

The Emerging Role of Antineoplastic Agents in the Treatment of Keloids and Hypertrophic Scars

A Review

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Abstract: The management of keloids and hypertrophic scars continues to challenge health-care providers. Though both forms of pathologic scarring are distinct entities at the macro and microscopic level, their etiologies and treatment are often similar. Potential treatment approaches are progressing, and combinations of treatment options have been proposed in the literature with promising outcomes. The treatment evolution has reached a level where molecular therapeutic modalities are being investigated. Currently, no gold standard treatment exists. Overall success rates and patient satisfaction seem to be slowly climbing, but additional investigational studies must continue to be performed.

Several studies have investigated antineoplastic agents, and there seems to be a marked improvement in rates of recurrence, patient satisfaction, and overall quality of scar when these agents are used. Intralesional injection and/or wound irrigation with interferon-a2b, interferon-g, mitomycin-C, bleomycin, or 5-fluorouracil seems to have a positive effect on the reduction of pathologic scars. There is mounting evidence that these drugs used alone or in combination therapy, have the potential to be an integral part of the treatment paradigm for hypertrophic scars and keloids.

Key Words: wound healing, keloids, hypertrophic scars, anti-neoplastic, interferon, mitomycin-c, bleomycin, 5-fluorouracil

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The skin is one of the largest organs of the human body and its first line of defense. It continuously interacts with the environment providing feedback for thermoregulation, pain sensation, and proprioception. To maintain that function if disrupted, it must regenerate rapidly, leading to the formation of a scar at site of insult. Normally the scar is an asymptomatic scar.¹ Skin healing after any disruption consists of 3 phases: inflammation, proliferation, and remodeling. This is a complex process which depends on constant regulation of tissue biosynthesis and degradation so excess tissue formation is avoided.² What happens, however, when this system of checks and balances malfunctions? Dysfunction of the healing process may lead to disorganized wound healing and excess scar formation, thus predisposed individuals eventually produce hypertrophic scars (HTS) or develop keloids. Despite extensive research and investigation, the exact mechanism of disordered wound healing remains incompletely understood.³

Distinguishing keloids from HTS can be a challenge. Both are pathologic deviations from normal wound healing. Although much debate has taken place as to whether keloids are actually a result of abnormal wound healing in genetically predisposed individuals or a type of benign fibrous tumor, both processes share uncomfortable signs and symptoms including: pain, erythema, itchiness, cosmetic unsightliness, and functional impairments.³ In contrast, there are unique clinical and histochemical characteristics for each entity, which absolutely characterize them by their different pathologic problems.^{4–6} At their most basic level, keloids clinically extend beyond the original wound, are unlikely to spontaneously regress, and usually recur. In contrast HTS remain confined to the wound edge, frequently regress, and recur less often than keloids.⁷ Though they are separate entities, physiologically keloids and HTS do share 2 similarities: both are characterized by excessive deposition of collagen in the dermis and subcutaneous tissues and both occur secondary to violation of the dermis and underlying supportive tissue.¹ This may happen through: lacerations, abrasions, piercings, surgical interventions, deep burns, and skin inflammation (chicken pox, acne, folliculitis, and zoster).^{2,8} The incidence of keloids and HTS can widely vary from 40% to 70% following surgery to 91% following burn injury.⁹ No data exist to substantiate that HTS are more common than keloids, although many clinicians often feel they observe this.¹⁰ Individuals with darker skin pigmentation are at higher risk of developing keloids, especially in individuals with African or mixed-African heritage.¹¹ Men and women are equally affected,¹² and have the highest incidence of recurrence of both keloids and HTS in the second decade.¹³

As scientists continue to strive to identify a treatment that could normalize wound healing in susceptible patients, it seems that prevention is presently the best approach to achieve optimum outcomes. Factors of paramount importance for better healing are: minimizing tension on wound closure, early and thorough infected wound debridement, hematoma prevention, and optimizing nutrition.³ Beyond prevention strategies, potential management options for improving scar quality are constantly evolving. No longer is simple excision the standard of care. Current therapies employ steroid injections, silicone sheeting, compression and massage, post-operative radiation, and cryotherapy with or without excision.³ Additionally, attempts to modify wound healing at the molecular level are achieving clinical recognition.^{14,15}

The authors describe how one should be able to distinguish between keloids and HTS at the micro and macroscopic level. Though these 2 pathologic problems are distinct in nature, their etiology and symptoms are very similar. Consequently, keloids and HTS can be treated in very similar manners. The literature demonstrates that both pathologic scars and keloids are completely different entities; they can be addressed similarly when considering treatment options.

Although various treatment options are available, there is no consensus as to what the optimum approach should be. In an effort to augment standard treatment modalities by adding emerging ther-

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TABLE 1. Keloids Versus Hypertrophic Scars

Lesion	Hypertrophic Scar	Keloid
Appearance	Erythematous and raised	Raised
Lesion confinement	Confined within wound margins	Beyond wound margins
Collagen type	Type III, parallel oriented	Type I and III, disorganized
Infiltration into surrounding tissue	No	Yes
Regression	No	Yes
Remodeling phase	Yes	No

opies, the authors review the use of antineoplastic agents (bleomycin, 5-flourouracil, mitomycin C, and IFN) in the treatment of keloids and HTS.

DISTINGUISHING HYPERTROPHIC SCARS VERSUS KEOLOIDS

As mentioned previously, HTS are usually raised, red or pink in color, pruritic, but do not extend beyond the general geographic margins of the wound. HTS primarily contain type III collagen, oriented parallel to the epidermal surface with abundant nodules and large extracellular collagen filaments. Contrastingly, keloids continue to evolve over time without a quiescent or regressive phase and do infiltrate the surrounding tissue. Keloids are primarily composed of abnormally thick, irregularly branched and septal, disorganized type I and III collagen bundles with no nodules and excess myofibroblasts.^{16–18} Keloids overproduce multiple fibroblast proteins, indicating persistence of wound healing or even failure of down-regulation of wound healing cells.^{6,19,20} In addition, keloids are not triggered to entering the final phase of wound healing, the “Remodeling” phase, whereas HTS will eventually do so^{6,19,20} (Table 1).

DEMOGRAPHICS

The majority of individuals who develop HTS and keloids are young with age ranging from 10 to 30 years old. The elderly rarely develop these lesions.²¹ This observation in part is attributed to the fact that young individuals are more prone to trauma, their skin generally possesses more elastic fibers resulting in greater tension, and the rate of collagen synthesis is greater in younger individuals.^{22,23} Keloids are more common in patients with darker skin with an incidence of 4.5% to 16% in the black and Hispanic population.^{23,24} As previously mentioned, men and women are equally affected.¹²

ETIOLOGY

Several factors contribute to the etiology of keloids and HTS formation. Genetic predisposition and dermal violation are the key factors for the development of keloids. The genetic link to keloids continues to be researched, and patients with keloids usually have a positive family history.^{25,26} In 14 large pedigrees, Marneros et al described familial keloids as an autosomal dominant entity with incomplete penetrance and variable expression.²⁷ Tension has been positively identified as a predisposing factor for keloids and hypertrophic scars.²⁸ The loss of tissue increases tension when an attempt to close the wound is made. Surgeons should keep in mind that incisions should be placed so that the underlying musculature applies the least tension across the wound surfaces.²⁹

At the histologic level, the greater the concentration of melanocytes that exist in an anatomic region, the greater the incidence of keloid formation. This observation is supported by the fact that

keloid formation is rare on the palms and soles where melanocytes concentration is minimal.³

It is also noted that fibroblasts persist longer in keloids than in normal scar tissue.⁷ They also show a greater capacity to proliferate and produce high levels of collagen (mainly type I), elastin, fibronectin, and proteoglycan.^{20,30–34} Some studies have demonstrated an abnormal balance between proliferative and apoptotic cell death in fibroblasts derived from keloids.^{35,36}

It is known that growth factors such as transforming growth factor-B (TGF-b), platelet derived growth factor (PDGF), and insulin-like growth factors (IGF) modulate wound healing. Several studies have associated TGF-b with increased collagen or fibronectin synthesis by keloid fibroblasts.^{37–39} TGF-b strongly promotes the chemotaxis of fibroblasts to the site of inflammation to begin the production of extracellular matrix proteins. The activity of TGF-b is normally turned off when repair is complete; however, dysregulation can occur leading to abnormal fibrosis and keloid formation.⁴⁰ IGF-1 increases the expression of types I and III procollagen and the IGF-1 receptor has been shown to be “overexpressed” in keloid fibroblasts.^{9,41}

Generally, collagen synthesis in keloids is approximately 20 times greater than in normal, unscarred skin and 3 times higher than in HTS.²³ The major type is type I, but type III is also implicated in the formation of keloids while the ratio of type I to type III was significantly elevated in keloids.⁴² Other factors that have been proposed to be responsible for keloid formation are: hypoxia, high levels of nitric oxide during wound healing, and a possible immune response to sebum.^{43–45}

Studies have supported the hypothesis that immunologic responses play a role in keloid formation.^{46,47} A study indicated a genetically determined risk factor for HTS to be located in the HLA region.⁴⁷ Studies have also shown heavy deposition of IgG, IgA, and IgM in keloid tissue.^{48–50} Autoimmune antifibroblast antibodies found on the keloidal tissue were thought to have a fibroblast stimulating role in the pathogenesis of keloids.⁷

CLINICAL MANIFESTATIONS

The clinical manifestations of keloids and HTS are variable, and correlate with the variety of causes that initiate this formation. It is established in the literature that keloids and HTS may not develop for several months after skin disruption. Severity of skin injury does not correlate with the formation of a keloid, thus a minor wound can cause a large lesion. Keloids and HTS are independent of motion and can develop anywhere on the body. Keloids, in particular, preferentially develop on earlobes, shoulders, and presternal skin.⁷ They range in size from papules to football size or larger. Initial lesions are erythematous and become brownish-red, then pale as they age. They are void of hair follicles or other glands and usually project above the level of the surrounding skin. HTS, however, rarely elevate more than 4-mm above the skin surface.⁵¹

PHARMACOLOGIC THERAPY

A comprehensive review of all current treatment modalities is beyond the focus of this paper as the authors' goal is to summarize the etiology and pathophysiology of HTS and keloids and then to indicate the role that antineoplastic agents might play in the management of pathologic scarring. Currently, common treatment modalities include: surgical excision, steroid injections, silicone sheeting, cryotherapy, radiation therapy, and compression therapy.²

Interferon

IFNs are cytokines that exhibit antiproliferative, antifibrotic, and antiviral effects in several cell types. They are widely used in a variety of clinical scenarios such as condylomata accuminata, basal

cell carcinoma, high risk melanoma, HIV associated Kaposi sarcoma, viral hepatitis, and in the presence of keloids as adjuvant therapy.⁵² IFNs decrease the overproduction of collagen and glycosaminoglycans by scar-forming fibroblasts and increase the level of collagenase activity.⁵³ Studies have shown that IFN- γ promotes myofibroblast apoptosis and inhibits its differentiation, while IFN- α inhibits wound contraction in vitro.^{54,55} The use of IFN has been associated with mild side effects such as flu-like symptoms. These symptoms can be relieved by prophylactic administration of 500 mg acetaminophen.^{7,56,57}

There is a mystery surrounding the full effects of IFN on keloids and HTS. After Berman and Duncan observed that IFN decreased collagen production in vitro, they introduced its use for the treatment of keloids in 1989.^{58–62} Since then, intralesional administration of IFN had been evaluated as a monotherapy as well as in conjunction with other therapeutic modalities. In initial studies, Berman and Duncan injected intralesional IFN- α twice and observed a decrease in the keloid surface area by 41%; however, the keloid recurred and became resistant to further IFN treatment.⁵⁸ This case report was the initiative for several clinical trials that tested the effect of IFN- γ and IFN- α on keloids. In a study made by Berman and Flores, injection of IFN- α into keloidal excision sites resulted in significantly lower recurrences (18.7%) compared with triamcinolone acetonide (58.5%) and excision alone (51.2%).⁶³ Additionally, a study by Larrabee et al showed a moderate size reduction and softening in 7 keloids after weekly intralesional injections of IFN- γ .⁶⁴ A double blinded clinical trial by Granstein et al showed early decreases but late recurrences in 6 of 8 keloids treated with IFN- γ alone.⁶⁵ Broker et al observed short-term improvement in 3 of 7 keloids treated with weekly INF- γ .⁶⁶ Lastly, in an uncontrolled series of 30 patients treated with CO₂ laser excision of keloids and adjuvant intralesional INF- α , Conejo-Mir et al found 66% success rate on long-term follow-up.⁶⁷

Although some studies have shown keloid remission following intralesional injection of IFN, other data in the literature do not favor IFN alone as a potent treatment approach for keloids and HTS. A prospective-controlled clinical trial by Davison et al investigated the efficacy of IFN- α as postexcisional adjuvant therapy for keloids. The recurrence rates were 7 of 13 for the IFN- α group as compared with 4 of 26 for the triamcinolone group.⁶⁸ Additionally, some placebo-controlled trials failed to demonstrate efficacy in keloid management.^{69–71} Another placebo-controlled trial by Al-Khawajah did not show any benefit from intralesional injection of IFN- α and suggested that injection in conjunction with surgery could improve the outcomes.⁷¹

On an experimental level, IFN has clearly shown potential efficacy as an antifibrotic agent which can potentially decrease the overproduction of collagen and glycosaminoglycans and simultaneously normalize the low level of collagenase activity observed in keloidal tissue.⁵³ Findings from clinical trials reveal conflicting data, however, for the efficacy of IFN on keloid treatment. Further clinical investigation, in terms of controlled, randomized trials, should take place to enrich the existing data and illuminate the prospective of IFN as a potent therapeutic agent in the treatment of keloids and HTS.

Bleomycin

Bleomycin was approved by the food and drug administration in 1975 for the treatment of several malignancies including: squamous cell carcinoma, testicular cancer, and malignant lymphoma.⁷² Bleomycin is a secondary metabolite of a strain of streptomyces obtained from soil and has antitumor, antiviral, and antibacterial activity. It acts by binding to DNA, both double stranded and single stranded, causing strand scissions.⁷²

In addition to the aforementioned applications, the use of intralesional bleomycin has been documented for the treatment of keloids and HTS with promising results.⁷³ Some studies have investigated the effects of intradermal bleomycin administration in the skin of healthy individuals.^{74,75} From a histologic point of view, bleomycin has been found to cause necrosis of keratinocytes and can also induce inflammatory infiltrate along with expression of various adhesion molecules.⁷⁴ Furthermore, the presence of apoptotic cells has been noted in common warts treated with bleomycin.⁷⁵ Despite these findings, however, the exact mechanism by which bleomycin induces keloid and HTS regression is not entirely clear. Concerning the side effects of intralesional administration of bleomycin, there are only a few cases where hyperpigmentation developed in the healthy skin surrounding the lesion and dermal atrophy.^{73,76} Systemic side effects of bleomycin, hepatotoxicity, and pulmonary fibrosis, are not of concern with intradermal/intralesional administration alone. The concentration and dosage is not sufficient to incite systemic problems.⁷⁷

A study by Espana et al used intralesional bleomycin to treat keloids and HTS in 13 patients using a multiple puncture method.⁷³ In each case the maximum dose applied was 2 mL/cm² of skin treated at a concentration 1.5 IU/ml and a maximum of 6 mL of bleomycin was given per session. The clinical response was impressive in all cases. Complete flattening (100%) was seen in 6 cases, highly significant flattening (>90%) was observed in 6 cases, and significant flattening (75%–90%) in 1 case. Only 2 patients presented with recurrences, a small nodule, 10 and 12 months, respectively, after the last administered dose. In a French study by Bodokh et al, intradermal administration of bleomycin was used for the treatment of 31 keloids and 5 HTS. Within one month, 3 to 5 intralesional infiltrations of bleomycin were administered. Total regression was noted in 84% of the patients. Keloid volume and functional impairment was significantly reduced.⁷⁸ Another study by Naeini et al comprised 45 patients with HTS and keloids which were randomly divided into 2 groups. Group A was treated with bleomycin tattoo and group B with cryotherapy combined with intralesional triamcinolone injections. Four therapeutic sessions at 1 month intervals took place, and patients were followed for 3 months after the end of treatment. Although responses were similar in both groups for lesions less than 100 mm² (88% regression), the larger lesions had a therapeutic response to bleomycin statistically significantly better than to cryotherapy combined with intralesional triamcinolone injection ($P < 0.03$).⁷⁹

A study by Aggarwal et al revealed interesting results. The study included 50 patients with keloids and HTS. All were treated with intralesional bleomycin through multiple superficial punctures. Three applications were given at intervals of 15 days, each followed by a fourth and final application 2 months after the last application. Of 50 patients, complete flattening was observed in 44%, significant flattening in 22%, adequate flattening in 14%, and lastly no response in 20%. Pruritus was relieved completely in 89% of patients.⁸⁰ Saray et al evaluated the effect of bleomycin on 15 keloids which had previously been unsuccessfully treated with injected triamcinolone acetonide. Multiple jet injections of 0.1 mL of bleomycin (1.5 IU/mL) were administered to each lesion. Once again, favorable results were noted. Complete flattening (100%) was observed in 73.3% of the lesions, along with highly significant flattening (>90%) in 6.7% of lesions, 13.3% significant flattening (75%–90%), and 6.7% showed moderate flattening (50%–75%).⁷⁶

In summary, it appears that intralesional bleomycin is a promising treatment option for keloids and HTS. Findings reveal that bleomycin not only improves cosmetic appearance but also relieves patients from pruritus and pain, symptoms often associated with pathologic scars.

Mitomycin C

Mitomycin C (MC) is an antineoplastic agent that inhibits DNA synthesis by forming a cross-linkage of strands of the DNA double-helix so that the neoplastic cell cannot proliferate.⁸¹ When administered intravenously, MC has been proven to be useful in the treatment of gastric, pancreatic, bladder, breast, cervical, eye, liver and prostatic cancer.⁸¹ In addition to the aforementioned pathology, topical administration of MC is used in glaucoma filtering surgery to prevent fibroblast proliferation and thus, decrease scar tissue formation at the extraocular drainage site so it remains open leading to a decreased rate of glaucoma recurrence.⁸² Some mild side effects of local MC application have been reported such as hyperpigmentation and skin atrophy.⁸³

In an *in vitro* controlled study, Simman et al evaluated the effect of MC on keloid fibroblasts.⁸¹ The team obtained keloid fibroblasts from 5 patients and exposed the cells to MC. A control group of normal and keloid cells was treated with phosphate buffered saline only. The DNA synthesis pattern of untreated normal and keloid fibroblasts was significantly increased over the first 2 weeks relative to the fibroblasts treated with MC ($P < 0.01$). Additionally, contrast microscopy showed a decrease in fibroblast density during the 3 weeks after exposure for normal and keloid fibroblasts relative to untreated fibroblasts. This was confirmed by total cell counts ($P = 0.1$) and measurement of DNA synthesis. Based on their findings, Simman et al suggested that MC could be used in clinical trials after surgical excision of keloids. In a study by Talmi et al, the effect of MC application as an adjuvant therapeutic approach following keloid excision was studied.⁸⁴ Eight patients were included in the study and the keloids were excised under local or general anesthesia. Prior to skin closure, a pledget with 1 mL of MC 0.4 mg/mL was applied for 5 minutes. In the postoperative period, all patients were satisfied, although complete disappearance of the keloid was evident only in 2. Prior to excision, keloid thickness was measured and ranged from 5 to 26 mm. Following surgery and MC application at 2 months, thickness ranged from 0 to 8 mm.

Stewart et al presented their results in a series of ten patients who were all treated with surgical excision of head and neck keloids followed by application of topical MC.⁸⁵ Of 10 patients, 9 had successful excision of the keloid lesion with no recurrence in the ensuing 6 to 14 months (8 months mean). Only one patient treated with combined excision and MC application had a recurrence. In a study by Bailey et al, the authors tried to evaluate whether application of MC to the base of shave-removed keloids would prevent their recurrence.⁸⁶ Ten patients had all or part of their keloid shaved/removed. Topical MC (1 mg/mL) was applied for 3 minutes. The same application was repeated 3 weeks later. Photos of the keloids were taken before treatment, and the patients were reviewed every 2 months for a total of 6 months, at which point a final photo of the keloid was taken. The outcomes were scored on a scale from 0 (disappointing) to 10 (delighted) by the patients and the clinical trials unit staff. The pretreatment and 6-month posttreatment photos were also evaluated by 2 dermatologists. Of the 10 patients 4 were delighted and only 1 was disappointed. On average, there was an 80% satisfaction rate.

Sewall et al evaluated the effect of topical MC on full-thickness skin wound contraction in hairless mice. The rate of wound contraction in the treated group was significantly slower than in the control group. Also, the treatment group had a significantly larger wound surface area after 1 month, whereas wound area in the control group contracted approximately 9 times more rapidly than in the treatment groups.⁸⁷

The aforementioned studies indicate that MC is a promising approach for the treatment of keloids and HTS, especially as an adjuvant therapy postexcision. There is mounting evidence that

although some very positive results have been reported, trials should be conducted to assess the optimum dose, duration, and frequency of MC treatment to establish the best outcomes. Further studies should also be designed to compare MC with more standard therapies.

5-Fluorouracil

5-Fluorouracil (5-FU), a pyrimidine analog widely used in cancer chemotherapy and in glaucoma surgery, has recently shown some efficacy in the treatment of keloids and HTS. Given the pathophysiologic importance of TGF- β in keloid and scar formation, molecular studies examined whether the clinical benefits from 5-FU treatment resulted from its capacity to interfere with TGF- β signaling and resulting activation of type I collagen gene expression. Through complex cellular signaling pathways, cellular level evidence is provided to explain the observed clinical benefits of 5-FU in the treatment of keloids and HTS.⁸⁸ Several studies exist which show the benefit that 5-FU has on keloids and HTS. The approach studied is often intralesional injection, or occasionally, surgical excision with a topical soak. Both approaches seem to be effective with decreasing the physical signs and symptoms of keloids and HTS and also improvement of histologic findings.

In one study by Manuskiatti and Fitzpatrick, patients with previously untreated keloidal or hypertrophic median sternotomy scars were treated with intralesional corticosteroid injection, 5-FU, 5-FU with corticosteroid, placebo, or 585-nm flash-lamp-pumped pulsed-dye laser treatments. Each patient's scar was delineated into 5 equal segments and treated with the aforementioned agents. When the main outcomes were measured (scar height, erythema, and pliability) it was noted that the 5-FU only group performed as well as all other intervention groups and did not exhibit the adverse sequelae seen in the intralesional corticosteroid group, notably hypopigmentation, telangiectasia, and skin atrophy. In addition, the 5-FU only group resulted in faster lesion resolution and scar induction resolution compared with the pulsed-dye laser group.⁸⁹

In a study by Kontochristopoulos et al, 20 patients were treated once weekly with intralesional injection of 5-FU. Biopsy specimens of some of the patients were taken pre- and postkeloid injection. The locations on the patient's varied, but no area seemed to have a higher propensity for resolution. The results were impressive. One patient showed total resolution of the keloid, 8 patients showed more than 75% improvement, 8 patients also showed 50% improvement, and 2 patients improved by 25%. Only 1 patient showed no improvement. Nine patients with short-lasting disease (<2 years) showed no relapse during the 1-year follow-up period, whereas 6 patients with long-lasting keloids (>2 years) relapsed. Histopathology was consistent with the improvement noted in the clinical findings. Biopsy specimens taken after 6 injections showed the following: diminution of the amount of hyalinized collagen fibers, diminution of the nodular concentric arrangement of the collagen fibers, less prominent vascularity, flattening of the dermal papillae without any signs of atrophy, pigmentary incontinence, reduction of Ki-67 expression, and slight reduction of TGF- β expression after treatment. Ki-67 is a marker associated with cell proliferation. Its overall reduction helps elucidate the mechanism of action on overall cellular proliferation in the presence of 5-FU.⁹⁰ This study along with others continues to support the notion that intralesional injection is appropriate to treat keloids and hypertrophic scars.^{91,92} Fitzpatrick reported improvement in the majority of 1000 patients treated with intralesional 5-FU injection; however, many of the cases had other treatment modalities incorporated, including: pulsed dye laser irradiation and/or intralesional corticosteroid injection.⁹³

In one report, Goldan et al reported using intralesional 5-FU to treat a patient who developed keloids and HTS status post facial dermabrasion. Despite therapy with topical silicone sheets and

TABLE 2. Cost of Antineoplastic Agents

Drug and Concentration	Cost per Vial of Dose From Column 1 (\$)	Dose per Lesion	No. Treatments
Kenalog, 40mg/mL	7.26	10 mg/cm of lesion	2–6
IFN- α , 18 million units/0.5 mL	215.55	1 million units/cm of lesion	2–4
Bleomycin, 15 units/10 mL	25.83	1.5 units/cm of lesion	3–5
Mitomycin C, 5 mg/mL	12.07	0.3–2 mg/lesion	1
5-FU, 500 mg/mL	1.83	50–100 mg/lesion	1–6

Kenalog (Bristol-Myers Squibb, New York, NY): triamcinolone.
5-FU indicates 5-fluorouracil.

intraleisional methylprednisolone acetate in multiple sessions spanning 2 months, the patient was noted to only have marginal improvement in the color and size of the lesions. No improvement in the fibrous texture of the scars and almost no relief from the pain and itching symptoms were noted up to 4.5 months status post initial treatment. At this point, intraleisional 5-FU injections were initiated with postinjection silicone sheets applied. The patient underwent 6 injections over a 3 month span. At a follow-up session 7 months after the last 5-FU injection, there was marked improvement in the size, color, and texture of the scars, with the patient reporting that the pain and itching had fully resolved.⁹⁴

Recently, Haurani et al conducted a prospective study to evaluate the efficacy of 5-FU in the treatment of keloids and HTS. Patients were divided into 2 groups, and their pathologic scars were treated. Patients in the keloid group ($n = 31$) underwent keloid excision followed by a series of treatments with 5-FU. Patients with HTS ($n = 21$) were treated with the same series of 5-FU injections; however, they did not undergo surgical scar excision. The post-treatment follow-up interval was 1 year. Patients were followed with respect to their scar volume. In addition, a questionnaire was given to obtain subjective data concerning the patient's thoughts on their results. All of the patients had previously undergone treatment with intraleisional steroid injections, and had no resolution of clinical signs or pathologic scarring. The results of the 5-FU injections were very promising. The recurrence rate was only 19% at 1-year follow-up for the keloid group with the scar volume ranged from 150 to 525% of the postexcision baseline value. In the HTS group, 86% of patients felt that they had partial or complete improvement of their symptoms at the end of the treatment.⁹⁵

The method of application of 5-FU does not have to be only intraleisional injection. One study in particular tested excising an ear keloid and then placing a 5-FU soaked pledge against the wound for 5 minutes prior to primary closure. On the contralateral ear, the keloid was excised and a phosphate-buffered saline soaked pledge was held against the wound for 5 minutes prior to primary closure. Biopsies were taken of the control and treated scars 1 month after treatment; the biopsy specimens were then subjected to immunohistochemical analysis as well as a functional assessment of cultured keloid fibroblasts. The immunohistochemical antigens assayed were ki67 (also called MID-1; a marker of cell proliferation); vascular cell adhesion molecule-1 (a marker of inflammation); TGF-b1 (a factor involved in scarring), and CD-68 (a macrophage-specific marker). Apart from CD-68, the wounds treated with 5-FU produced scars that had a significant reduction in all the markers assayed. The keloid scar score was performed monthly on a score sheet by observers blinded as to which scar was treated. The results showed that all the scars healed well and had a lower keloid scar score (indicating improvement in the scar) in the 6 month follow up period.⁹⁶

COST

With the introduction of any new treatment modality, one must consider the cost of initiating and/or employing the new approach. After investigating average amounts of drug used per centimeter of lesion length, it was concluded that utilizing antineoplastic agents could be a cost saving treatment when combined with, or instead of, intraleisional steroid use. After careful analysis of generic drug costs at our institution, we prepared a table to compare the costs of the aforementioned antineoplastic agents and standard steroid preparation (Table 2). It can be concluded that 5-FU is an effective pharmacologic agent to use when treating pathologic scars and is substantially cheaper than Kenalog (Bristol-Myers Squibb, New York, NY) (triamcinolone).

CONCLUSION

The management of keloids and HTS continues to be a challenge for health-care providers. Potential treatment approaches and combination treatment options have been proposed in the literature with promising outcomes. The evolution of treatment choice has included molecular therapeutic modalities are being investigated. Although several studies have evaluated all of the aforementioned therapeutic options, currently no gold standard treatment for the management of keloids and HTS exists. Overall success rates and patient satisfaction seem to be slowly improving, but additional investigational studies must continue to be performed.

In investigating some of the antineoplastic agents, one seems to find a marked improvement in rates of recurrence, patient satisfaction, and overall quality of scar. In addition to all these, the antineoplastic agents seem safe to use in the management of keloids as none of the studies found any serious systemic manifestations or adverse effects.

There is mounting evidence that these drugs, used alone or in combination therapy, have the potential to be an integral part of the treatment paradigm for pathologic scars.

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