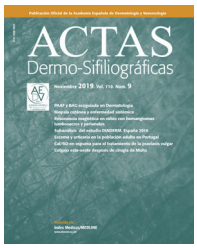
Actas Dermosifiliogr. 2020;111(7):609–610

ACTAS
Dermo-Sifiliográficas

Full English text available at
www.actasdermo.org



RESIDENT'S FORUM

RF - Pharmacological Prevention of Nonmelanoma Skin Cancer in High-Risk Patients*

FR - Prevención farmacológica del cáncer cutáneo no-melanoma en pacientes de alto riesgo

X. Bosch-Amate,* D. Morgado-Carrasco, N. Martínez

Servicio de Dermatología, Hospital Clínic de Barcelona, Universitat de Barcelona, Barcelona, Spain

KEYWORDS
Basal cell carcinoma;
Squamous cell carcinoma;
Skin cancer;
Prevention;
5-Fluorouracil

PALABRAS CLAVE
Carcinoma basocelular;
Carcinoma escamoso;
Carcinoma espinocelular;
Prevención;
Cáncer cutáneo;
5-Fluorouracilo

Nonmelanoma skin cancer (NMSC) is the most common neoplasia in humans. It includes basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). Its main risk factors are accumulated exposure to sunlight, immunosuppression, and infection with the beta human papillomavirus. The use of topical sunscreen is frequently indicated in secondary prevention. In recent years, new evidence supports the use of some drugs as chemoprophylactics (Table 1).

A randomized double-blind clinical trial in 932 high-risk patients (98% Caucasian males, with a mean age of 71 years) was recently published. Chemoprevention was studied using a cycle of 5% topical fluorouracil (every 12 h for 4 weeks) (n = 468) versus placebo (n = 464) on the appearance of NMSC of the face and ears with surgical indication. In the first year after treatment a lower number of SCC was detected (1% versus 4%) (risk reduction of 75% [95% CI, 35%–91%] [*P* = .002]). No differences were found in BCC (10% versus 11%), although the number of Mohs surgeries in the first year dropped. After 4 years of follow-up, no differences were found in the number of SCC or BCC between the 2 groups (39% versus 38%). In terms of adverse effects, 92% of the group receiving fluorouracil presented erythema (21% described it as severe), but 85% would use the treatment again if necessary.[1] These results suggest that a cycle of topical fluorouracil would be useful in secondary prevention of SCC for a year. It remains to be demonstrated whether an annual cycle of 5% topical fluorouracil is an effective long-term strategy. We must remember that 5-fluoracil is not sold in Spain and must be formulated. This may limit its potential use in Spain.

Previously, a phase-III randomized, double-blind, placebo-controlled clinical trial in 386 high-risk patients

* Please cite this article as: Bosch-Amate X, Morgado-Carrasco D, Martínez N. FR - Prevención farmacológica del cáncer cutáneo no-melanoma en pacientes de alto riesgo. Actas Dermosifiliogr. 2020;111:609–610.

* Corresponding author.
E-mail address: xavi_bosch92@hotmail.com (X. Bosch-Amate).

Table 1 Drugs Used in Secondary Prevention of Nonmelanoma Skin Cancer.

Drug	Route of Administration	Dosage	Evidence in Favor
5-Fluorouracil	Topical, 5%	Twice daily for 4 weeks (an annual cycle?)	RCT in high-risk patients (n = 932). Reduced rate of SCC in the 1st year[1]
Retinol	Oral	25,000 IU/day for 5 years	RCT in high-risk patients (n = 2297). Reduced risk of SCC while treatment lasted[3]
Acitretin	Oral	30 mg/day for 6 months	RCT in kidney-transplant patients (n = 44). Reduced risk of NMSC while treatment lasted[4]
Nicotinamide	Oral	500 mg twice daily for a year	RCT in high-risk patients (n = 386). Reduced risk of NMSC and AK while treatment lasted[2]

Abbreviations: SCC indicates squamous cell carcinoma; NMSC, nonmelanoma skin cancer; RCT, randomized clinical trial; AK, actinic keratosis.

had demonstrated the efficacy of oral nicotinamide (500 mg/12 h of vitamin B3) as chemoprevention for NMSC. In the 12 months that the nicotinamide was used, the number of NMSC per person was reduced (1.8 versus 2.4), with a risk reduction of 23% (95% CI, 4%–38%) ($P = .02$), and the drug was well tolerated. This protective effect was lost 6 months after the treatment ended.[2]

Oral retinoids have been shown to be of use in chemoprevention of NMSC while they are being used. In a randomized, placebo-controlled clinical trial (n = 2297), the risk of SCC was lower among those who received 25,000 IU/d of retinol (vitamin A) (hazard ratio, 0.74 [95% CI, 0.56–0.99] [$P = .04$]).[3] Other smaller studies have shown the efficacy of isotretinoin and oral acitretin in reducing the risk of NMSC, but with greater toxicity.[2,4]

Other oral drugs studied include capecitabin, celecoxib, and ibuprofen, but greater evidence is required for their use to be recommended. Most of the above-mentioned treatments have demonstrated efficacy in preventing SCC but not BCC. This may be explained by their different etiologies, including the fact that UV radiation damage and viral infection are not as important in BCC. In terms of treatment of NMSC precursor lesions, different topical agents have been shown to be effective, such as ingenol mebutate, imiquimod, and diclofenac. Photodynamic therapy is also highly effective in the treatment of these lesions.

In solid-organ transplant and immunosuppressed patients, it is important to reduce immunosuppression to the minimum effective dose and to replace calcineurin inhibitors (cyclosporin and tacrolimus) with mTOR inhibitors (sirolimus or everolimus). The use of sirolimus has been associated with a significant reduction in the risk of NMSC.[5]

Different pharmacological options exist for patients with a high risk of developing NMSC, such as 5% topical fluorouracil, retinoids, and oral nicotinamide to reduce this risk and the associated morbidity and mortality.

References

1. Weinstock MA, Thwin SS, Siegel JA, Marcolivio K, Means AD, Leader NF, et al. Chemoprevention of basal and squamous cell carcinoma with a single course of fluorouracil, 5%, cream: a randomized clinical trial. JAMA Dermatol. 2018;154:167–74, http://dx.doi.org/10.1001/jamadermatol.2017.3631.
2. Chen AC, Martin AJ, Choy B, Fernández-Peñas P, Dalziell RA, McKenzie CA, et al. A phase 3 randomized trial of nicotinamide for skin-cancer chemoprevention. N Engl J Med. 2015;373:1618–26, http://dx.doi.org/10.1056/NEJMoa1506197.
3. Moon TE, Levine N, Cartmel B, Bangert JL, Rodney S, Dong Q, et al. Effect of retinol in preventing squamous cell skin cancer in moderate-risk subjects: a randomized, double-blind. Cancer Epidemiol Biomark Prev. 1997;6:949–56.
4. Bavinck JN, Tieben LM, Woude FJ, Tegzess AM, Hermans J, ter Schegget J, et al. Prevention of skin cancer and reduction of keratotic skin lesions during acitretin therapy in renal transplant recipients: a double-blind, placebo-controlled study. J Clin Oncol. 1995;13:1933–8, http://dx.doi.org/10.1200/JCO.1995.13.8.1933.
5. Yanik EL, Siddiqui K, Engels EA. Sirolimus effects on cancer incidence after kidney transplantation: a meta-analysis. Cancer Med. 2015;4:1448–59, http://dx.doi.org/10.1002/cam4.487.