

CASE REPORT

Intralesional 5-fluorouracil in the treatment of keloid scars

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SUMMARY

Two patients with keloid scars are described. The first patient presented with extensive keloid scarring on both cheeks secondary to acne. The second patient developed a keloid scar on her chest following excision of a mole. Both patients' scars were diagnosed clinically and treated with fortnightly injections of a mixture of 5-fluorouracil and betamethasone acetate and betamethasone sodium phosphate. At each injection session up to 1.6 mL of 5-fluorouracil at a concentration of 500 mg/10 mL and 0.4 mL of betamethasone acetate and betamethasone sodium phosphate (as betamethasone acetate 3 mg in suspension and betamethasone sodium phosphate 3.9 mg in solution) were used. Multiple treatments were required to obtain resolution of the keloid scars. Improvement was maintained in both patients at 1 year post treatment.

Key words: cytotoxics, hypertrophic scars.

INTRODUCTION

The treatment of keloid scars poses a therapeutic challenge for the clinician. There is no entirely satisfactory method for all lesions. Current treatment protocols are individualized and are usually based on a combination approach that includes surgical, medical and physical treatments.

The pathophysiological mechanisms that lead to keloid formation remain unclear; thus treatment is often inadequate. However, it is known that keloid fibroblasts proliferate faster than normal fibroblasts and produce more collagen types 1 and 3 messenger (m)RNA.¹

5-Fluorouracil (5-FU) is enzymatically converted intracellularly into its active substrate, which is, instead of uracil, ultimately incorporated into DNA, thus inhibiting DNA synthesis.² Rapidly proliferating cells, such as fibroblasts that are synthesizing increased amounts of DNA are preferentially targeted by 5-FU. Both fibroblast proliferation and fibroblast-populated collagen lattice show dose-related decline with fluorouracil *in vitro*. A potential role for 5-FU in preventing keloid development and promoting keloid scar resolution has recently been suggested.¹

This report shows the effect of intralesional injections of 5-FU in conjunction with a very low concentration of betamethasone (5.7 mg/mL) in promoting the resolution of keloid scars in two patients, a 22-year-old man with facial keloid scarring and a 23-year-old woman with a keloid scar on the chest.

CASE REPORTS

Case 1

A 22-year-old man presented with a 7-year history of facial acne causing extensive keloid scarring on both cheeks. His acne was treated with oral erythromycin and oral isotretinoin, which arrested further development of facial acne and, subsequently, further keloid scar formation. One year later the patient presented for treatment of his facial keloid scars. The scars were initially treated with intense pulsed-light therapy, in combination with silicone sheets and gel for several months, without effect. Hence, medical treatment was undertaken using intralesional injections of a mixture of 5-FU, 1.6 mL at a concentration of 500 mg/10 mL (David Bull, Mulgrave North, Vic., Australia) and betamethasone 0.4 mL at a concentration of 5.7 mg/mL as betamethasone acetate 3 mg, in suspension, and betamethasone sodium phosphate, in solution (Celestone Chronodose, Schering Plough, Baulkham Hills, NSW, Australia) (5-FU/BB). Intralesional injections of 5-FU/BB were administered using a 1-mL Luer lock syringe with a 30-gauge needle, at 1 cm intervals along the scar in quantities large enough to cause slight blanching. The total dose of 5-FU never exceeded 80 mg per treatment session. Before each injection of 5-FU/BB the patient received a local anaesthetic ring block using 1% lignocaine with adrenaline 1:100 000. The treatments

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were well tolerated. Side-effects were stinging that was experienced once the effect of the local anaesthetic had worn

off (and therefore attributed directly to the injected 5-FU) and, subsequently, hyperpigmentation that was treated with hydroquinone lotion. Regular blood screening for signs of bone marrow depression showed no change in the patient's blood count before treatment, during the course of treatment or after the last treatment and in particular there were no decreases in the patient's white blood cell count.

The patient received a total of 14 injections over a period of 18 months. A maximum of 2 mL of the 5-FU/BB mixture, as described above, was used at each treatment session. The total amount of 5-FU used was 1120.00 mg and the total amount of betamethasone used was 20.02 mg. A 50% reduction in the size of the keloid scars was noted by the fifth treatment and, by the ninth treatment, resolution of 90% of the keloid scarring had occurred (Fig. 1) At 1 year after the last injection the patient's keloid scar volume remains stable without any further increase in scar formation.

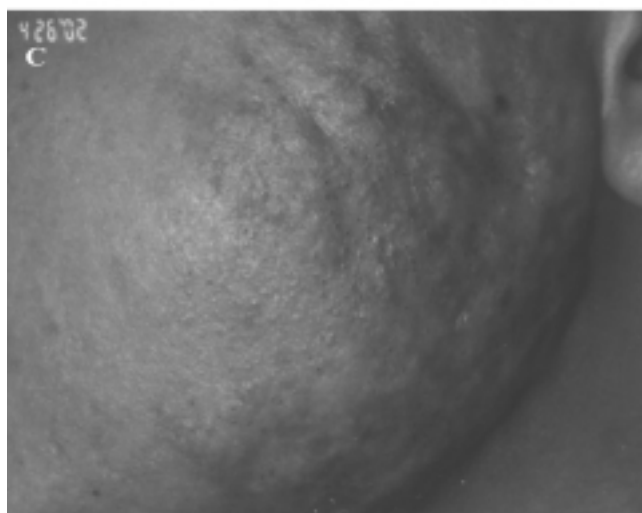
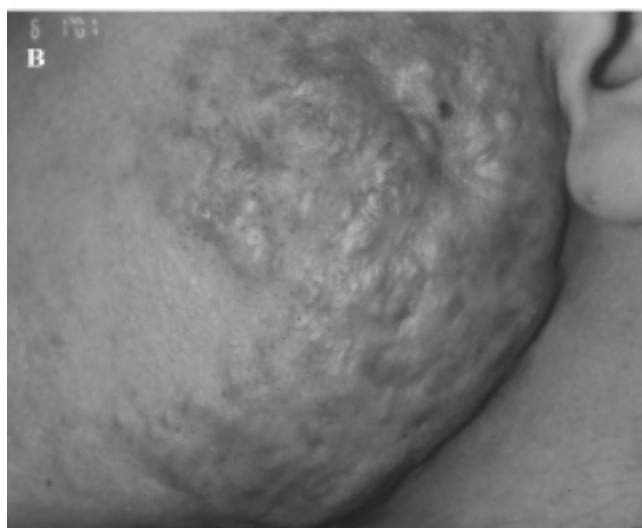
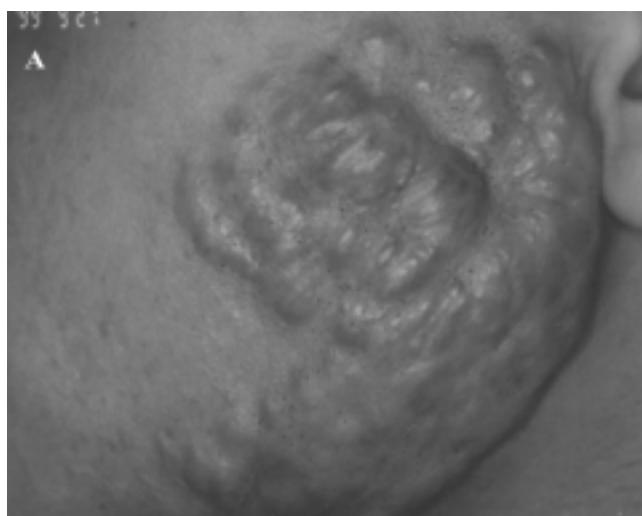


Figure 1 Patient 1 (a) before, (b) half-way through and (c) at the end of treatment with fluorouracil and celestone chronodose.

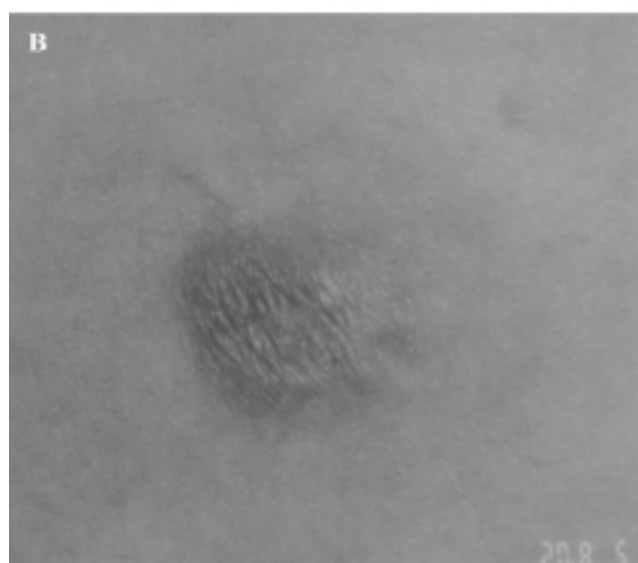
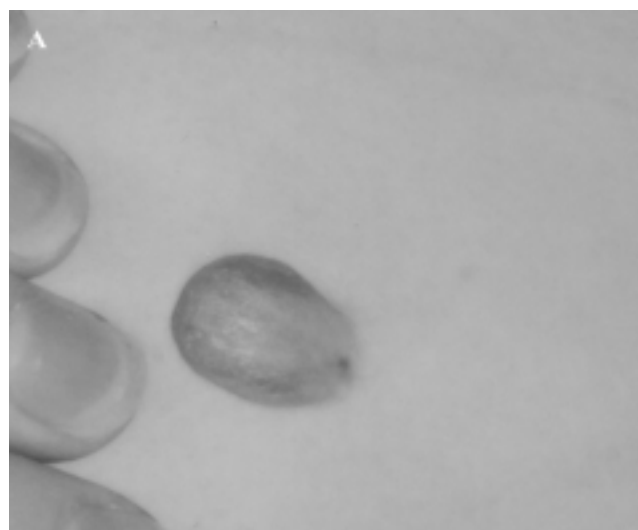


Figure 2 Patient 2 (a) before and (b) after treatment of chest wall keloid.

Case 2

A 25-year-old Anglo-Saxon woman noticed the development of a keloid scar on her right chest wall after the excision of a mole. There was a positive family history of keloid scar formation. The patient had not received any treatment before presentation.

The keloid scar was injected with a combination of 5-FU (either 0.8 or 1.6 mL at a concentration of 500 mg/mL) and betamethasone (either 0.2 or 0.4 mL at a concentration of 5.7 mg/mL) on a fortnightly basis. A maximum of 2 mL of 5-FU/BB was used at each treatment session, but towards the end of the treatment course a total dose of only 1 mL per session was used. Topical anaesthetic cream consisting of lignocaine, prilocaine (eutectic mixture) 5%; 1:1 oil in water emulsion (EMLA; AstraZeneca, Sydney, NSW, Australia) was used before injecting local anaesthetic into the area in the first two treatment sessions. Local anaesthetic consisting of 1% lignocaine and adrenaline 1:100 000 was given before all intralesional injections of 5-FU/BB. The patient received a total of five injections before any noticeable change in the keloid scar size was achieved. By the tenth injection the keloid had completely flattened and scar tissue was no longer palpable (Fig. 2). A total dose of 320 mg of 5-FU was given. Side-effects consisted of one episode of ulceration that healed with scabbing in 2 weeks and was followed by hyperpigmentation. The hyperpigmentation resolved spontaneously without need for medical intervention. Treatment was recommenced after the ulcer had healed and the patient showed no further adverse effects to subsequent injections of 5-FU/BB.

Follow up at 1 year after the last injection was received confirmed that the scar had not regrown.

DISCUSSION

As one of the oldest chemotherapy drugs, 5-FU is used against many malignancies. It has been injected intralesionally for the treatment of nodular basal cell carcinoma and keratoacanthoma.³⁻⁵ In addition, studies suggest that it is effective in treatment of keloid scars.^{6,7} Intralesional injection of 5-FU 50 mg/mL (80%) in combination with triamcinolone 10 mg/mL (20%) resulted in regression without recurrence of all keloid scars <2 cm in diameter.⁷ Using a similar combination we found it to be effective in the treatment of both small and large keloid scars.

Administration of 5-FU should be under strict medical supervision. Contraindications to its use such as existing bone marrow depression, severe intercurrent infection, pregnancy and lactation should be excluded before the commencement of treatment. As systemic 5-FU can cause anaemia, leucopenia and thrombocytopenia, patients should have their full blood count closely monitored before, during and after treatment. Although we did not exceed 80 mg 5-FU at each injection session, the use of higher doses without development of adverse haematological effects has been reported.^{6,7}

Two complications of intralesional 5-FU were seen in our patients. One episode of ulceration occurred, but the

ulcer eventually healed and no further side-effects were encountered on recommencement of injections. The second complication was hyperpigmentation that faded spontaneously in one patient but was treated in the other, owing to his skin type and his increased chance of developing lasting hyperpigmentation.

It has been suggested that the addition of local anaesthetic to the syringe of intralesional treatment mixture does not decrease the pain of the injection, but that the addition of corticosteroid to the mixture does have a beneficial anti-inflammatory effect.⁷ In our patients intralesional betamethasone was mixed with the 5-FU and ring blocks were used, topical anaesthetic cream being applied at the first two treatment sessions in the case of patient 2. The corticosteroid used in these cases was employed for its effect on potential 5-FU-induced inflammation and was not deemed of a high enough concentration to have achieved resolution of the keloid scars. All the literature relating to the role of corticosteroids in keloid therapy suggests that a dose of 10–40 mg/mL of triamcinolone or equivalent is required to effect change in hypertrophic or keloidal scars and that 40 mg/mL of triamcinolone is probably required for significantly effective monotherapy.⁸ The mixture of corticosteroid we used (betamethasone acetate and betamethasone sodium phosphate) is usually regarded as equipotent to triamcinolone 10 mg/mL; hence dilution to 20% of its original strength, as in our cases, would result in a concentration equivalent to 2 mg/mL of triamcinolone, which would not be expected to have any efficacy in treatment of the level of scarring seen in the two patients described. The use of adjunctive corticosteroid is probably unnecessary, as 5-FU used alone has been shown to be efficacious and well tolerated,^{6,7,9} and in future patients we will use monotherapy.

We employed fortnightly or monthly injections, at the patient's discretion, but injection sessions as frequent as three times per week are reported as being used for resistant cases.⁷

The results in the two cases presented suggest that intralesional 5-FU mixed with low-dose corticosteroid may be a possible alternative for the treatment of keloid scars after physical treatments have failed and may have fewer undesirable side-effects such as atrophy, hypopigmentation and telangiectasia when compared with intralesional potent corticosteroids alone.^{6,8,9} Further studies are required to determine the exact role of this drug used alone in the resolution of keloid scars.

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