Topical Treatment of Skin Squamous Cell Carcinoma with Potassium Dobesilate Cream

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Abstract: Skin squamous cell carcinoma, the second most common skin cancer arises from the malignant proliferation of keratinocytes in the epidermis. Although it is locally invasive, surgical excision or topical therapy is usually curative. However, surgical management of skin squamous cell carcinoma located in certain regions of the body may require reconstructive procedures. This can result in significant scarring and increased morbidity and dysfunction. Topical therapy may be preferable to surgery depending on anatomic localizations, and in instances where patients reject it or are poor surgical candidates. Fibroblast growth factors are variously implicated in skin tumorigenesis where they may be involved in the enhancement of tumor cell proliferation and viability, induction of angiogenesis and stimulation of tumor invasiveness. We investigated the efficacy and safety of the fibroblast growth factor inhibitor, dobesilate, administered as a 5% potassium cream, for the treatment of skin squamous cell carcinoma. Two months application of dobesilate cleared squamous cell carcinoma probably due to inhibition of cell proliferation and angiogenesis, and induction of tumor cell apoptosis. No local side effects were observed in relation with treatment. This report highlights the need for efficient and safe topical therapies in the management of skin neoplasms and supports the use of potassium dobesilate in non-melanoma skin cancers treatment.

Keywords: Fibroblast growth factor, Fibroblast growth factor inhibitor, Topical therapy, Nonmelanoma skin cancer, STAT3.

INTRODUCTION

Non-melanoma skin cancers account to half of cell cancer diagnosed in the United States totalling over 1 million new cases every year [1]. Squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) are the most common forms of non-melanoma skin cancer. SCC is the most aggressive form of non-melanoma skin cancer and unlike BCC can metastasize. Skin SCC arises from the malignant proliferation of keratinocytes in the epidermis. Actinic keratosis (AK) constitutes the initial epidermal lesion in a disease continuum that may progress to skin SCC [2,3,4]. AK are lesions typically 2 to 6 mm in diameter, that are more easily felt than seen. Although skin SCC is locally invasive, surgical excision or topical therapy is usually curative. However, surgical management of SCC at some regions of the skin may require reconstructive procedures that can result in significant scarring and increased morbidity and dysfunction. Topical therapy may be preferable to surgery depending on anatomic localizations and when patients reject it or are poor surgical candidates. 5% 5-fluorouracil (5-FU) cream has been postulated for treatment of skin SCC but clinical evidence of the efficacy of the aforementioned 5-FU cream is not excessively convincing. Furthermore, the drug can cause inflammatory reactions, wound infections, ulcers and scarring [5].

The major causative factor for skin cancers is ultraviolet radiation (UVR) from sunlight. UVR, besides resulting in characteristic DNA damage, also causes tumor promotion by inducing various signal transduction pathways which can lead to distinct cellular responses. Very recently it has been shown that UVR promotes, by altering the Notch pathway, the transformation of dermal fibroblast, which subsequently begin to express the characteristic markers of cancer activated fibroblasts (fibroblast growth factors, matrix metalloproteinases, as well as an abundant deposition of Tenascin C and Periostin, two interacting matricellular proteins that are known to form cancer stem cell niches), at the same time as the number of inflammatory cells *in situ* increases [6,7]. Fibroblast growth factor (FGF) has been shown to play a critical role in the hallmark biological processes of cancer development, invasion and metastasis [8]. In addition, many direct evidences support the involvement of FGF in inflammatory processes, which may explain the rapid and effective clinical reversion of pine caterpillar-induced allergic contact dermatitis driven by topical dobesilate, a well characterized FGF inhibitor [9, 10]. Accordingly, drugs that disrupt inappropriate FGF signals should have significant therapeutic and

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preventive effects in a variety of cancers regardless of their origin. We report here the safety and efficacy of topical application of dobesilate in a patient having a scalp SCC.

Case presentation

A 83-years-old man presented field cancerization characterized by several AK lesions located in the face and in the scalp. After approval of our Institution Ethical Committee, patient signed an informed consent form, which includes a comprehensive description of dobesilate. We decide to treat first the face AK lesions with a 5% potassium dobesilate cream that was prepared at the pharmacy Department of the Hospital Universitario Ramón y Cajal in Madrid, Spain, according to treatment of this disease already described [11]. This formulation does not contain any keratolytic agent. Dobesilate cleared facial keratosis lesion. After two months the patient returned for the management of the scalp AK lesion. At this time, patient revealed a skin SCC of 6 mm in diameter in the scalp originated from a previously identified hyperkeratotic AK (Figure **1A**, **B**). Topical dobesilate 5% cream was self applied by the patient twice a day on the scalp SCC for 4 weeks. At that time, potassium dobesilate has induced a complete clearance of SCC lesion (Figure **1C**). There was an excellent postreatment cosmesis after dobesilate application. No recurrence of tumor was observed after six months follow-up.

DISCUSSION

Topical agents currently available to treat skin tumors necessitate prolonged courses of field directed therapies that often produce skin irritation and usually associate with less than optimal compliance, which, in turn, adversely affects lesion clearance.

Dobesilate is the most efficient member of a FGF inhibitor family of phenyl derivatives recently described and characterized in detail, using animal models as well as high resolution molecular and physico-chemical approaches, by Fernández *et al*. [10]. Dobesilate recognized both FGF and its receptors (FGFR), displacing heparin from their respective binding site, modifying the three-dimensional structure of the growth factor at its receptor recognized site, and, consequently, dissociating the receptor-growth factor signalling complex [10]. We previously reported the efficacy of dobesilate in experimental melanoma [12] as well as in human BCC [13-15] and AK [11]. The successful results prompted us to widen these studies to skin SCC, since the FGFR1 gene is amplified in SCC, and its increased expression promotes keratinocyte proliferation and tumor progression [16]. AK and skin SCC are both strongly associated with sun exposure [17].

AK is a common dermatological condition thought to precede the development of skin SCC [7]. SCCs are very malignant tumors in humans, occurring in organs, such as skin, oral mucose and upper digestive tract, lung and urogenital apparatus. Although, initially, FGF has been implicated in pathogenesis of SCC localized in oral mucose and upper digestive tract [18], it has been later implicated in lung SCC [19], and more recently in skin SCC [6, 7]. Mutation or epigenetic inactivation by UV light in dermal cells promotes activation of cancer activated fibroblasts (CAF) that up regulate FGF, which in turn attracts inflammatory cells. This biological process has been postulated in the evolution of AK to skin SCC [6].

FGFs are a highly conserved pleitropic signaling molecules involved in many biological processes including proliferation, differentiation, angiogenesis, cell migration and survival [20]. The wide pleiotropism of

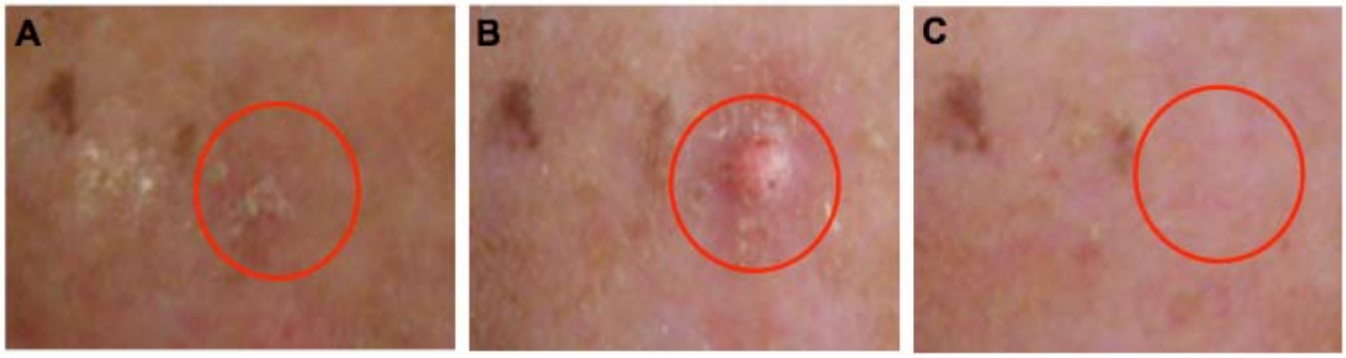

Figure 1: Efficacy of topical dobesilate in clearing scalp skin squamous cell carcinoma. The AK lesion in (**A**) evolves in two months to a skin squamous cell carcinoma (**B**). Dobesilate cream cleared squamous cell carcinoma (**C**).

these proteins requires that FGF availability is stringently controlled. Thus, it is not surprising that inappropriate levels of FGF have been implicated in various diseases including cancer development, progression and metastasis [20-23].

Increased evidence supports that the oncogenic potential of signal transducer and activator of transcription 3 (STAT3) plays an important role in skin tumorigenesis [24-25]. Persistent STAT3 activation in malignant cells stimulates proliferation, survival, angiogenesis, invasion and tumor-promoting inflammation. Moreover, STAT3 activation within immune cells enables suppression of anti-tumor immunity and promotes differentiation and recruitment of immature myeloid cells (iMCs) and tumor-associated macrophages (TAM) [26]. Although in many cancers STAT3 is not directly activated by oncogenic mutations, it exerts critical oncogenic functions in both cancer and immune cells within the microenvironment. This implies that drugs that disrupt STAT3 signaling should have significant therapeutic and preventive effects in a variety of cancers regardless of their origin. FGF activates STAT3 [27]. We have previously reported that STAT3 which is activated in glioma cells and in BCC could be inhibited with dobesilate [15, 28].

The results here reported, clearly shows clearance of skin SCC after topically applied dobesilate cream. This report highlights the need for use of efficient and safe topical therapies in the management of skin neoplasms and supports the use of potassium dobesilate in nonmelanoma skin cancers treatment. Obviously, the actual clinical value of dobesilate in skin SCC described here needs to be further investigated in a prospective randomised clinical trial with a longer follow-up. This study is ongoing.

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