Dermatology Practical & Conceptual

Real-World Experience With Topical 5-Fluorouracil 4% (40 mg/g) Cream for the Treatment of Actinic Keratosis

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ABSTRACT

Introduction: 5-fluorouracil (5-FU) is one of the most effective topical treatments for actinic keratosis (AK). A new 4% formulation of 5-FU was recently approved in Europe.

Objectives: This study aimed at evaluating 4% 5-FU cream safety and effectiveness in a real-world setting.

Methods: Adult AK patients were retrospectively selected from the University of Campania Dermatology Unit database. Selection criteria included a diagnosis of non-hyperkeratotic, non-hypertrophic AK (Olsen grade I and II) of the face, ears, and/or scalp, treatment with 4% 5-FU once daily for 4 weeks, and at least 3 follow-up visits (4 and 8 weeks after treatment initiation, and 6 months after treatment end). The primary objectives were to evaluate AK lesions improvement at 8 weeks and relapse rate at 6 months. Patient-reported erythema and burning sensation intensity were also assessed at 4 weeks.

Results: Ninety-eight patients were included in this analysis (male/female 80/18, mean age 74.7 years). AK lesions improvement at 8 weeks resulted complete or significant in 74.5% and 20.4% of the patients, respectively. At 6 months, 65.3% of the patients did not show AK relapses. Burning sensation at 4 weeks was reported as light, moderate, or absent by 44.9%, 22.4%, and 31.6% of the patients, respectively. Erythema was reported as light, moderate, or absent by 37.8%, 51%, and 10% of the patients, respectively. Burning sensation and erythema disappeared gradually during follow-up. No other side effects were reported.

Conclusions: In this real-world study 4% 5-FU proved to be highly effective for AK lesions clearance with a favorable safety profile.

Introduction

Actinic keratosis (AK) is a common skin disease caused by chronic sun exposure [1]. Clinically, AK presents with small, dry, erythematous, scaly and sometimes pigmented papules [2]; these lesions result from abnormal proliferation of atypical epidermal keratinocytes and are located in chronically sun-exposed body areas such as the face, scalp, neck, hands, and forearms [1,2].

Italy shows one of the highest prevalence of AK worldwide [2,3]. In a retrospective, observational study published in 2017, which enrolled 7,284 outpatients attending Italian general dermatology clinics, the overall mean prevalence of AK was 27.4%, with a significantly higher rate in males compared with females (34.3% versus 20.0%, respectively; P <0.001) [2]. The same study confirmed in the Italian population the well-known, independent risk factors of AK, i.e. older age, male gender, fair skin (Fitzpatrick phototypes I-II), prolonged UV exposure for professional or recreational reasons, and alcohol consumption [1,2].

AK is considered a precursor of invasive squamous cell carcinoma (SCC), a malignancy which can produce distant metastases [2,3]. The AK progression rate is highly variable (from 0.025% to 20%) and increases with the number of lesions, being 11-fold higher in patients with >20 lesions [1,4]. Since it is impossible to predict lesions risk of transformation based on their morphological features, a prompt diagnosis and treatment of every AKs are essential to reduce the risk of SCC [2,3,5]. Importantly, according to the "field cancerization" (FC) concept, treatment should also target the skin surrounding AK lesions, where subclinical lesions with the potential of malignant transformation could be present [6]. The cutaneous FC is due to chronic ultraviolet radiation exposure, which results in clonal proliferation of p53-mutated fields, high burden of both clinical and subclinical actinic damage, and high risk of developing multiple SCCs; these, in turn, are associated with relevant mortality, morbidity and high costs for national healthcare systems [6].

Given the need for an effective AK treatment, several therapeutic options have been developed. They include lesion-directed treatments, such as cryosurgery, curettage, and excision surgery, which remove atypical keratinocytes of every single lesion, and field-directed treatment, such as photodynamic therapy (PDT) and topical treatments, whose therapeutic action is extended to the whole FC [1].

5-fluorouracil (5-FU) is an antineoplastic drug commonly used as a topical, field-directed treatment for AK [7]. 5-FU is a pyrimidine analogue, which irreversibly inactivates thymidylate synthase, interfering with DNA synthesis and causing apoptosis of the high proliferative AK keratinocytes [1,8]. It was the first drug for AK field-directed treatment and its approval dates back to 1962 [3]. 5-FU is available for AK treatment in various formulations, with concentrations ranging from 0.5 to 5% [8]. The 5% 5-FU cream efficacy is supported by a substantial number of studies. In a network meta-analysis published in 2019 by Wu et al, including 11 studies and more than 2200 patients, 5% 5-FU was more likely to be effective in AK lesions total clearance compared with the association of 5-FU with salicylic acid, 3% diclofenac sodium, and cryosurgery (56.8% vs 37.5%, 6.6%, and 0.9%, respectively) [7]. 5% 5-FU resulted also more likely to be the most effective treatment among patients with lesions reduction from baseline (98.6%).

In a multicentre, single-blind, randomized trial published by Jansen et al in 2019, patients treated with 5% 5-FU showed a significantly higher cumulative probability of remaining free from treatment failure at 12 months compared with patients who received 5% imiquimod, methyl aminolevulinate PDT, or 0.015% ingenol mebutate (74.7% vs 53.9%, 37.7%, and 28.6%, respectively; P ≤0.001) [9].

Finally, according to a recent secondary analysis of a randomized clinical trial, 5% 5-FU seems to reduce long-term SCC risk compared with other field-directed AK treatments [10]. In this analysis, conducted on 624 patients with AK, the 4-year risk of cutaneous SCC in the treated area resulted lower in subjects who initially received 5% 5-FU (2.2%) compared with imiquimod (5.8%), methyl aminolevulinate PDT (3.6%), or ingenol mebutate (3.0%) [10].

In 2020, the European Medicines Agency approved a novel 4% 5-FU formulation for the treatment of Olsen grade I or II AK [11,12]. The 4% formulation has a more convenient dosage compared with twice daily 5% 5-FU: it should be applied once daily for a maximum of 4 weeks, potentially improving treatment compliance [12,13].

In a multicenter, randomized, double-blind, parallel-group, phase III study conducted in 841 subjects with AK, 4% 5-FU efficacy was similar to 5% 5-FU in terms of 100% lesions clearance at 4 weeks (54.4% versus 57.9%, respectively), ≥75% lesions clearance at 4 weeks (80.5% versus 80.2%, respectively), and percentage change from baseline in AK lesions count (80.1% versus 79%) [11,13]. Notably, 4% 5-FU showed an improved safety profile compared with 5% 5-FU, with a lower rate of adverse events leading to treatment discontinuation (10.1% versus 14.9%, respectively) [11,13].

These results were confirmed by a recently published network meta-analysis which included 75 randomized clinical trials [14]. In this analysis, 4% 5-FU was compared with 5% formulation, placebo and several other topical treatments for AK (diclofenac sodium, imiquimod, ingenol mebutate, and PDT). The Surface Under the Cumulative RAnking (SUCRA) values ranked 4% 5-FU as having the probability of being the best treatment in achieving ≥75% clearance of AK lesions, followed by 5% 5-FU (SUCRA 89.98 versus

88.95, respectively); moreover, 4% 5-FU ranked second, following 5% 5-FU, in the probability of being the best treatment for complete AK lesions clearance (SUCRA 78.26 versus 84.74). Notably, SUCRA values showed a lower risk of withdrawal due to adverse events associated with 4% 5-FU treatment compared with 5% 5-FU (SUCRA 70.89 versus 70.89 respectively) [14].

Objectives

Due to 4% 5-FU formulation recent approval, real-world evidence on this treatment in AK is lacking. This study aimed to fill this gap, reporting the experience of an Italian Dermatology Centre using 4% 5-FU to treat subjects with AK in routine clinical practice.

Methods

This study was a retrospective analysis of the University of Campania Dermatology Unit (Naples, Italy) patient database. Adult subjects with a diagnosis of grade I or II AK (based on the 4-point Olsen scale), localized on the face, ears, and/or scalp, consisting of visible and palpable lesions neither hypertrophic nor hyperkeratotic, treated with 5-FU 4% cream (Tolerak®, Pierre Fabre) once daily for 4 weeks from September 2021 to November 2021 were selected. Only patients with at least 3 follow-up visits were included: the first and the second one after 4 and 8 weeks from treatment initiation respectively; the third one 6 months after the second visit.

The primary objective of the study was to evaluate the 4% 5-FU cream efficacy in terms of AK lesions improvement at 8 weeks and relapse rate at 6 months. AK lesions improvement is routinely assessed at our Centre with the 7-point Investigator Global Improvement Scale (IGI; -2, significantly worse; -1, slightly worse; 0, no change; +1, slightly improved; +2, moderately improved; +3, significantly improved; +4, completely improved), and the availability of this measurement was included in the patients' selection criteria.

The secondary objective was to evaluate the safety of 4% 5-FU cream in terms of erythema and burning sensation intensity at 4 weeks. These adverse events are routinely assessed at our Centre with the patient-reported Scale for Clinical Assessment (SCA; 0, absent; 1, light; 2, moderate; 3, severe); only patients with these measurements available were selected.

Statistical analyses were performed with Software R. Descriptive statistics of the cohort are provided with confidence intervals. Chi-squared test for categorical variables and the t-test for continuous variables were used. Statistical significance was set at $P < 0.05$.

Results

Overall, 98 patients satisfied the inclusion criteria and were selected for the study. Most of these patients were males (N = 80/98; 81%) and the mean age at first visit was 74.7 years. The mean number of follow-up visits resulted slightly higher than the number required for the inclusion in the study (3.05 versus 3) since 5 patients required 1 or 2 additional consultations because of side effects. The mean follow-up duration in our sample was 212 days.

According to the IGI scores, after 8 weeks from treatment initiation (4 weeks after the end of treatment) AK lesions were completely or significantly improved compared with baseline in the vast majority of the patients (74.5% and 20.4%, respectively; Figure 1). In only 4 patients the investigators graded the improvement as moderate or slight (4.1%) and 1 patient (1%) showed no change in AK severity. Moreover, no patient showed a worsening of the disease.

4% 5-FU treatment results were sustained during follow-up, and 64 patients (65.3%) did not show AK relapses at the 6 months visit.

Patients-reported burning sensation after 4 weeks from treatment initiation was generally light (N = 43, 43.9%) or moderate (N = 22, 22.4%; Figure 2A). Only 1 patient (1%) reported severe burning sensation, and 31 patients (31.6%) did not report this adverse event. Similar results were obtained for patients-reported erythema at 4 weeks (Figure 2B), which was generally graded as light (N = 37, 37.8%) or moderate (N = 50, 51%). Only 1 patient (1%) reported a severe erythema, while 10 patients (10.2%) did not report this adverse event.

In patients with burning sensation and/or erythema, these adverse events disappeared gradually during follow-up, and they could be managed with moisturizing and/or topical antibiotics on the basis of the investigator clinical judgment. No other side effects were reported.

Conclusions

In our study, 4% 5-FU proved to be an effective and safe topical treatment for adults with non-hyperkeratotic, non-hypertrophic AK (Olsen grade I and II) of the face, ears, and/or scalp, in a real-world clinical setting. Almost the totality of our patients (99%) showed a clinical improvement after 8 weeks from treatment initiation, which was considered significant or complete in 94.4% of the cases (Figure 3). Moreover, although the natural course of AK is characterized by the recurrence of lesions, the clearance obtained with 4% 5-FU was sustained during follow-up, with more than 64% of the patients free from AK recurrences at 6 months [15].

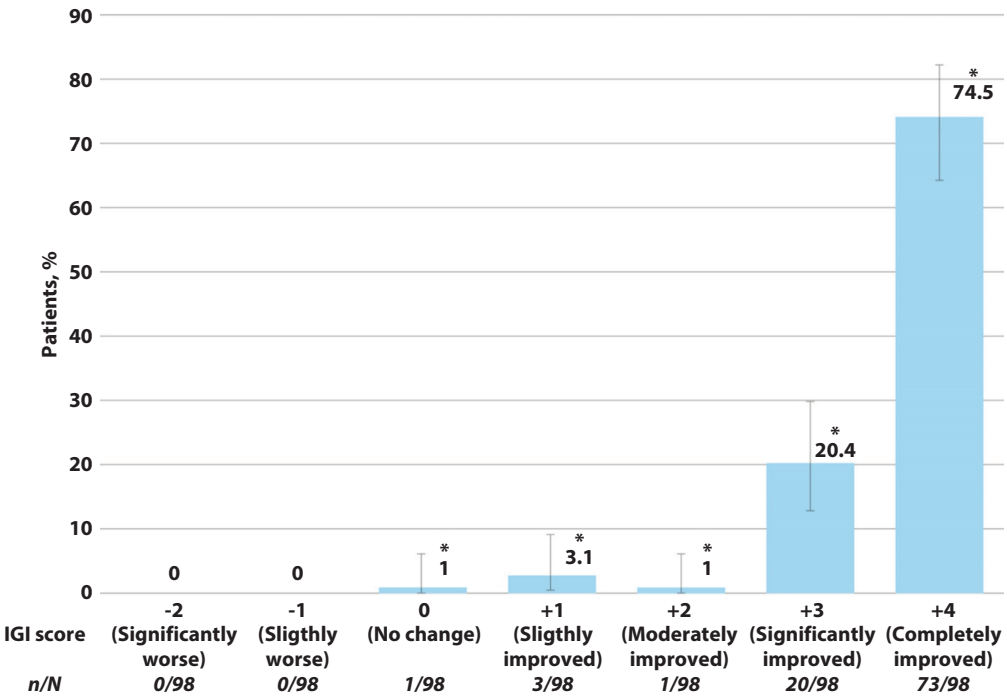

Figure 1. AK lesions improvement from baseline at 8 weeks.

Percentages of patients with AK lesion improvement assessed with IGI scale after 8 weeks from 8 weeks after treatment initiation. Error bars show 95% CIs. *P <0.001.
AK = actinic keratosis; IGI = Investigator Global Improvement; CI = confidence interval.

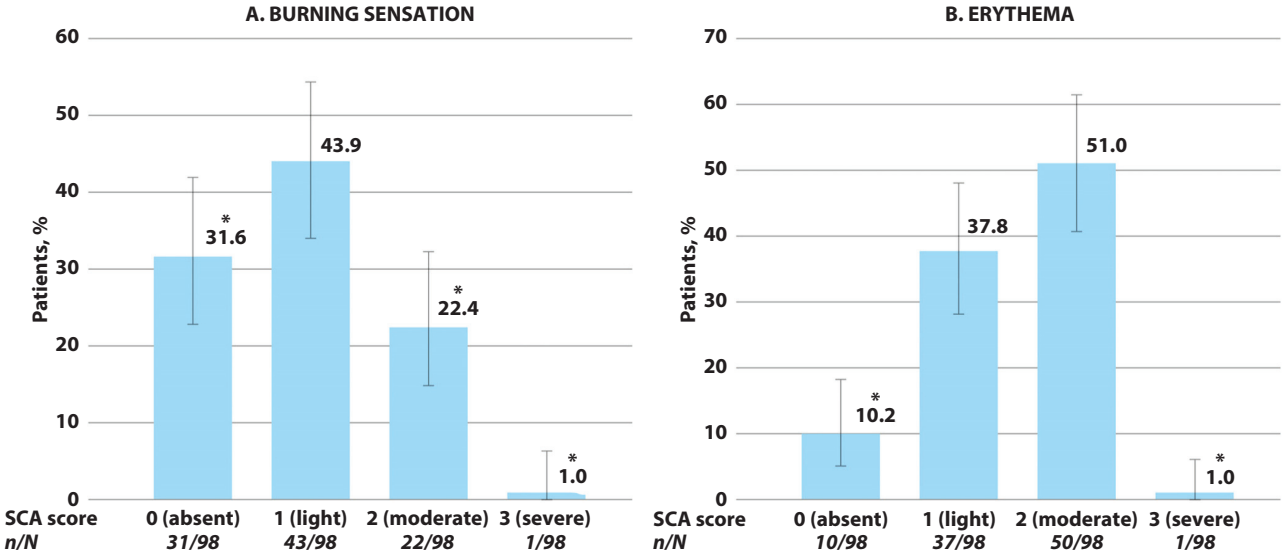

Figure 2. Safety assessment at 4 weeks.

(A) Burning sensation assessed with SCA after 4 weeks from 4 weeks after treatment initiation.
(B) Erythema assessed with SCA after 4 weeks from 4 weeks after treatment initiation.
Error bars show 95% CIs. *P <0.001.
SCA = Scale for Clinical Assessment; CI = confidence interval.

These results confirm previously published evidence on 5-FU, which is currently considered one of the most effective topical treatments for AK lesion clearance based on several randomized clinical trials and meta-analyses [7,9,13,14]. Furthermore, our study confirms that reducing 5-FU concentration from 5% to 4% does not affect its efficacy, even when used in real-world clinical practice.

4% 5-FU was well tolerated in our patient population, with no side effects reported other than erythema and burning sensation. After 4 weeks of treatment, erythema was light or moderate in almost 90% of the subjects, and only 1 patient graded it as severe. 31.6% of patients did not report any burning sensation, which was severe in only 1 patient. In all the patients both erythema and burning sensation were

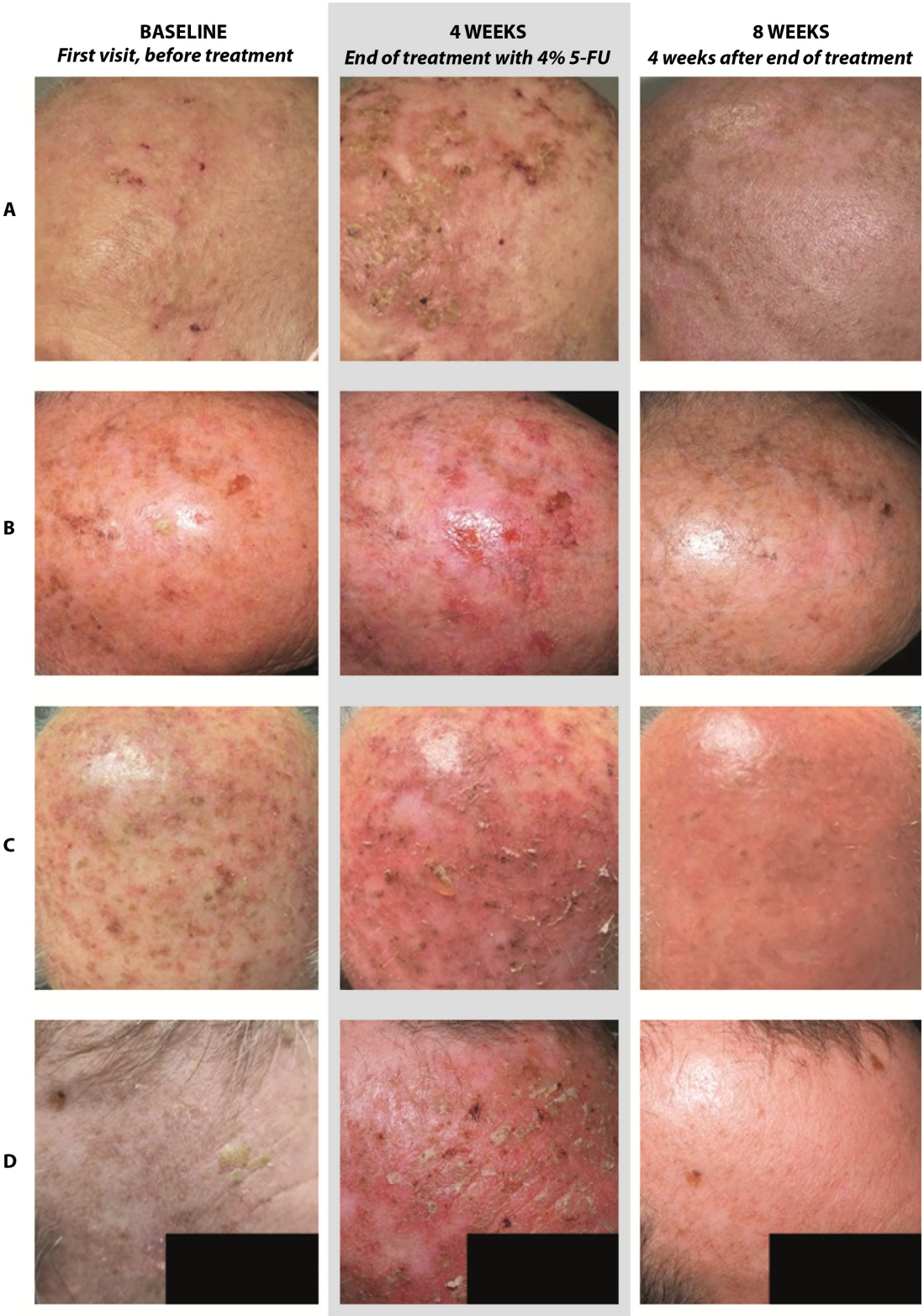

Figure 3. Effects of 4% 5-FU treatment.

These pictures show 4 patients with diffuse AK of the scalp, forehead and/or face at baseline, treated for 4 weeks with 4% 5-FU. They confirm the normal pattern of response to 4% 5-FU: at the end of treatment, the inflammatory response associated with 5-FU pharmacological action on dysplastic AK cells reaches its peak, characterised by mild-moderate erythema (and burning sensation); after 8 weeks from 8 weeks after treatment initiation, the inflammatory response is resolved, and AK lesion clearance is noticeable.
(A) 86-year-old male patient; (B) 76-year-old male patient, (C) 67-year-old male patient; (D) 76-year-old male patient.
5-FU = 5-fluorouracil.

limited to the acute phase and they gradually disappeared during follow-up, being managed, when needed, according to the investigator's clinical practice.

These results are in line with the well-known 5-FU safety profile, which resulted to be favorable both in challenging patients (such as those immunosuppressed) and in sensitive skin areas (such as the periocular region) [16,17].

This study has two limitations. First, its retrospective design, with the lack of a placebo group to account for the natural regression of AK lesions. Second, we did not include patients who either suspended or discontinued the therapy, since our first aim was to evaluate the treatment response. This did not allow us to calculate the rate of treatment withdrawal. However, we are convinced that patient education is crucial for achieving a satisfactory compliance to 5-FU treatment. Patients should be taught to consider erythema and burning sensation as normal and transient signs of 5-FU pharmacological action on dysplastic AK cells, with a peak after 4 weeks of treatment and then gradually resolving. In our study this simple strategy resulted in a low rate (5.1%) of additional consultations for adverse events.

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