Field Treatment of Actinic Keratoses – Focus on COX-2-Inhibitors

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Abstract. Actinic keratoses (AK) represent the most common carcinoma in situ of the skin and show continuously increasing incidences worldwide. Clinically, AK occur as multiple lesions in sun-exposed areas, which has been referred to as field cancerization. Novel treatment modalities for actinic field cancerization include 3% diclofenac in 2.5% hyaluronic acid (HA). Recent investigations have gained insights in the mode of action of diclofenac in HA, showing that the induction of apoptosis is the major mode of action of this treatment.

Herein, we give an overview about actinic keratosis focusing on treatment with the COX-2 inhibitor diclofenac 3% gel and summarize current concepts of its antineoplastic mode of action.

Key words: actinic keratoses, carcinoma in situ, diclofenac, hyaluronic acid, apoptosis, COX-2.

Introduction

Actinic keratoses (AK) represent the most common carcinoma in situ of the skin showing continuously increasing incidences worldwide. However, as AK are not recorded in tumor registries, the real incidence remains unknown and seems to be underestimated. Risk factors driving this rise in AK numbers include UV exposure and increasing numbers of older people in the population. The importance of UV radiation in skin carcinogenesis is reflected in the geographic distribution that shows a correlation of increased prevalence of AK in areas of high UV exposure. Furthermore, the increase of recreational sun exposure during the past decades has contributed to the current epidemiologic developments. Other risk factors for AK include fair skin type, immunodeficiency, e.g. after organ transplantation, arsenic exposure and hereditary disorders (xeroderma pigmentosum). Immunocompromised individuals show a significant increase of AK with a 250-fold higher risk for AK and 100-fold increase for invasive squamous cell carcinoma (SCC) when compared to the normal population. Moreover, progression of AK to invasive SCC is more common in organ transplant recipients, with 40% of AKs developing into invasive SCC.

Clinically, AK appear as hyperkeratotic, rough lesions that occur on areas of chronically sun damaged skin including the scalp, face, ears, forearms and dorsum of the hands. AK have been previously referred as preneoplastic lesions, but are nowadays defined as carcinoma in situ of the skin.
Histopathologically, AKs are characterized by an epidermal proliferation of atypical keratinocytes starting from the basal cell layer. Morphologically, the cells of AK and SCC may be indistinguishable. According to the epidermal involvement of dysplasia, three subtypes may be differentiated. A recent classification proposed by Roewert-Huber et al classifies AK into early in situ SCC type AK I (mild), early in situ SCC type AK II (moderate) and in situ SCC type AK III (severe). This classification describes the disease continuum from AK to SCC in the context of field carcinization.

Skin Carcinogenesis

The most important factor in the pathogenesis of AK is chronic UV exposure. UV-B radiation (290-320 nm) has been shown to directly induce DNA and RNA mutations via thymidine dimer formation. In this regard, the mutation of p53 is of special importance. This tumor suppressor gene is located on chromosome 17p132 and leads to cell cycle arrest, allowing repair of DNA damage. Dysregulation of p53 results in uncontrolled growth and proliferation of damaged keratinocytes and potentially neoplastic cells, representing an early step in the carcinogenesis of AK and SCC. These mutations are detected in both AK and SCC as they occur in the early phase in the continuum from early keratinocyte dysplasia to AK and SCC. Other molecular markers that may indicate an increased likelihood of malignancy include the expression of p16

Apoptosis is defined as programmed cell death and represents a critical point in tumor cell formation. In normal cells, apoptosis leads to the ordered destruction of damaged cells via two different pathways. The extrinsic pathway is initiated by binding of cell death ligands (TNF α, TRAIL, CD 95/FasL) on cellular receptors and activation of the caspase pathway. The intrinsic pathway involves p53 and mitochondria and leads to the release of pro-apoptotic factors including cytochrome c. The mitochondrial pathway of apoptosis is controlled by pro- and anti-apoptotic Bcl-2 proteins. Inactivation of apoptotic pathways leads to uncontrolled proliferation of cells and, therefore, represents a critical step in cancerogenesis. Furthermore, they may be responsible for treatment resistance. Apoptosis-inducing therapeutic strategies represent an important approach in the development of effective cancer therapy. These treatment approaches aim to restore p53 activity, downregulate anti-apoptotic Bcl-2 or NF-κB and upregulate extrinsic, death receptor-mediated pathways as the main course for tumourigenesis are defects in pro-apoptotic signal pathways.

The Role of COX-2 in the Pathogenesis of Skin Cancer

Cyclooxygenases (COX) are enzymes which activate the release of several prostaglandins with different biological properties. Of these, prostaglandin E2 (PGE2) represents the main mediator of inflammation and tumor growth. Prostaglandins belong to the class of eicosanoids and are ubiquitously present in most cell types. The initial step of prostaglandin synthesis is the COX mediated synthesis of prostaglandins PGH2, PGI2, PGD2, PGF2α and thromboxane A2 (TXA2). Two different classes of COX can be distinguished, COX-1 and COX-2. Whereas COX-1 is constitutively expressed and plays a role in physiological effects such as cytoprotection of gastric mucosa or renal circulation, COX-2 is induced by pro-inflammatory cytokines, growth factors and tumour promoters including protein kinase C (PKC), mitogen-activated protein kinase (MAPK) and NFκB. The upregulation of COX-2 is strongly related to non physiological conditions like inflammation and cancer and high expression of COX-2 has been shown to be a risk factor for cancer development.
been demonstrated in several solid tumours including colon, lung, breast and epithelial skin cancer. In this regard, COX-2 upregulation was shown in AK, SCC and BCC\textsuperscript{26,27}.

Mode of Action of COX-2 Inhibitors in the Treatment of Actinic Keratosis

Recently, the COX-2 inhibitor diclofenac has been introduced in a formulation with hyaluronic acid (3\% diclofenac in 2.5\% hyaluronic acid) for the treatment of actinic keratoses. The main mode of action of this COX-2 inhibitor seems to be the induction of apoptosis, which has been demonstrated in several cancer models\textsuperscript{19}. Furthermore, a strong correlation between COX-2 activity and expression of the anti-apoptotic protein of the Bcl-2 family has been demonstrated. Apoptosis induced by diclofenac and other non steroidal anti-inflammatory drugs (NSAIDs) involves the extrinsic pathway and activation of caspases, mainly caspase 9. Xenograft models have shown the pro-apoptotic effects of NSAIDs in vivo\textsuperscript{26,29} and topical application of diclofenac 3\% gel in colon adenocarcinoma xenografts in nude mice inhibited prostaglandin synthesis and increased the apoptotic index\textsuperscript{30}. A recent study by Eberle et al\textsuperscript{20} investigated the effects of 3\% diclofenac in 2.5\% hyaluronic acid (diclofenac /HA) on induction of apoptosis in four cutaneous SCC cell lines (SCL-1, SCL-II, SCC-12 and SCC-13) derived from SCC lesions of the face, and three cultures of normal human keratinocytes (NHK). Apoptosis was significantly induced by diclofenac /HA in three of four SCC cell lines (SCL-II, SCC-12 and SCC-13) and activation of the caspase cascade was shown. Furthermore, the study showed that diclofenac was responsible for the induction of apoptosis, whereas hyaluronic acid did not show any anti-apoptotic effects. Hyaluronic acid is a high molecular polysaccharide chain, which is part of the normal extracellular matrix. In diclofenac 3\% gel, it may provide a more sustained delivery of diclofenac to the skin cells. Furthermore, it has been shown that HA binds the CD44 receptor of keratinocytes which may lead to an increased bioavailability of diclofenac within the epidermis, resulting in prolongation of its half-life\textsuperscript{31}.

Besides the induction of apoptosis as the main mode of action, other mechanisms seem to be involved in the antitumoral effectivity of NSAIDs such as antiangiogenesis and direct inhibition of tumor cell proliferation\textsuperscript{32,33}.

Treatment of Actinic Keratosis with 3\% Diclofenac in Hyaluronic Acid

Several randomized, double-blind, HA gel vehicle-controlled clinical studies have evaluated the efficacy of topical diclofenac HA gel in patients with AK. The 30-day interval between the end of treatment and the evaluation of efficacy was due to earlier findings stating a significant advantage for diclofenac HA gel over placebo, when efficacy was evaluated 4 weeks after the end of treatment. The product significantly reduced lesions when applied for 60 or 90 days, however, the efficacy was significantly increased after 90 days of application. A double-blind, randomized, placebo-controlled multicenter study showed response rates of 79\% (treatment group) versus 45\% in the placebo group; a complete healing was seen in 50\% (treatment group) versus 20\% in the control group (p < 0.001\%\textsuperscript{34}). Other controlled studies showed similar effects\textsuperscript{35,36}.

Adverse effects were skin related and mild to moderate in severity (pruritus, erythema, dry skin, hypo and parasthesia). Systemic bioavailability of diclofenac was demonstrated to be considerably lower after topical application than after systemic administration and the drug demonstrated a good safety profile.

Recent investigations have shown the efficacy of 3\% diclofenac in HA for the treatment of actinic keratosis in organ transplant recipients with response rates comparable to those seen in the immunocompetent population, and an excellent safety profile\textsuperscript{37}. Furthermore, diclofenac 3\% gel has also shown efficacy in the treatment of actinic cheilitis. A recently published case series showed histological clearance in 4/6 patients\textsuperscript{38}.

Conclusion

Actinic keratoses are currently defined as carcinoma in situ of the skin and represent a continuum from keratinocyte dysplasia to invasive squamous cell carcinoma. Diclofenac 3\% gel is a novel treatment approach for field cancerization which has shown efficacy for AK in several studies. Recent insight in the mode of action of diclofenac 3\% gel indicates that apoptosis represents the major mode of action of this treatment. The efficacy of diclofenac 3\% gel has also been shown for AK in organ transplant recipients and for the treatment of actinic cheilitis.

Conflict of interest
Authors have no conflict of interest to declare.

References


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