Intralesional and Perilesional Treatment of Skin Cancers

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In this chapter, various intralesional and perilesional agents that have been used in the treatment of skin cancers will be presented by practitioners familiar with their use. The four medications reviewed—methotrexate, interferon, 5-fluorouracil, and bleomycin—have been in widespread use for many years in the treatment of cutaneous neoplasms and extracutaneous neoplastic and inflammatory conditions. Therefore, the efficacy, toxicity, delivery, indications, and costs for these agents are well established, and they are widely available. However, the most common routes of administration for such medications are oral, intravenous, and topical. An intralesional and perilesional approach to therapy is less often utilized, leading to less familiarity in clinical practice. It is our hope that a detailed review of these agents delivered in such a manner, along with a variety of clinical examples, will facilitate their use in practice and increase the variety of treatment options available to patients with cutaneous tumors.

I. METHOTREXATE

Methotrexate (MTX) has an appealing mechanism of action for the potential treatment for rapidly growing tumors, as it inhibits DNA synthesis in actively dividing cells. A folic acid analog, methotrexate irreversibly binds to dihydrofolate reductase, thereby blocking the formation of tetrahydrofolate and subsequently preventing the downstream synthesis of the purine nucleotide thymidine. Although methotrexate has demonstrated activity against a number of cutaneous malignancies including malignant melanoma, squamous cell carcinomas, and basal cell carcinoma, its use in most of these settings has been in combination with other chemotherapeutic agents, and through oral, intravenous, intra-arterial, or intrathecal routes of administration.

Intralesional MTX, however, has gained increasingly widespread recognition for its utility in the treatment of solitary keratoacanthoma (KA), and this first section will emphasize the application. Keratoacanthoma is a cutaneous neoplasm that some consider a less-aggressive subtype of cutaneous squamous cell carcinoma while others claim it is a distinct, typically benign neoplasm that occasionally behaves more aggressively. Its classification and pathophysiology remain enigmatic and have been debated in the literature over many years.

Despite difficulties in characterization, classification, and predicting the course of KA in individual patients, this tumor has potential for local tissue destruction, disfigurement, and occasionally may metastasize. Given these realities, in settings where destructive or surgical modalities may be less desirable, intralesional therapy with methotrexate has proven safe and useful in a number of instances.

Other agents, including bleomycin, interferon, 5-fluorouracil, and rarely corticosteroids have been injected into KA tumors. The utility of intralesional interferon, 5-fluorouracil, and bleomycin for cutaneous tumors is discussed later in this chapter.

For patients with multiple or syndromic keratoacanthomas, including well-accepted subtypes...
such as Witten-Zak, Grzybowski, and Ferguson Smith, intraleisional therapy is usually not indicated, and systemic retinoids\textsuperscript{29,30} may be more useful in treatment and chemoprevention (see Chapter 21).

**Indications and Contraindications**

KA typically occurs as a solitary lesion on sun-exposed skin in older patients. These tumors usually develop rapidly over several weeks or a few months, and display distinct histology, with a keratin-filled crater lined by a proliferating, atypical squamous epithelium, often with the rim forming an overhanging appearance—the so-called “buttress.” While these tumors may eventually involute spontaneously, some do not, and occasionally may metastasize.\textsuperscript{9,10,14}

KA tumors that are most amenable to intraleisional MTX are those with a classic clinical course, and where surgery would otherwise be challenging. Typical locations would be close to critical facial structures such as the periorbital region, perioral area, nose, and ears. Another common clinical scenario is if the tumor is not in a critical anatomic location, but of a size where surgery would produce excessive tension on nearby tissue, or require a flap or graft repair. Those who are often excellent candidates for MTX injection include patients who might tolerate surgery poorly because of the duration required to complete an excision, or who have comorbidities such as anticoagulation, diabetes, liver disease, or alcohol or tobacco abuse.

Caveats include patients who are immunosuppressed by medications for autoimmune disease or organ transplantation, or advanced human immunodeficiency virus (HIV) disease. These patients warrant similar concern if watchful waiting for involution is the initial management approach chosen, given their relative lack of tumor immunity. Patients who have difficulty with several weeks of wound care or who are intolerant to a more prolonged clinical course might be better served by one of the other treatment approaches described elsewhere in this text. Since MTX causes tumor necrosis, KA typically become more friable, and eventually ulcerate before resolution. The appearance of the site, and the care required, are not tolerated well by some patients.

There are many alternatives to injectable methotrexate for solitary KA, including standard excision\textsuperscript{9,10} Mohs excision\textsuperscript{31,32} radiotherapy\textsuperscript{33,34} curettage and electrodesiccation\textsuperscript{35–37} and intraleisional 5-fluorouracil (IL-5-FU).\textsuperscript{22–25} The recent literature suggests intraleisional interferon alfa-2\textsubscript{b}\textsuperscript{38} and topical imiquimod\textsuperscript{39} may have utility, but these approaches are less established.

**Pre-treatment Considerations**

From a global management perspective, it is our most common practice that cases of suspected KA be confirmed histologically prior to any nonexcisional therapy, since high-risk, rapidly growing squamous cell carcinomas or other aggressive cutaneous malignancies may be confused with KA. In addition, despite histopathological confirmation of KA, any tumor that does not respond following two MTX injections should be reevaluated and possibly sampled again for microscopic assessment.

Patients who fail to respond demonstrate the importance of clinical judgment in treating patients with suspected KA. Ultimately, the diagnosis of KA is highly dependent on clinicopathologic correlation. The possibility that a suspected KA is truly a squamous cell carcinoma must always be considered, and the failure to respond to intraleisional or other non-surgical approaches should prompt alternative evaluation and intervention. Fortunately, successful treatment courses with intraleisional MTX for KA last less than 2 months, allowing caregivers to establish an alternative therapeutic path should injectables fail.

Two cases of pancytopenia occurring in patients treated with single 25-mg doses of IL-MTX have been reported.\textsuperscript{40,41} These were patients with hemodialysis-dependent renal failure who presumably lacked sufficient renal excretion after systemic absorption of the MTX, leading to transient bone marrow suppression. Other significant adverse effects have not been reported to date in patients without renal disease,
but given the potential for subclinical cytopenia, obtaining a baseline and 1-week-post-injection complete blood count (CBC) for all patients is reasonable. In patients with known renal dysfunction, such precautions are strongly suggested.

The use of intralesional MTX for KA should be kept in clinical perspective. Standard excisional surgery is the treatment of choice for many solitary KA, offering both prompt definitive treatment as well as providing a complete specimen for histologic evaluation. Smaller KA, in particular, may resolve after biopsy alone. Surgical intervention, however, may lead to sizable defects in some cases, along with significant functional or cosmetic morbidity. Some patients with comorbidities such as cardiovascular disease, poorly controlled diabetes, or chronic liver disease may be poor surgical candidates. In these circumstances, IL-MTX may offer the advantage of being less invasive, quickly administered, and tissue-sparing, as well as being cost-effective. Cosmetic results for KA treated with MTX are typically quite good. Intralesional 5-FU has been demonstrated to be an effective treatment for KA and is a worthy alternative. Intralesional 5-FU may require more frequent injections and may require more local anesthesia; however, these aspects vary with practitioner experience.

Injectable MTX is relatively inexpensive. At our institutions, MTX solution is ordered from the hospital pharmacy at a cost of approximately $2 for a 2-ml vial at a concentration of 25 mg/ml. The brevity of time required to administer the injection also contributes to the overall low therapeutic expense.

Preparing MTX for Injection

Since MTX is a chemotherapeutic agent, most pharmacies require more stringent precautions for mixing than for agents such as corticosteroids or anesthetics. A telephone conversation with a local pharmacy or community hospital pharmacy several days in advance of the planned injection is helpful. The medication should be prepared at the pharmacy, and placed in a Luer-lok 3 ml syringe with a secure cap before delivery. Refrigeration is not required, but the medication should be administered within 24 h of preparation. A concentration of either 12.5 or 25 mg/ml should be chosen—typically the lower concentration for smaller tumors (less than 1 cm), or the higher concentration for larger ones. Depending on clinical response after the first injection, the dose can be maintained if a second injection is required, or altered. If the tumor becomes substantially necrotic and nearly resolves after the first injection, the lower dose should be chosen for the next injection. If the tumor responds minimally, then a higher dose should be chosen for the subsequent injection.

Description of Technique

Our standard practice for injection is as follows: using a 27-gauge needle, 0.3–2.0 cc of MTX in a concentration of either 12.5 mg/ml or 25 mg/ml is injected at each treatment session. We tend to favor the lower concentration for smaller tumors. Small KAs, less than 1 cm, are typically injected in a single central point at the base of the lesion whereas larger KAs are injected in four quadrants as well as at the central lesion base. Very large KA may require more than four injection points, working around the tumor circumferentially and aiming toward the center. The skin is usually just prepped with an alcohol swab and MTX is injected until an endpoint of uniform tumor blanching is achieved. Given the poor cohesion between tumor cells, roughly 50% leakage of the total injected MTX volume typically occurs and can be sponged off with clean gauze. The procedure is well tolerated in most patients without the use of local anesthesia, though use of injected lidocaine or topical anesthesia may be utilized without loss of efficacy. The overall approach to MTX injection for KA is highly analogous to injecting keloids with corticosteroids, though the pressure on the plunger required to inject a KA is less than that needed for the typical keloid. The volume instilled, the depth of injection, and the attempt at uniform distribution through the quadrants and base is quite similar. Patients feel the pain of injection, but as with triamcinolone, the discomfort afterward is minimal.
Treatment Pearls

1. Review all options and expectations with the patient before proceeding with injection.
2. A baseline and post-injection complete blood count, blood urea nitrogen, and creatinine should be considered, especially for patients with underlying chronic medical conditions or advanced age, given the rare reports of cytopenias in patients with renal insufficiency.
3. Local anesthesia is a reasonable option prior to MTX injection, especially for larger KA or anxious patients.
4. Leakage of MTX through the central crust or prior biopsy incisions is expected and should not reduce clinical efficacy.
5. Eye protection and Luer-lok™ syringes are important protective measures prior to injection. Usually, a 30-gauge needle is sufficient; ½ in for smaller KA, and 1 in for larger KA.
6. KA smaller than 1 cm can usually be injected with a single well-placed needle insertion from a peripheral site with the target for the needle tip located at the deeper central portion of the lesion. Larger KA benefit from several injections placed serially around the periphery and directed toward the center. The technique is highly analogous to injecting corticosteroids into hypertrophic scars.
7. Crusting and necrosis are expected 7–10 days after each injection. Gentle debridement of necrotic tissue prior to the next injection assists in delivering the agent to viable residual neoplastic tissue as opposed to injection into the crust.

Post-injection Care

A non-adherent dressing with a small amount of petrolatum centrally is sufficient to protect the recently injected KA. Thereafter patients may cleanse the area daily or twice-daily with dilute acetic acid or dilute hydrogen peroxide before reapplying a dressing. Soaking the surface first with a clean damp cloth or in the shower may help if the crusting is significant.

Expected Course of Treatment and Follow-Up

We recently reported our own experience with injectable MTX for KA over a 15-year period, and combined our data with that published by others over the past several decades. Detailed information on our clinical approach to such patients follows shortly. However, a brief summary of our findings regarding technique, efficacy, and caveats is provided first. The results are also summarized in Table 5.1.

| Table 5.1 Injectable methotrexate for keratoacanthoma recent study and review |
|-----------------------------|-----------------|
| Total number of patients    | 38              |
| Mean tumor size             | 1.9 cm (1.0–4.0 range) |
| Anatomic location           | ~75% head and neck |
| Histopathologic confirmation at baseline | ~66% |
| Methotrexate concentration utilized | 12.5 mg/ml in 49% of patients |
|                             | 25 mg/ml in 51% of patients |
| Methotrexate mean volume    | 1.0 ml          |
| Methotrexate cumulative mean dose | 36 mg         |
| Mean interval between injections | 18 days           |
| Mean number of treatment sessions | 2 (range 1–4) |
| Complete response rate      | 92% (35/38)     |
| Mean time of follow-up      | 1.8 years       |

In our study and review, the average age of the 38 evaluable patients was early 60–70s, gender distribution was even, and tumors were between 1.0 and 4.0 cm with a mean of 1.9 cm. Nearly 75% were located on the head and neck, with the remainder on trunk and extremities. Histologic confirmation was determined in advance in 2/3 of cases. Patients typically received either 12.5 mg/ml (49% of injections) or 25 mg/ml (51% of injections) concentration of MTX per injection, spaced 2–3 weeks apart. Specifically, the mean interval between injections was 18 days, and the total cumulative average dose for each of the 38 patients was 36 mg of MTX. The mean volume injected was 1.0 ml per treatment session, and the concentration selected appeared to be related more to institutional bias rather than tumor characteristics. The average number of treatment sessions was 2, with a range of 1–4.
Our study revealed a complete response rate of 92% (35 of 38 patients). KA resolution was determined by physical examination and clinical behavior in the vast majority of cases (33/38) while tumor resolution was also determined histologically in 5 of 38 patients. The mean interval of follow-up was 1.8 years. Importantly, 8% (3/38) of KA tumors did not resolve and subsequently required surgical extirpation. Non-respondent lesions were somewhat larger than the 92% of KA that did respond: 2.8 cm versus 1.9 cm, respectively. Two of the non-responders had tumors on the face and the other was a recurrent hand lesion failing prior surgical excision. No significant adverse events occurred in all of the 38 cases examined.

Several case examples follow that illustrate the typical clinical course for patients treated with intralesional MTX for KA.

**Illustrative Case 5.1**

A 70-year-old Caucasian woman presented with a 1-month history of a rapidly enlarging, mildly pruritic nodule on the right forehead. Her general health was excellent and she was on no medications. Her examination revealed a solitary keratotic 1.5 cm nodule on the right forehead with no lymphadenopathy (Fig. 5.1). Wedge biopsy demonstrated a keratoacanthoma-like squamous cell carcinoma.

Three days later she underwent injection of 1 ml of 25-mg/ml concentration MTX. She developed additional crusting over the surface of the nodule, with partial resolution noted 3 weeks later (Fig. 5.2). At that time, she underwent a second injection at the same concentration and volume. One month subsequently, there was minimal residual eschar, and no remaining nodule (Fig. 5.3). She continued to heal well over the next month (Fig. 5.4) with moist occlusive wound care and remained free of recurrence 1 year later, with an excellent esthetic result (Fig. 5.5).
Illustrative Case 5.2

A 48-year-old Caucasian woman, with no prior medical conditions and on no medications, developed a rapidly growing nodule of the left upper lip and melolabial fold over a 2-month time period. The lesion had failed to respond to a 10-day course of oral antibiotics prescribed by a previous health care provider. On examination, there was a $2.3 \times 1.4$-cm hyperkeratotic and crusted nodule with a central crater. A suture was in place at the inferior border at the site of a recently performed wedge biopsy (Fig. 5.6). There was no clinical lymphadenopathy.

Biopsy revealed a well-differentiated squamous cell carcinoma with keratoacanthoma-like features.

After discussing surgical and non-surgical options, she underwent injection of $1 \text{ ml}$ MTX at a concentration of $25 \text{ mg/ml}$. At 3 weeks the lesion was approximately 50% of its prior height, though its peripheral dimensions were similar to baseline (Fig. 5.7). The size of the central crater was greatly diminished. The patient underwent a second MTX injection at the same concentration and volume that day. Four weeks subsequently, the overall size of the
lesion was $1.5 \times 1.0$ cm (Fig. 5.8). A final injection of MTX—once again at 25 mg/ml concentration and 1 ml total volume—was performed. One month later, a small, smooth 4-mm area of tissue remained inferiorly and clinically appeared to be a small scar (Fig. 5.9). This was confirmed by punch biopsy 6 weeks later, which also effectively smoothed the clinical residual. She had no recurrence of disease 2 years later, but did develop one additional small squamous cell carcinoma of the left shoulder in the interim, excised with clear margins and an uneventful post-operative course.

### Illustrative Case 5.3

An 87-year-old Caucasian female with multiple prior basal cell carcinomas developed a rapidly growing nodule on the right temple above the right eyebrow over a 3-month period. She noted occasional tenderness, crusting, and intermittent yellow drainage. The patient also had multiple underlying medical problems, including Parkinson’s disease, a prior cerebrovascular accident, hypothyroidism, cervical cancer, and hypertension. Examination revealed a $2.6 \times 2.4$-cm keratotic plaque on the right temple adjacent to the eyebrow (Fig. 5.10). There was no lymphadenopathy. A wedge biopsy demonstrated squamous cell carcinoma with keratoacanthomatous features.

Given her age and multiple comorbidities, she underwent injection of MTX 25 mg/ml concentration and a volume of 1 ml. She received 4 ml of 1% lidocaine with 1:100,000 epinephrine prior to MTX administration (Figs. 5.11, 5.12, and 5.13). Three weeks later, the center had become necrotic (Fig. 5.14) and was removed prior to injection of the base and periphery with an additional 1 ml of MTX at the same concentration (Fig. 5.15). After three additional weeks, healthy granulation tissue was evident at the base, and no additional injections were required.

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**Fig. 5.8** After an additional 3 weeks, the keratoacanthoma continues to involute. She underwent a third and final injection of methotrexate, once again at a volume of 1.0 ml and concentration of 25 mg/ml.

**Fig. 5.9** Appearance of the upper lip 6 weeks later, showing a small fold of skin at the prior inferior border of the keratoacanthoma. A punch biopsy demonstrated scar and no residual tumor.

**Fig. 5.10** An 87-year-old woman with a $2.6 \times 2.4$-cm nodule rapidly developing over 3 months on the right temple adjacent to the eyebrow. A wedge biopsy confirmed squamous cell carcinoma with keratoacanthomatous features.
Twice-daily dilute acetic acid soaks followed by the application of white petrolatum, and a non-adherent dressing were employed for the following month, with complete re-epithelialization observed. She had no recurrence of the lesion, or new lesions over the subsequent 3 years (Fig. 5.17).

II. INTERFERON

Every epithelial carcinoma has been reported to have occasional total regression—stage and tumor burden notwithstanding—brought about by immune attack. The immune system routinely kills neoplastic cells, and it is the overwhelming of this function that allows tumors to grow. In an immunocompetent individual, non-melanoma skin cancers are constantly attacked by tumor infiltrating lymphocytes (TIL), and it is through stimulation of these cells that complete regression of skin cancer can occur.43–47

**Fig. 5.11** Blanching of the skin surrounding the tumor resulting from administration of 4 ml of 1% lidocaine with 1:100,000 epinephrine prior to intralesional methotrexate injection

**Fig. 5.12** Injection of methotrexate at 25 mg/ml concentration through the superior rim of the tumor with a 30-gauge 1-inch needle directed centrally and parallel to the skin surface. Approximately 0.2 ml was administered, with the remaining volume to be distributed around the periphery, sequentially. The 4 × 4-inch gauze serves both to protect the eye from extravasating methotrexate and to absorb any drug that extrudes through the crust

**Fig. 5.13** Injection of an additional aliquot of 0.2 ml of methotrexate at the lateral aspect of the tumor. The inferior and medial injections followed, but are not depicted in this series

**Fig. 5.14** Crusted and necrotic center of the keratoacanthoma 3 weeks later
Indications and Contraindications

Essential to the success of perilesional interferon treatment of skin cancer is screening of both the patient and the tumor. The patient should be an individual who understands that immune cells routinely kill cancer cells and one who is comfortable waiting 2–3 months for evaluation of efficacy. Since there are side effects of influenza-like symptoms, even though mild, it is important that this will not be of major concern to the patient. The physician must be comfortable and confident in recommending treatment, and knowledgeable as to the mechanism of action and expected outcome.

The most beneficial treatment for skin cancer is that which eradicates the tumor and produces the least morbidity. Immunomodulatory IFN therapy, which is an alternative to destructive methods, meets these criteria for “most beneficial” with selected tumors.

Pre-treatment Considerations: Basal Cell Cancers

The tumors that respond virtually 100% to immunomodulatory treatment are superficial and nodular basal cell carcinomas (BCC).47 The location where there is a clear cosmetic benefit over destructive/excisional treatment is the trunk. Therefore, a physician who wishes to begin using this therapy should select a superficial or nodular BCC on the trunk. The experience gained will provide confidence and the opportunity to expand the range of tumors treated. Basal cell carcinoma, which is highly differentiated toward adnexal structures (hair follicle, eccrine sweat gland), does not respond to IFN treatment. Periorificial BCC tumors have a somewhat lower response rate, even with typical histology.
Pre-treatment Considerations: Squamous Cell Cancers and Malignant Melanomas

Because of the greater potential for metastatic spread of squamous cell cancer (SCC) and malignant melanoma (MM) great caution in selection of tumors for which injectable interferon (IFN) treatment is “most beneficial” is needed. The only SCC suggested for selection are those where the patient has refused surgery (Figs. 5.18 and 5.19), or a superficial or in situ SCC that has failed to respond to previous therapies (Figs. 5.20, 5.21, and 5.22). SCC can invade

Fig. 5.18 Biopsy-proven large SCC on the lip of an elderly patient who refused surgical treatment

Fig. 5.19 Complete clinical resolution of the SCC on the lip 6 months later with slight delling at the tumor site, and skin markings present

Fig. 5.20 Biopsy-proven verrucous SCC in situ near the medial canthus with lateral extension outlined in ink. Previous treatments over 15 years included multiple cryotherapies, curettages, and curettage with electrodesiccation

Fig. 5.21 Resolving tumor 1 week after the final IFN injection, typical for SCC but not seen with BCC

Fig. 5.22 Complete clinical resolution of tumor with intact skin markings. Photo taken 14 months after Fig. 5.21
deeply and be neurotropic—further factors for caution in tumor selection.

Malignant melanoma has great metastatic potential. The only MM suggested for selection are biopsy-proven MM in situ for which surgery is deemed not to be a viable option (Figs. 5.23 and 5.24).50

![Fig. 5.23 Biopsy-proven recurrent MM in situ 2 years after wide excision](image1)

![Fig. 5.24 Biopsy-proven and clinically seen complete resolution 7 years after IFN treatment](image2)

**Obtaining Interferon α2b**

Interferon alpha-2b (IFN) is not FDA-approved in the United States but is approved in Europe and Canada. However, approximately one-third of patients may be able to get help from their insurance companies for purchasing IFN. A prescription is given for Intron A, 18 million units, NDC # 0085-1100-01. The manufacturer has labeled this as a “single-use vial,” not for intralvesional use. However, this is the same solution used in the early trials that showed great efficacy and does not have the risk of reaction to the preservative compounded in vials labeled “for intralvesional use.”

The diluent that comes in the package is used and additional bacteriostatic saline is further added to bring the concentration to 500,000 U per 0.1 ml (3.6 cc total volume). This vial is immediately and constantly refrigerated except when drawing up the injection. Routine sterile technique is used for multiuse vials. The reconstituted and diluted IFN retains its clinical efficacy when continuously refrigerated for up to 6 months.

The cost to the patient at a nationwide low-cost retail pharmacy is $270. Alternatively, the physician’s office may purchase the medication and charge the patient for it. Since approximately 4 million units will be left over after giving all nine injections, the patient may be treated at a slightly reduced medication cost.

**Description of Technique (BCC, SCC, MM)**

**Administering Interferon α2b**

The use of 1 cc syringes with plungers that push virtually all fluid into the 30-gauge needle is preferred (Norm-Ject, www.delasco.com). The site is prepared with alcohol and the end of an ice cube is placed on the specific small area where the needle will enter the skin for about 6 s to decrease pain.

**Make sure to always:**

1. Inject into the dermis, not the subcutis, since the maximum local effect on the immune system depends on intradermal placement.
2. Inject perilesionally, not intralvesionally. The solution, if properly placed, will cause swelling and blanching of the surrounding skin as well as
the tumor (Figs. 5.25 and 5.26). Intralesional injection will cause loss of suspended IFN due to leaking of fluid from the less cohesive tumor tissue. It is the immune response in the normal surrounding dermis that attacks the tumor. Some IFN solution may leak out or come out in a spray from hair follicles; adjusting the depth of the needle point or injecting in a different area will correct the loss of medication. Any IFN solution that has leaked onto the skin may be sucked back into the syringe and re-injected.

3. Inject superior to the tumor.

4. Pre- and post-medicate individuals receiving IFN injections. The symptoms that an individual with a cold or flu experiences are due to the body’s immune response to the virus, particularly interferon, not the virus itself. These same symptoms can be reproduced by the intradermal injections of interferon and are dose-dependent.

Ibuprofen or acetaminophen—based on patient preference, medical history, and size—is recommended 1 h prior to injection, 3 h after injection (the time of onset of symptoms typically), the evening of the injection, and the following morning. Sensitivity to interferon-induced flu-like side effects varies among individuals. Tachyphylaxis of symptoms occurs if injections are given 2–3 days apart. However, after 5 days without an injection, symptoms are similar to the initial injection. Since symptoms may even vary between injections, the author highly recommends the use of the above regimen for all patients being treated with IFN.

The amount of IFN injected depends on the tumor size, the injection sequence, and the sensitivity of the individual to side effects. While the standard dose of IFN per treatment is $1.5 \times 10^6$ units (0.3 cc), using a lower dose for the first and second injections—such as $1 \times 10^6$ units (0.2 cc)—is recommended. The standard dose of $1.5 \times 10^6$ units is given by the third or fourth injection. For a small tumor (e.g., $1 \times 1 cm$), the lower dose may be used throughout. For larger tumors, larger doses may be given compatible with patient tolerance. In general, the effective dose range correlates with $1 \times 10^6$ units for tumor size $1 \text{ cm}^2$, and increases by $0.5 \times 10^6$ units for each additional $\text{ cm}^2$. Dilution up to $0.25 \times 10^6$ units per 0.1 ml may be made for very large superficial BCC. This flexibility allows for individual variations based on tumor size and sensitivity to side effects.
Treatment Pearls

1. If four or five days have elapsed since the last injection, flu-like symptoms will be stronger, as with the first injection, so the dose may need adjustment.

2. It is the stimulation of the local immune system “over time,” not the total dose that produces the desired results. Three large doses given over a week are not as effective as nine small doses given over 3–4 weeks.

3. The dilution of the IFN solution to $0.5 \times 10^6$ units per 0.1 cc increases efficacy over more concentrated solutions. When it is more concentrated, the ramifications of losing a small amount of the solution during transferring or injection are greater.

4. Less than 1% of patients treated with this regimen have no response. Another treatment modality is necessary in such cases.

5. Rare individuals will have only a partial response with marked tumor shrinkage. Since the tumor has responded partially, complete response can be obtained if retreatment with another course of IFN is desired by the patient.

6. The location where there is a clear cosmetic benefit of IFN over destructive/excisional treatment is the trunk.

7. The amount of IFN injected depends on the tumor size, the injection sequence, and the sensitivity of the individual to side effects.

Post-injection Care

As with any intradermal injection, local treatment is the placement of petroleum jelly, gauze, and pressure for 2–3 min and/or an adhesive bandage to protect clothing from seepage from the injection site.

Expected Course of Treatment and Follow-Up (BCC, SCC, MM)

Three types of local responses may occur, typically between injections six to nine:

1. The tumor may become red and indurated, sometimes with slight surrounding erythema and rarely with a tender lymph node or folliculitis (Figs. 5.27, 5.28, and 5.29).

2. Slight erythema of the tumor occurs with little induration; and

3. Little to no erythema is observed throughout the course, but slight induration occurs. If local response 1 occurs, 100% tumor resolution has been the rule. However, in greater than 90% of tumors with responses 2 or 3, complete resolution also occurs.

The tumor often stops crusting after injection #6 and less leakage of interferon occurs. Following the ninth injection, the patient is instructed to return for evaluation in 3 months. Little to no regression of BCC is seen during the actual treatment of BCC but occurs weeks later once treatment has finished.

If no response of the tumor is observed (e.g., redness, swelling, induration) surgical removal should be performed. For the other 99% of BCC tumors, the 3-month post-treatment evaluation is sufficient.

SCC often show clinical partial resolution during the 3- to 4-week period of treatment (Figs. 5.20, 5.21, and 5.22). Occasionally, BCC or SCC will develop milia-like cysts, which resolve over the following 3–6 months.48

MM resolve in a similar time period to SCC. For pigmented MM, resolution of the pigment, as well as the malignant melanocytes, is expected (Figs. 5.23 and 5.24).

The question of whether there is always a need to biopsy post-treatment is best answered (other than MM which should always be biopsied following treatment) with close evaluation of the treated site. Normal skin lines should return following treatment (Figs. 5.30 and 5.31) in contradistinction to curetted and electrodesiccated lesions (Fig. 5.32). Even with very large and deep tumors, where considerable post-treatment hypopigmentation and/or delling may occur, there is a return of normal skin lines (Figs. 5.33 and 5.34). This allows effective post-treatment clinical follow-up, making biopsy unnecessary.

In the largest double-blind, placebo-controlled study of IFN treatment of BCC, no subclinical tumor was found on excision of the treated site at
Fig. 5.27  Two superficial BCCs on the chest of a man with numerous truncal BCCs. The man sought treatment for these tumors that would not yield prominent scar formation (see Fig. 5.32)

Fig. 5.28  Erythema and induration of the chest BCCs after the seventh IFN injection; typical for a type 1 response to treatment

Fig. 5.29  Complete clinical resolution at 6 months post-treatment with slight hypopigmentation and normal skin markings

Fig. 5.30  Superficial BCC on back

Fig. 5.31  Complete clinical resolution of superficial BCC with normal skin markings

Fig. 5.32  Electrodesiccation and curettage scar for BCC on the arm of the patient whose chest BCCs are seen in Figs. 5.27, 5.28, and 5.29. Note lack of skin markings after 1 year
1-year post-treatment if no tumor was visible by clinical inspection. Long-term follow-up for 10 years or longer has confirmed the extremely low incidence of persistent or recurrent tumor with this immunomodulatory treatment.

III. 5-FLUOROURACIL

5-Fluorouracil (5-FU) is a structural analog of thymidine that interferes with synthesis, resulting in the death of rapidly proliferating malignant cells. It has been used topically for years to treat actinic keratoses, Bowen’s disease and superficial basal cell carcinoma (Chapter 2). 5-FU has been used intralesionally in the treatment of keratoacanthomas and nodular basal cell carcinomas (Figs. 5.35, 5.36, 5.37, 5.38, and 5.39).

Keratoacanthomas

Klein was the first to use intralesional 5-FU in 1962 to treat KAs. Since then there have been many reports of KAs treated effectively with intralesional 5-FU. In two separate studies, 55 keratoacanthomas located on the face, head,
and extremities were studied. Following an average of three weekly injections of 0.2–0.6 ml of an aqueous solution of 50 mg/cm³ 5-FU, 53 of the 55 lesions (96%) showed histologic clearing.53,54 In another case report, Eubanks et al. observed total clearing of all of a patient’s 14 KAs treated with doses of 0.1–0.2 ml over five to nine weekly injections.16

Squamous Cell Carcinomas

Intralesional 5-FU has been used to treat SCCs.56 Twenty-three patients with biopsy-proven SCCs of less than 6 months’ duration, located on the face, head, neck, arms, or hands and varying from 0.24 to 7.50 cm were treated with intratumoral 5-FU/epinephrine gel. The patients received weekly injections of 1.0 ml or less of a combination of 30 mg/ml of 5-FU and 0.1 mg/ml of epinephrine gel for 4–6 weeks. Only one patient failed treatment and all had a good to excellent cosmetic result. Morse et al. treated an SCC on the right nasolabial fold with eight weekly injections of 5-FU with doses ranging from 0.8 to 2.4 ml. Histological clearance was achieved and the patient was tumor-free at 5-month follow-up.18

Basal Cell Carcinomas

Intralesional injection of 5-FU has been effective in nodular basal cell cancers.57 At 2-year follow-up, intralesional 5-FU was successful for 3 keratoacanthomas and two of three BCCs. It was found that 5–6 injections were needed to treat the BCCs, a finding in agreement with an earlier study. An average of 8 injections of 5-FU was required to treat the KAs. Odom et al. were able to treat them with 2.8 injections.53
Indications

These are similar to MTX, used when a patient refuses surgical intervention, or in cases where a patient’s medical condition contraindicates surgery, or in cases where the surgery will result in a large defect.

Contraindications

Hypersensitivity to 5-FU, or difficulty with following the protocol, are contraindications.

Pre-treatment Considerations

These are similar to MTX.

Obtaining and Preparing

Use 5-fluorouracil commercially available for systemic chemotherapy (50 mg/ml). Local anesthesia can be used with it, as an option (1% lidocaine).

Description of Technique

Infiltrate in and around lesion once or twice weekly until neither palpable nor visible. Thorough and complete infiltration of the tumor with 5-FU is essential for efficacy.

Note on Technique

Compared with intralesional methotrexate, intralesional 5-fluorouracil is more painful. The authors have no strong opinion about the relative effectiveness, and we are not aware of a controlled comparison study. It is important to abort the therapy if it clearly is not working, and resort to surgery, radiation therapy, or some other modality. One of the authors (RR) is aware of one case of treatment of a keratoacanthoma of the periorbital area with intralesional 5-fluorouracil that was ineffective, resulting in a lawsuit. The lesion had continued to grow despite the intralesional treatment, and eventually the patient had to have an ocular enucleation.

Post-injection Care

This is similar to intralesional MTX.

Expected Course and Follow-Up

If KAs do not demonstrate necrosis clinically after two to three weekly intralesional 5-FU treatments, alternative treatments should be considered.

Adverse Effects

Kurtis and Rosen reported the development of SCC within a BCC that was treated with intralesional injections of 5-FU. Intralesional injections can result in pain, necrosis, and ulceration. Systemic effects similar to intravenous 5-FU therapy can occur, but generally only when the above doses are exceeded.

IV. BLEOMYCIN

Originally isolated from the fungus Streptomyces verticillis, bleomycin is used as an antitumor agent for the treatment of various kinds of malignancy. Other dermatologic uses include the treatment of recalcitrant warts, hypertrophic scars, and keloids. Bleomycin has been shown to block the cell cycle at G2, cleave single- and double-stranded DNA, and degrade cellular RNAs. Bleomycin forms a complex with metal ions such as Fe (II), which is oxidized to Fe (III), resulting in the reduction of oxygen to free radicals which in turn cause cell breaks, leading ultimately to cell death. While systemic bleomycin is FDA-approved for the treatment of SCC of the head and neck, cervix, penis, and skin, Hodgkin’s and non-Hodgkin’s lymphoma, testicular carcinoma, and malignant pleural effusion, there are no current FDA-approved indications for intralesional bleomycin. The cytotoxic effect of bleomycin is enhanced considerably by coupling it with local anesthetics which increase its cellular uptake. Electrical stimulation also disturbs the cell membrane and enhances bleomycin cytotoxicity in a process known as electroporation. While bleomycin alone has not shown desirable outcomes for the treatment of cutaneous malignancies, when combined with
electrocorporation, results have been very successful. In electrocorporation, a circular configuration of electrode needles is used to deliver brief, high-intensity, pulsed electrical currents directly into the target tumor. The combined use of electrocorporation and a chemotherapeutic agent is termed electrochemotherapy (ECT).

**Squamous Cell Carcinoma/Keratoacanthoma**

Keratoacanthomas have been treated with intraleisional bleomycin without ECT. While no controlled, randomized studies have been conducted, in seven cases of KAs treated with intraleional bleomycin alone, a 100% cure rate and no side effects were reported. In these cases a 0.5% solution of bleomycin was used, diluted with saline and lidocaine. Using a 27-gauge needle, 0.2–0.4 mg of solution was injected. At most, four courses of treatment were needed at weekly follow-up sessions.

**Basal Cell Carcinoma**

In a case series of 20 patients with 54 tumors treated with ECT, Glass et al. noted a complete response rate of 94% and a partial response rate of 6%, no reports of non-response or disease progression. No reports on response rates for the different histologic subtypes of BCCs, cost-effectiveness or direct comparison between ECT and conventional treatment. There is one report of ECT and bleomycin used to treat a metastatic BCC with squamous differentiation.

**Metastatic Cutaneous Malignant Melanoma**

Of the studies performed, treatment protocols varied, with 0.5–1.0U bleomycin per calculated cc of tumor, electrical amplitude between 560 and 15,000 V/cm/s. Complete response rates reported from 72 to 89%, partial response rates (greater than 50% reduction in calculated tumor size-5–10%). Long-term follow-up was not reported.

**Indications**

Similar to MTX.

**Contraindications**

Those with Raynaud’s phenomenon or peripheral vascular disease should not be treated with bleomycin. It should be avoided in the pregnant or nursing patient.

**Pre-treatment Considerations**

Same as MTX.

**Obtaining and Preparing**

A common dilution of bleomycin is to take a vial of 15 international units of powder, and dilute it with 15 ml of normal saline to make a solution of 1 unit per ml. Other authorities have used more dilute preparations.

**Description of Technique**

One of the authors (RR) generally injects less than 0.6 ml of this solution weekly into a lesion for up to 8 weeks (0.1–0.2 ml for smaller lesions). Care must be taken to inject it specifically into the dermis associated with the lesion, and not into the fat, where larger amounts become easily injected, with very little effect on the malignancy.

**Post-injection Care**

Similar to MTX.

**Expected Course and Follow-Up**

One of the authors (RR) used bleomycin in a case of a large verrucous carcinoma of the sole (Fig. 5.40), with the idea that human papillomavirus plays a role in this type of carcinoma. The intraleional
bleomycin in the illustrated case did very well at eradicating the verrucous carcinoma (Fig. 5.41), but portions of it subsequently recurred (Fig. 5.42).

**Adverse Effects**

The following reactions occur immediately after injection and include erythema with swelling, pain, and a burning sensation. The pain usually lasts for 72 h and is relieved with acetaminophen. Blackening of the skin and eschar formation have also been observed. Rarely-onychodystrophy, hypopigmentation, atrophic, and hypertrophic scarring. Raynaud’s phenomenon, anaphylaxis, and flagellate hyperpigmentation have been reported. If combined with electrical impulses to increase uptake (electrochemotherapy), patients may experience discomfort, local muscle contraction, skin burning, erythema and edema, and muscle fatigue.

**References**


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