized controlled trials evaluating 242 organ transplant recipients demonstrated complete clearance rates of actinic keratoses in patients treated with imiquimod (27.5–62.1%), diclofenac (41%), and 5-FU (11%) [143]. Combination therapy of imiquimod and topical 5-FU has also shown clinical efficacy in an open-label study [144]. However, consulting with the transplant physician, when contemplating imiquimod therapy in transplant patients, is advisable since there is controversy regarding immune-enhancing therapies in the setting of therapeutic immunosuppression.

Delayed Mohs Micrographic Surgery

For surgical candidates with BCCs whose MMS procedure is delayed (i.e., scheduling conflicts, travel, insurance issues), the authors employ imiquimod or 5-FU during the waiting period (Table 2.8). The authors treat SCCs in a similar manner with some reservation, depending on the characteristic of the tumor. Although NMSCs are slowly evolving tumors, we feel that the benefits of treating with imiquimod outweigh the alternative of doing nothing during the treatment delay, especially when the length of delay is unclear. The behavior of untreated NMSCs may be unpredictable and pose potential risk of increasing in size or worse. When the patient is ready for MMS, the authors observe for residual disease and often find the tumor has considerably decreased in size or even cleared. Of course, it is important to take either good photographs or measurements using skin landmarks to accurately assess the tumor location posttreatment.

Table 2.8 Pearls for using topical therapies when MMS is delayed

Patients with scheduling conflicts, travel, or insurance issues may use either topical agent in the same manner as recommended for preoperative use until they can return for surgery
When the patient is ready for surgery, careful inspection for residual disease is performed using the prior confirmation of the pretreatment lesion site by photograph and/or measurements
Even when the tumor appears to be cleared, a frozen biopsy may be helpful on the day of MMS to confirm tumor removal. MMS or surgery is advisable for invasive SCC depending on location and tumor characteristics

The Skip Area Controversy

An issue often raised by physicians is whether skip areas will occur after presurgical treatment with imiquimod or 5-FU. In other words, can the topical therapy destroy only parts of the tumor so as to make it appear clinically resolved, when in fact, it is now broken up into subclinical islands of tumor? To answer this question, the authors treated 72 BCCs, in a randomized, double-blind controlled fashion, with imiquimod, then performed MMS, followed by posttreatment biopsies. Note that this was obtained from unpublished data because the evaluation of the tissue, from skip areas, was not deemed to have been part of the initial intent to treat analysis; see reference [145]. The biopsies and MMS were performed regardless of whether tumor appeared clinically resolved posttreatment. Accuracy, of the biopsies and MMS, was established through the use of pretreatment plastic templates localizing the anatomic sites and tattooing of the treatment site. In this double-blind, randomized,

placebo-controlled trial, there was no statistically significant increase in skip areas in the treatment versus placebo arm. Five skip areas were identified in the placebo group, and one skip area was noted in the imiquimod arm. Thus, there does not seem to be any greater risk of leaving behind untreated BCC by topical pretreatment prior to surgery. The authors have not performed a similar study with 5-FU in the pretreatment of SCC. However, an unpublished QI review of more than 40 patients, treated by the authors in this manner, did not reveal any higher incidence of recurrence or complications with SCC tumor pretreatment with 5-FU prior to surgery.

Summary

Topical therapies, including immunomodulators, provide a useful addition to the list of agents used to treat skin cancers, and it behooves the physician to be conversant with their modes of action. Their value lies not just as monotherapy or combination therapy but also as adjuncts either before, during, or post-surgery. As the incidence of NMSC continues to rise, further advances can be expected in the use of topical therapies for the treatment of NMSC.

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