

Topical Chemotherapy for Actinic Keratosis and Nonmelanoma Skin Cancer: Current Options and Future Perspectives

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Abstract. Actinic keratosis is currently considered not to be a precursor of squamous cell carcinoma but, rather, an initial stage of the disease. Furthermore, the incidence of both squamous cell carcinoma and basal cell carcinoma continues to increase. Topical drugs are now becoming widely used in the therapeutic management of nonmelanoma skin cancer and its precursor lesions. Here, we review the various topical drugs that are currently available and discuss their advantages and drawbacks. Therapeutic options include retinoids, 5-fluoracil, diclofenac, imiquimod, and photodynamic therapy.

Key words: actinic keratosis, nonmelanoma skin cancer, topical treatment.

TRATAMIENTO QUIMIOTERÁPICO TÓPICO DE LA QUERATOSIS ACTÍNICA Y EL CÁNCER CUTÁNEO NO MELANOMA: SITUACIÓN ACTUAL Y PERSPECTIVAS

Resumen. Actualmente se considera que la queratosis actínica no es un precursor del carcinoma de células escamosas, sino un estadio inicial del mismo, y la incidencia tanto del carcinoma escamocelular como del basocelular está en continuo aumento. Dentro del manejo terapéutico del cáncer cutáneo no melanoma, así como de las lesiones precursoras, se está imponiendo el uso de agentes farmacológicos tópicos. En el siguiente artículo se revisan las diversas alternativas farmacológicas tópicas de las que se dispone actualmente y se discuten sus ventajas y limitaciones. Entre estas alternativas se encuentran los retinoides, el 5-fluoracilo, el diclofenaco, el imiquimod y la terapia fotodinámica.

Palabras clave: queratosis actínica, cáncer cutáneo no melanoma, tratamiento tópico.

Introduction

The incidence of both nonmelanoma skin cancer and its precursor lesions continues to increase. An adequate training in oncology is therefore important, not only to reach the correct diagnosis but also to select the appropriate therapeutic management. Though controversial, the majority of authors now consider that actinic keratosis is not a precursor of squamous cell carcinoma but, rather, an initial stage of the

disease and, as such, it must be treated. Additionally, although a large proportion of nonmelanoma skin cancer is already invasive at the time of clinical presentation, and requires surgical treatment for complete and safe eradication, there are situations in which surgery presents certain limitations: when it is poorly tolerated by the patient, when there is a large number of tumors or an extensive area to be treated, or when it is cosmetically unacceptable. Nevertheless, early treatment can now be safely provided for certain superficial, precancerous or cancerous lesions without having to resort to aggressive treatments. Specifically, a number of therapies have been developed for the treatment of actinic keratosis and some forms of superficial nonmelanoma skin cancer. Among the various topical pharmacological options available are the retinoids, 5-fluoracil, diclofenac, imiquimod, and photodynamic therapy (Table).

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Table. Main Characteristics of Topical Treatments for Actinic Keratosis and Nonmelanoma Skin Cancer

Topical Treatment	Indications	Dose/Duration of Treatment	Advantages	Disadvantages
5-Fluoracil Efudix	Actinic keratosis Bowen disease Superficial basal cell carcinoma	Actinic keratosis: 2 times/d for 2-4 wk Basal cell carcinoma: 2 times/d for a minimum of 6 wk	Treatment of large areas Subclinical lesions Easy to apply Well established	Intense local inflammatory reaction Relatively long treatment period Partial efficacy in hyperkeratotic actinic keratosis
Diclofenac Solaraze	Actinic keratosis (only approved in USA)	2 times/d for 60-90	Easy to administer Patient acceptance	Lower total efficacy Local reactions No efficacy in basal or squamous cell carcinomas
Imiquimod Aldara	Superficial basal cell carcinoma Nonhypertrophic actinic keratosis of face and scalp	Basal cell carcinoma: 5 times/wk for 6 wk Actinic keratosis: 3 times/wk for 4 wk	Long-term efficacy and safety (5 y) Complete histological resolution with no residual scar Minimal rate of recurrence	Erythema, ulceration, edema and desquamation Cost
MAL Metvix	Actinic keratosis Superficial and nodular basal cell carcinoma Bowen disease	Occlusive dressing for 3 h prior to application of light Actinic keratosis: 1 session Basal cell carcinoma and Bowen disease: 2 sessions separated by 1 wk	Possibility for repetition Cosmetic result Fluorescence diagnosis Good response	Cost Time Pain in the treated area Erythema, edema, scabs Low penetrating capacity

Abbreviation: MAL, methyl aminolevulinate.

Topical Retinoids

The retinoids, vitamin A analogs, are common ingredients nowadays in many cosmetic products as, due to their mechanism of action, they are considered to be agents with a certain chemopreventive effect. In some studies they have been shown to have a degree of efficacy in the treatment of actinic keratosis.¹ In a study in which 0.05% tretinoin was applied once a day for 3 months, a reduction of 45% was observed in the actinic keratoses versus 23% in patients treated with placebo.² In another study, however, no reduction in the number of actinic keratoses was achieved after the use of topical retinoids.³ Few studies have looked at their efficacy in the treatment of basal cell carcinoma, and none has demonstrated sufficient efficacy.⁴ For this reason, the retinoids currently appear to be of interest only for the prevention of precancerous lesions and as adjuvants for other treatments.⁵ They are not recommended for use as monotherapy.

Topical 5-Fluoracil

5-Fluoracil has been considered the topical treatment of choice for actinic keratosis for many years, since its approval in 1970 by the US Food and Drug Administration.⁶

It acts by blocking DNA synthesis through inhibition of the enzyme thymidylate synthase. There are a number of preparations of 5-fluoracil, and it is available both as a cream (Efudix 5%, Fluoroplex 1%, and Carac 0.5%) and as 5%, 2%, or 1% solution. It is approved for the treatment of actinic keratosis, Bowen disease, and superficial basal cell carcinoma.

The established treatment regimen for actinic keratosis is 1 application twice a day for 2 to 4 weeks, achieving a complete clinical cure rate of 82%.⁷ No differences in the efficacy of 5-fluoracil have been found between 1% and 5% preparations.⁸

This therapy allows large areas to be treated, as well as subclinical lesions; however, it has a major drawback that has been reported in all the studies reviewed, and this is the intense local inflammatory reaction that it produces, with undesirable and painful erosions that, in many cases, could favor patient noncompliance or require early interruption of the treatment. A number of cases of contact dermatitis and 1 case of inflammatory colitis have been reported.⁹ Alternative therapeutic protocols have been proposed in an attempt to reduce these effects; they include the concomitant use of topical steroids and/or antibiotics, and the use of pulsed therapy,¹⁰ in which the treatment is applied less frequently and for a longer period of time

(this reduces the inflammation but also decreases the efficacy of the treatment). A preparation with a lower concentration (0.5%) is the most recently approved product for actinic keratoses of the face and scalp and, even though there are no demonstrated differences in efficacy and tolerance in comparison with the 5% concentration, it is preferred by patients due to the lower number of daily applications.

Other disadvantages of this treatment are the relatively long treatment period and the partial efficacy in deep or hyperkeratotic actinic keratoses.

Topical 5-fluoracil has also been used in the treatment of basal cell carcinoma, though in a more restricted manner, only being recommended for the treatment of superficial basal cell carcinoma using the 5% concentration with twice daily applications for a minimum of 6 weeks. The cure rate is approximately 93%.⁷ The efficacy of 5% 5-fluoracil has also been reported in selected cases of in situ squamous cell carcinoma.⁷ In these cases of skin cancer, the response to treatment must be carefully monitored.

Because of its local irritant action, 5-fluoracil has also been considered useful as a preoperative marker of the tumor margins in superficial tumors, being applied twice a day for 7 to 10 days prior to surgery.

Topical Diclofenac

The preparation of 3% diclofenac in 2.5% hyaluronic acid (Solaraze) is a nonsteroidal anti-inflammatory drug that has been formulated in a topical gel for the treatment of actinic keratosis; at present it is only approved for use in the United States of America. Its mechanism of action is not well understood, though it has been shown to have an antitumor effect through inhibition of arachidonic acid metabolism. It is applied twice a day for a period of 60 to 90 days. Several studies have demonstrated its efficacy in the treatment of actinic keratosis,^{10,11} achieving complete resolution of the lesions in 47% of patients, while 77% showed a significant improvement.^{12,13} The total efficacy appears to be lower than that achieved with 5-fluoracil.⁷

Although it is generally a well-tolerated drug, it causes local reactions in up to 70% of cases,¹³ producing mild or moderate inflammation, though significantly less than that which occurs after the application of 5-fluoracil. Cases of allergic contact dermatitis have also been reported. To date, there is no evidence for its efficacy in the treatment of basal cell carcinoma or squamous cell carcinoma.

It is considered a good therapeutic option, easy to administer, and with a higher probability of acceptance by the patients than 5-fluoracil, despite requiring a long period of treatment.

Imiquimod

Imiquimod in a 5% cream (Aldara) is an immune response modulator with antiviral and antitumor activity. It acts by inducing the local release of interferon- α , tumor necrosis factor α , and other cytokines that stimulate both the innate and cellular immune responses. Additionally, it has the ability to induce tumor cell apoptosis (Figure 1). It is approved in Europe for the treatment of superficial basal cell carcinoma and has also recently been approved for use in the treatment of nonhyperkeratotic, nonhypertrophic actinic keratosis of the face and scalp.

A number of studies attempting to determine the ideal treatment regimens have shown that the higher the dose the better the response, although the adverse effects also increase.^{14,15} At the present time, the most effective regimen is considered to be once-daily application, 5 times a week for 6 weeks in basal cell carcinoma—evaluating the response clinically 3 months after completing treatment—and 3 times a week for 4 weeks in actinic keratosis, with a second treatment cycle if, after 4 weeks without treatment, the response is insufficient. However, treatment should be individualized in order to achieve the greatest efficacy with the best tolerance and greatest compliance.

Its efficacy and safety in the treatment of basal cell carcinoma has been demonstrated in numerous clinical trials and studies, achieving clinical response rates between 69% and 100% in superficial basal cell carcinoma.^{16,17} Complete histological resolution of the lesion was observed in 82% of patients.¹⁸

The cure rate in the treatment of actinic keratosis varies between 45% and 84%.¹⁹ A recent meta-analysis performed by Gupta et al²⁰ shows that the efficacy of imiquimod in the treatment of actinic keratosis is greater than that of 5-fluoracil, with total mean cure rates of 70% and 52%, respectively.

An open, multicenter, phase III study was performed to evaluate the long-term efficacy of treatment.²¹ One hundred eighty-two patients with tumors less than 2 cm in diameter participated in the study and were treated with imiquimod 5 times a week for 6 weeks, achieving sustained, high cure rates that were very similar between the first and second years (97.5% and 88.7%, respectively). Another study has recently been published in which sustained efficacy in basal cell carcinoma was observed for up to 5 years.²²

Imiquimod is therefore considered to be a good therapeutic alternative that has shown good long-term efficacy and safety, for up to at least 5 years, with excellent cosmetic results.

The most common adverse effects are limited to the area of application and include erythema, ulceration, edema, and desquamation. If these develop, treatment can be

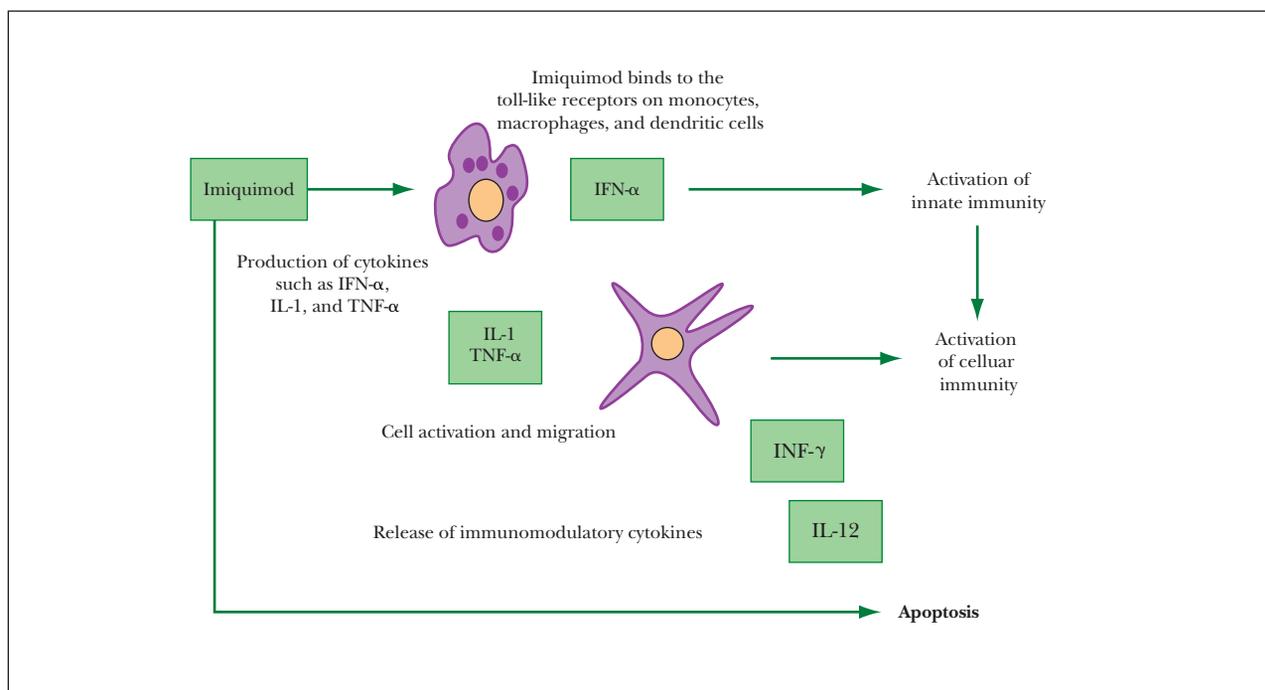


Figure 1. Mechanism of action of imiquimod. IFN- α indicates interferon alfa; IFN- γ , interferon γ ; IL, interleukin; TNF- α , tumor necrosis factor α .

interrupted for a few days without this appearing to interfere with efficacy of the treatment.

Although it has still not been approved for use in other clinical forms of basal cell carcinoma, there is sufficient evidence in the literature of its efficacy, with complete remission in 71% to 100% of cases in the nodular type,²³ and a number of cases of remission in the sclerodermiform and infiltrative types.²⁴

Imiquimod has also been shown to be effective in bringing about the complete or partial remission of multiple basal cell carcinomas in patients with Gorlin syndrome²⁵ or xeroderma pigmentosum,²⁶ and also in immunodepressed patients²⁷ and patients with in situ squamous cell carcinoma.²⁸

Some of the future applications of this immune modulator will be preoperative treatment to reduce tumor size and mark poorly defined tumor margins, and prophylaxis against recurrence after surgical treatment.

Photodynamic Therapy

Photodynamic therapy is a relatively new treatment modality that is based on the application of a photosensitizing substance followed by illumination of the lesion with visible light in order to produce molecules of activated oxygen that selectively destroy the target cells. It has been approved in Europe for the treatment of actinic

keratosis and superficial and nodular basal cell carcinoma and has also recently been approved in 22 European countries for use in the treatment of Bowen disease.²⁹ The photosensitizers used are topical 5-aminolevulinic acid (ALA), and its derivative, methyl aminolevulinate (MAL). This latter substance is marketed in Europe (Metvix) and has the advantage of being more selective and requiring a shorter time for absorption.

The optimal treatment regimen is the application of MAL at a concentration of 160 mg/g under an occlusive dressing for 3 hours prior to the application of light. Previous curettage of the lesion is recommended to eliminate hyperkeratosis or for tumor reduction in the case of nodular basal cell carcinoma.

Many studies have demonstrated the efficacy of this therapy. Responses of up to 90% have been observed in actinic keratosis³⁰ and 93% in Bowen disease, with a recurrence rate of 17% at 64 months.³¹ The response rate varies between 80% and 97% in superficial basal cell carcinoma, with a 4-year recurrence rate of 22%, and between 73% and 94% in nodular basal cell carcinoma, with a 5-year recurrence rate of 14%.³² The highest indices of response were obtained after performing initial curettage of the lesion.

In general, the treatment is well tolerated, and the most common adverse effect is a painful burning sensation in the treated area. Erythema, edema, and scab formation

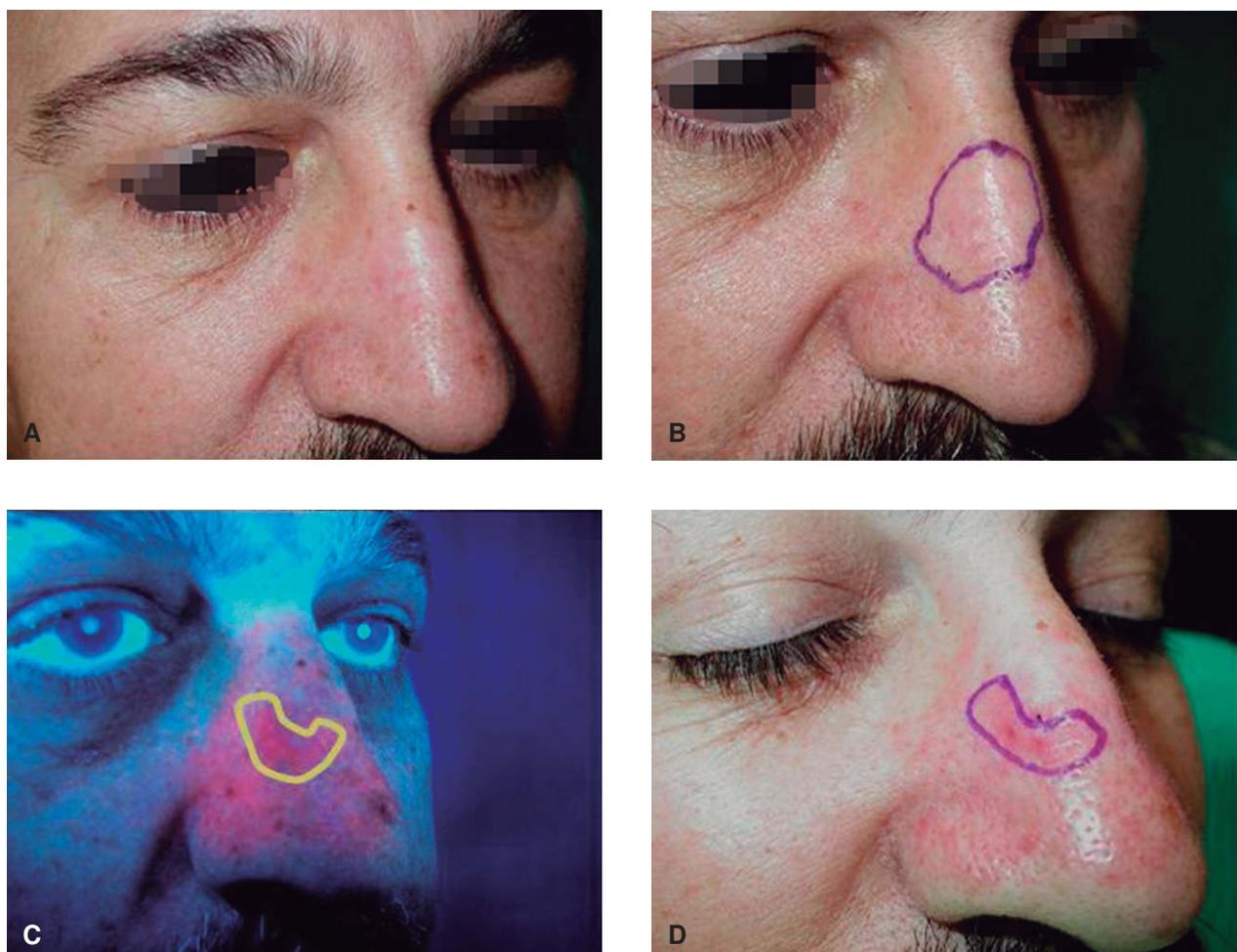


Figure 2. A, Basal cell carcinoma on the dorsum of the nose. B, Clinical margins. C, Margins by fluorescence. D, Reduction of the area of excision.

have also been reported. These effects are considered to be less pronounced than those caused by 5-fluoracil. Allergic reactions have been reported, though these are very rare.

Other advantages of photodynamic therapy are the possibility for repetition of the treatment as many times as is necessary, without complicating possible surgery, and the excellent cosmetic result, with a clear reduction in the signs of aging, leading to it being relatively well accepted by patients. Additionally, fluorescence diagnosis enables the extension of the lesion to be determined when the margins are poorly defined (Figure 2), and recurrences to be detected after previous treatments.

Guidelines for the application of photodynamic therapy have recently been published.²⁹ In these, photodynamic therapy is recommended as first line treatment for actinic keratosis and Bowen disease, as an effective and safe treatment for superficial and nodular basal cell carcinoma,

and as a prophylactic treatment for actinic keratosis and skin cancer in immunodepressed transplant patients.³³ Although a number of studies with ALA have demonstrated its efficacy in the treatment of superficial squamous cell carcinoma,²⁹ the high risk of recurrence and the metastatic potential of this tumor have limited its use. There are no articles published on the use of MAL in this tumor. Photodynamic therapy cannot therefore be recommended at the present time for the safe and effective treatment of squamous cell carcinoma.

The principal limitation of this therapy is its low penetrating capacity in skin, reducing its efficacy in deep lesions. In the near future, the development of new photosensitizers and vehicles that improve penetration will increase the efficacy of this therapy.

Conflicts of Interest

The authors declare no conflicts of interest.

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