

The use of chemotherapeutics for the treatment of keloid scars

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Abstract

Keloid scars are pathological scars, which develop as a result of exaggerated dermal tissue proliferation following cutaneous injury and often cause physical, psychological and cosmetic problems. Various theories regarding keloidogenesis exist, however the precise pathophysiological events remain unclear. Many different treatment modalities have been implicated in their management, but currently there is no entirely satisfactory method for treating all keloid lesions. We review a number of different chemotherapeutic agents which have been proposed for the treatment of keloid and hypertrophic scars while giving insight into some of the novel chemotherapeutic drugs which are currently being investigated. Non-randomized trials evaluating the influence of different chemotherapeutic agents, such as 5-fluorouracil (5-FU); mitomycin C; bleomycin and steroid injection, either alone or in combination with other chemotherapeutic agents or alternative treatment modalities, for the treatment of keloids were identified using a predefined PubMed search strategy. Twenty seven papers were identified. Scar improvement $\geq 50\%$ was found in the majority of cases treated with 5-FU, with similar results found for mitomycin C, bleomycin and steroid injection. Combined intralesional 5-FU and steroid injection produced statistically significant improvements when compared to monotherapy. Monotherapy recurrence rates ranged from 0-47% for 5-FU, 0-15% for bleomycin and 0-50% for steroid injection. However, combined therapy in the form of surgical excision and adjuvant 5-FU or steroid injections demonstrated lower recurrence rates; 19% and 6% respectively. Currently, most of the literature supports the use of combination therapy (usually surgery and adjuvant chemotherapy) as the mainstay treatment of keloids, however further investigation is necessary to determine success rates over longer time frames. Furthermore, there is the potential for novel therapies, but further investigation is required to elucidate their true efficacy.

Introduction

Keloid scars have afflicted humans for many centuries, described as far back as 3000 BC in the Edwin Smith papyrus.¹ Keloids are proliferative scars, defined as benign mesenchymal tumors that extend beyond the wound margin, that do not regress spontaneously and tend to recur following excision.^{2,3} They are characterized by extensive intradermal collagen and glycosaminoglycan deposition.^{4,5}

Keloids are a common manifestation following abnormal wound healing, with an incidence of 5% to 16% in high-risk populations, which includes Africans, Asians and Hispanics.^{5,6} Although benign, keloid lesions can cause pain, paresthesia and pruritus, as well as functional and aesthetic impairment. Consequently, patients may be burdened with marked physical and psychosocial sequelae.⁷

Many studies have examined the pathophysiology of keloid scarring at the cellular level, but at present the exact underlying mechanisms are yet to be comprehensively understood. Many factors such as wound tension, skin pigmentation, genetic predisposition, immunoregulation and skin injury have been implicated in the etiology of keloidogenesis.^{3,8,9} Research into epithelial-mesenchymal interactions between keloid keratinocytes and fibroblasts has suggested that the overproduction of numerous growth factors and cytokines, such as transforming growth factor beta (TGF- β), platelet-derived growth factor, vascular endothelial growth factor (VEGF), insulin-like growth factor (IGF), interleukin 1 and 6 (IL-1 and IL-6), interferon beta (INF- β) and tumor necrosis factor alpha (TNF- α) are involved in keloid pathology.^{4,5,10} In addition, it has also been proposed that abnormalities in the apoptosis pathway may also be linked to keloid genesis; in normal wound healing, apoptosis mediates a reduction in cellularity between granulation tissue and normal scarring.⁹ Mutations in key apoptosis regulator genes, such as p53, bcl-2 and fas, have been demonstrated in keloid fibroblasts, which resulted in lower rates of apoptosis compared to normal controls.^{3,9,11} On histopathological examination, keloid scars are composed of thick bundles of closely packed type I, III, IV and V collagen and dilated vessels, both of which are arranged in a haphazard manner.^{9,12} In addition to excessive collagen production, keloid fibroblasts also synthesize more elastin, fibronectin and proteoglycan and show abnormal responses to cytokine stimulation compared to normal fibroblasts.^{3,4}

With little known regarding the exact pathophysiological events underlying this condition, the management of a keloid scar is clinically challenging. Many treatments have been advocated either alone or in combination, including

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surgical excision, intralesional chemotherapeutic injection, radiotherapy, laser therapy, cryotherapy, topical silicone, systemic chemotherapy and pressure therapy, most of which have had varying and transient success.^{10,13,14} In addition, adverse effects from the different treatments may significantly limit any benefits.¹⁵

Despite the wide range of available treatments, recurrence rates are typically 50-70%.¹⁰ At present the most commonly used treatment is intralesional corticosteroid injection, isolated or in association.^{3,5,16-18} This review will focus on the use of chemotherapeutics for the treatment of keloids and hypertrophic scars.

Chemotherapeutic drugs

It has been well established that through production of ground substance components, collagen synthesis and wound edge tension, fibroblasts are important in the wound healing response.¹⁹

At present the main classes of chemotherapeutic drugs which are used in pathological scar treatment are the antitumor/antimetabolite drugs and steroid drugs which include 5-fluorouracil, mitomycin C, bleomycin and corticosteroid. These drugs work by halting mitosis in different phases of the cell cycle and consequently inducing suppression of fibroblast proliferation.¹⁵

5-Fluorouracil

5-Fluorouracil (5-FU) is a fluorinated pyrimidine analogue with antimetabolite activity. It disrupts the interconversion of uridine into thymidine through inhibiting thymidylate synthase.^{20,21} It was originally used in the 1980's as an adjuvant to glaucoma filtering surgery and in recent years for the treatment of a variety of malignancies.^{2,20} Both *in vitro* and *in vivo* experiments have shown that 5-FU can inhibit fibroblast proliferation.^{19,22} In addition, it also has an inhibitory effect on TGF- β induced expression of the type I collagen gene.¹⁶ Consequently, several studies have investigated the potential application of intralesional 5-FU, either as an adjunct to conventional therapy or as an alternative to it, in preventing keloid development and promoting keloid scar resolution.^{23,24}

Following positive evidence regarding 5-FU's safety and efficacy in preventing scar formation after trabeculectomy surgery, Fitzpatrick began to investigate its use in hypertrophic and keloid scar therapy. Over a 9-year period, he was able to demonstrate the efficacy of intralesional 5-FU (50 mg/mL) injected into the scars of over 1000 patients as a single agent and as combined with triamcinolone acetate (TAC) (1 mg/mL), with and without concomitant use of a pulsed-dye laser.^{2,24} Most patients responded favorably to the 5-FU injections. The most significant responses were obtained with scars that were symptomatic and inflamed, whereas the older, non-inflamed, asymptomatic scars responded less. Similar findings have also been reported in another study.²⁵ It has been demonstrated that keloid and hypertrophic scars respond most effectively to intralesional 5-FU when it is given either once weekly or once every 2 weeks.^{7,16} This correlates well with the other findings of Fitzpatrick in that scar response was dramatically improved with more frequent injections.²

Nanda and Reddy treated the keloid scars of 28 patients with intralesional 5-FU (50 mg/mL) at weekly intervals for a period of 12 weeks. In 78.5% of the patients, improvement (with respect to keloid size, height, induration and associated symptoms) was more than 50%, with no patient showing failure to therapy and no signs of recurrence during a 24-week follow-up period.²² Similar findings for small keloids were reported by Gupta and Kalra.²⁶

Kontochristopoulos *et al.* did a similar study whereby they treated 20 patients once weekly for on average 7 weeks with intralesional 5-FU (50 mg/mL) injections. In 85.0% of the patients, the improvement was more than 50%. In contrast to Nanda and Reddy, one of their patients did not respond to therapy. Of the 19 patients who did, there was a 47.4% recurrence rate within 1 year. They also reported that recurrence correlated directly to keloid duration following successful treatment with

5-FU.²⁵

Manuskiatti and Fitzpatrick compared the treatment response of keloids and hypertrophic sternotomy scars to intralesional triamcinolone alone or combined with 5-FU, 5-FU single therapy and the 585-nm flashlamp-pumped pulsed-dye laser (PDL).¹⁹ All of the methods produced a statistically significant clinical improvement, however no method was found to be significantly superior.¹⁹

In contrast, Zhang *et al.* reported that the effectiveness rate of 5-FU injection alone is 62.5%, whereas the efficacy of combined 5-FU and glucocorticoids was significantly better at 92%. Other authors also reported positive effects using similar methods.^{15,21}

In a recent study, Haurani *et al.* showed that surgical excision combined with monthly intralesional 5-FU (50 mg/mL) injections, was an effective way to treat keloid scars in patients who had previously been unresponsive to corticosteroid injections. The recurrence rate was 19% at 1 year follow up.²⁰

Intralesional 5-FU is generally well tolerated, commonly encountered adverse effects include: pain at the injection site, ulceration, burning and hyperpigmentation.^{2,16,19,22,23,25} Regarding the aforementioned studies, no systemic complications of 5-FU, such as anemia, leucopenia and thrombocytopenia were reported.^{16,23}

Mitomycin C

Mitomycin C is an antibiotic that was first isolated from *Streptomyces cespitosus* by Wakaki in 1958.²⁷ It has both antineoplastic and antiproliferative properties and was initially used in 1963 by Kunitomo and Mori for the treatment of pterygium.²⁸ Since the 1980's, it has been used as an anticarring agent in ophthalmologic, airway and sinonasal surgery, as well as for the treatment of tumors of the oral cavity, lungs, pancreas, stomach and bladder.^{10,27-29} Mitomycin C alkylates and cross-links DNA at the adenosine and guanine nucleotides, therefore inhibiting DNA, RNA and protein synthesis.²⁷⁻²⁹ It has been shown to inhibit fibroblast proliferation and decrease scar formation both *in vivo* and *in vitro*.^{28,29} In addition, mitomycin C has been shown to reduce DNA synthesis and decrease the density of cultured keloid fibroblasts.¹⁰ Furthermore, Sewall *et al.* demonstrated that topical application of mitomycin C to full thickness skin lesions in mice resulted in significantly smaller rates of wound contraction.²⁹ These properties have contributed to its interest in recent years as a potential agent for the treatment of keloid scars.

In one study, Stewart and Kim treated 10 patients with topical mitomycin C (0.4 mg/5

mL) for 4 minutes following the excision of head and neck keloids. At mean follow up of 8 months (range, 6 to 14 months), there was a 10% recurrence rate.¹⁰

In contrast, when Saunders *et al.* treated post excisional keloid wound beds with topical mitomycin C (0.4 mg/mL) for 5 minutes the recurrence rate at 9 months was 28.6%. However, there was no significant difference in outcome between treated and untreated keloids ($P > 0.99$) thus the authors concluded that topical mitomycin C made no difference in the prevention of keloid recurrence following surgical excision.³⁰ Recently, Ribeiro *et al.* demonstrated that when mitomycin C was topically applied to rats it caused delayed wound healing in the first four weeks following treatment. However, after twelve weeks both the treated and untreated wounds showed the same histological characteristics.²⁷ The authors suggested that this drug delays, but does not inhibit, the final degree of fibrosis.²⁷ Similar results were found by Simman *et al.* following application of mitomycin C (0.1 mg/mL) to human keloid fibroblasts *in vitro*.³¹

When used topically, mitomycin C appears to be a relatively safe and well tolerated agent, however further studies should be undertaken to determine effective dosages and application intervals.^{10,27}

Bleomycin

Bleomycin is a cytotoxic antibiotic derived from *Streptomyces verticellus*. It has antineoplastic, antibacterial and antiviral properties and has been used for many years in dermatological practice for treating recalcitrant plantar warts, cutaneous neurofibromas and keratoacanthomas.^{4,14,32} In addition, it is frequently used for treating various malignancies.³² More recently, its use has been focused in the treatment of keloid and hypertrophic scars. The exact mechanism of action by which bleomycin resolves keloids and hypertrophic scars is unclear but several possible explanations have been proposed.¹⁴ It has been shown that cultured human dermal fibroblasts treated with bleomycin have diminished collagen synthesis, even when TGF- β 1 is applied.^{14,33} Similarly, administration of bleomycin to cultured fibroblasts has been found to cause a reduction in lysyl-oxidase levels.³⁴ Lysyl-oxidase is a cross-linking enzyme involved in collagen maturation.¹⁴ Its concentration may be normal or raised in keloid and hypertrophic scars.⁴ Furthermore, it has also been reported that bleomycin induces apoptosis.¹⁴

In 1996, Bodokh and Brun were the first to report the use of bleomycin for scar therapy. They treated 31 keloids and 5 hypertrophic scars with 3 to 5 intralesional infiltrations of

bleomycin within a 1-month period. Total regression was obtained in 84% of scars.³²

In another study, Espana *et al.* injected 1.5 U/mL bleomycin into keloid and hypertrophic scars of 13 patients using a multiple needle puncture approach. Patients received between 1-5 treatments, each session held 1-4 months apart. All patients were relieved of pruritus after the first session. Complete flattening of the scar was achieved in 53.8% of patients and in the other 46.2% of patients there was a >75% resolution in scar thickness. At 12 months follow up, there was a 15.4% recurrence rate.³² Using a different approach, Saray and Gulec administered monthly intralesional bleomycin (1.5 U/mL) into 15 keloid and hypertrophic scars using a jet injector. Here, 73.3% of scars became completely flat and in the other 26.7% there was >50% reduction in thickness. During the mean follow up period of 19 months, there were no reported recurrences.¹⁴

More recently, Naeini *et al.* compared the efficacy of bleomycin tattoo monotherapy with that of cryotherapy combined with intralesional triamcinolone (TAC) injection. In the cryotherapy combined with TAC group, lesions less than 100 mm² showed a significantly better response than larger lesions ($P=0.007$), whereas in the bleomycin group, the size of lesion did not affect the rate of resolution. There was no statistical difference between the two groups in lesions less than 100 mm². However in larger lesions, the therapeutic response to bleomycin was significantly better.⁴ In contrast to the study by Espana *et al.*, 22% of patients in the bleomycin group remained symptomatic.

The most commonly encountered side effects include: pain, superficial ulceration and crusting at the sites of injection, transient hyperpigmentation (seen in skin phototypes III and IV) and dermal atrophy.^{4,14,32} It is known that systemic administration of high dose bleomycin can cause pulmonary, renal and cutaneous fibrosis, hepatotoxicity and bone marrow suppression. At present, no systemic toxicity has been reported with low doses of this drug.¹⁴

Corticosteroids

Corticosteroids have been used for the treatment of keloid and hypertrophic scars since 1960.³⁵ Many different corticosteroids are used clinically, with intralesional triamcinolone acetate (TAC) being the most common, whether alone as a monotherapy or combined with another type of treatment.^{17,35} All the literature relating to the role of TAC in keloid and hypertrophic scar therapy suggests that a dose of 10-40 mg/mL is required to be effective.⁷ The

recommended treatment interval has arbitrarily varied from intervals of 4 to 6 weeks; given for a period of several months or until the scar is flattened.¹⁶

Intralesional corticosteroid administration has shown a clinical efficacy of 50-100% and a recurrence rate ranging between 9% and 50%.^{16,35}

There are numerous reported mechanisms by which corticosteroids influence scar formation. Some of the described modes of action include: reduction in fibroblast proliferation, suppression of components involved in the inflammatory response, attenuation of pro-collagen and ground substance synthesis and decreased endothelial budding.^{17,35-37} In addition, many studies have demonstrated that corticosteroids regulate the expression of numerous growth factors that are involved in wound healing, such as TGF- β , insulin-like growth factor-1, VEGF and alpha-globulins.^{17,35,38} Carroll *et al.* found that application of TAC to *in vitro* human dermal fibroblasts obtained from normal skin and keloid scars caused the production of basic fibroblast growth factor (bFGF) and TGF- β 1 to increase and decrease respectively.³⁵ Recently, Wu *et al.* found that dexamethasone retarded keloid fibroblast proliferation and suppressed endogenous VEGF-A mRNA expression.⁵ VEGF is a proangiogenic cytokine which promotes neo-vascularization and cell growth during wound healing. *In vitro* studies have indicated that VEGF expression is higher in keloid fibroblasts compared to controls.^{5,39} Corticosteroids exert their effects through binding to a glucocorticoid cytoplasmic receptor, which ultimately influences the transcription of various genes.

In studies where intralesional TAC has been used as a monotherapy, it has been shown to cause a statistically significant decrease in keloid height, length, width, associated pruritus and erythema, and improves pliability.^{7,16} In addition, subjective and objective improvements in keloid appearance have also been noted in patients treated with intralesional TAC.^{7,16}

However, in studies where corticosteroids have been used in combination with other modes of therapy, such as 5-FU, IFN- α 2b and 585-nm flashlamp-pumped pulsed-dye laser (PDL), the measured parameters, which included scar height, length, width, volume, pliability, associated erythema and pruritus, and subjective and objective assessment of improvements in keloid appearance, all showed statistically significant improvements compared to patients treated with TAC monotherapy.^{7,16,35}

TAC has also been found to show efficacy when used as an adjunct to surgical excision.³⁶ Using this method, recurrence rates are on average less than 50%.³⁵ It has been suggested that surgical excision with intraoperative

injection of intralesional TCA followed by weekly injections over a 2 to 5 week period and then monthly injections for 4 to 6 months may produce optimal results.³⁵ Using a similar approach, Hamrick *et al.* reported a 6% recurrence rate at 6 months follow up when they treated paediatric earlobe keloids with intralesional TAC preoperatively, intraoperatively and at 4 weeks post-operatively.⁴⁰

Donkor described a technique of injecting intralesional TAC (40 mg/mL) into head and neck keloid scars at 10-14 days post-operative and then at 4-week intervals on 2 additional occasions. At 2 years follow up, there was no recurrence.³⁶

Despite the benefits of intralesional corticosteroids, several adverse side effects have been reported, which include altered pigmentation, telangiectasia, skin atrophy, injection pain, ulceration and cushingoid habitus.^{4,7,16,35} It has been suggested that the combined use of intralesional 5-FU and low-dose corticosteroid may yield fewer undesirable side effects compared with intralesional corticosteroid monotherapy.²³ Furthermore, lignocaine anesthesia may be co-administered with intralesional TAC to reduce injection pain.³⁵

On account of their side effect profile, the use of topical steroids was proposed as an alternative to intralesional steroids. However, recently it was demonstrated that topically applied steroids failed to diminish scar formation.¹⁵

Potential therapies

In addition to the aforementioned chemotherapeutic agents, there are numerous alternative pharmacological agents that are currently being investigated for the management of hypertrophic scars and keloids. These include imiquimod, colchicine, botulinum toxin, tamoxifen citrate, and angiotensin converting enzyme (ACE) inhibitors.⁴¹

Imiquimod is a topical therapeutic agent that acts as an immune-response modulator by inducing expression of interferon alpha and gamma (IFN- α , γ), tissue necrosis factor alpha and interleukins -1, -6, -8 and -12.^{6,9} Jacob *et al.* found that imiquimod significantly altered pro-apoptotic gene expression in keloid tissue.⁹ From its ability to induce IFN- α and γ expression, which in turn inhibits human fibroblast collagen production, studies have been undertaken to see if it could be used as an adjuvant to surgical excision. The results have been variable, with some studies reporting low rates of recurrence, while others report high rates.^{13,42}

Colchicine is an antimitotic agent commonly used for cancer therapy because of its ability to inhibit collagen synthesis, cause microtubule

lar disruption and increase the activity of collagenase.^{21,41} Peacock *et al.* studied the effects of colchicine in 10 patients with scars and reported positive results. However, because of its narrow therapeutic window its application is restricted.²¹

Through its ability to reduce wound edge tension, there has been recent interest in the potential role of botulinum toxin type A as a therapeutic agent for reducing scar tissue formation.⁴¹ Zhibo and Miaobo carried out a twelve patient study whereby they administered intralesional botulinum toxin type A (35 U/mL) at 3-month intervals for a maximum of 9 months. Good results were obtained in all of the patients and there were no serious adverse sequelae. Keloids of long duration and large size were responsive to botulinum toxin type A and after one year follow up there was no evidence of recurrence.⁴³

Transforming growth factor (TGF) β 1 is a key cytokine involved in wound repair. It has been demonstrated that both TGF- β 1 and β 2 are overproduced by keloid fibroblasts compared with normal fibroblasts.^{44,45}

Tamoxifen citrate is a synthetic anti-estrogen, which through its ability to modulate the synthesis of multiple growth factors has been shown to inhibit keloid fibroblast proliferation and decrease collagen production.⁴⁶ Recent keloid fibroblast culture studies have shown that tamoxifen causes a dose-dependent reduction in the production of TGF- β in these cells.^{44,47}

The local renin-angiotensin system is also known to play a role in the control of collagen biosynthesis and wound healing. When Ardekani *et al.* topically applied captopril, a ACE inhibitor, to New Zealand white rabbits, they effectively prevented hypertrophic scar formation. Recently, they reported the first successfully treated human case.⁴⁸

In addition to the above, research evaluating the use of camptothecin and DHMEQ as anticancer treatments has been conducted.^{3,37}

Zhang *et al.* studied the effects of camptothecin (CPT), a topoisomerase I inhibitor, on collagen synthesis in cultured dermal fibroblasts obtained from normal skin and keloid scars. Here, the keloid fibroblasts showed a dose-dependent reduction in synthesis of type I collagen without significant cellular toxicity.³

Makino *et al.* found that dehydroxymethylpoxiquinomicin (DHMEQ), a NF- κ B inhibitor, markedly reduced keloid fibroblast proliferation and type I collagen expression *in vitro*.³⁷ Nuclear factor kappa B (NF- κ B) is a transcription factor involved in the regulation of genes associated with the immune and inflammatory pathway, cellular proliferation and apoptosis. Recently, it has been reported that the NF- κ B pathway is also involved in keloid pathogenesis.

Further investigation of these two novel

therapies is required to elucidate their true efficacy.

Conclusions

Although the exact mechanisms which underlie the physiopathogenesis of keloid scars are yet to be fully understood, a variety of therapies have been tested in an attempt to combat the characteristic aggressive and expansive nature of these benign cutaneous tumours.^{4,19} Many of the chemotherapeutic agents that have been used in the treatment of keloid scars, work by modulating tissue repair. Through direct and indirect effects on dermal fibroblast proliferation and collagen synthesis, many of these agents have proved quite effective at preventing recurrence and improving the aesthetic features of the scar. However, at present no one single agent has demonstrated the ability to cause complete scar resolution and thus the treatment of keloid scars and hypertrophic scars still presents a major therapeutic dilemma.¹⁵ In addition to problems with drug efficacy, intolerance and side effects, many of the studies themselves have limitations. For example, there is a significant variation in study design, size and methods of classifying the groups, with many combining both hypertrophic scars and keloids when describing the treatment regimens.¹⁸ Many of the studies treat all scars with the same regimens even though they vary according to size and age; potentially a standardized grading system would allow for more objective treatment comparisons. The criteria used for patient self-assessment and observer assessment of scar improvement needs to be more clearly clarified. Furthermore, there has been considerable variation in the follow-up period post treatment and many studies have problems with patient compliance during this period.¹⁸ At present, since there is no optimal treatment modality, all potential adverse effects should be explained to the patient when deciding on the most appropriate therapy so that compliance is improved.

Currently, the majority of the literature supports the use of combination therapy as the mainstay treatment of keloids.⁴⁰ Many of the combination therapies, such as surgical excision combined with adjuvant intralesional TAC, or combined 5-FU, TAC and 585 nm-PDL have shown greater efficacy and fewer side effects when compared to controls. However, further investigation will be necessary to determine success rates over longer timeframes.⁴⁹

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