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REVIEW ARTICLE

Photodynamic therapy for skin field cancerization: an international consensus. International Society for Photodynamic Therapy in Dermatology

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Abstract

Field cancerization is a term that describes the presence of genetic abnormalities in a tissue chronically exposed to a carcinogen. These abnormalities are responsible for the presence of multilocular clinical and sub-clinical cancerous lesions that explains the increased risks of multiple cancers in this area. With respect to the skin, this term is used to define the presence of multiple non-melanoma skin cancer, its precursors, actinic keratoses and dysplastic keratinocytes in sun exposed areas. The multiplicity of the lesions and the extent of the area influence the treatment decision. Providing at least equivalent efficacy and tolerability, field directed therapies are therefore often more worthwhile than lesion targeted approaches. Photodynamic therapy (PDT) with its selective sensitization and destruction of diseased tissue is one ideal form of therapy for this indication. In the following paper the use of PDT for the treatment of field cancerized skin is reviewed and recommendations are given for its use.
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Conflict of interest

Dr Braathen has received speakers' honoraria from Galderma and received financial support from Galderma and PhotoCure for performing clinical trials. He has consulted for PhotoCure. Dr Morton has received financial speakers' honoraria from Galderma and is a member of Leo Pharma and Basilea advisory boards. He has received travel scholarships from 3M, PhotoCure and Phototherapeutics Ltd. Dr Basset-Seguin does consultant work for Galderma, 3M, Meda, PhotoCure,Vichy, Roche, Novartis and P Fabre. She has received financial support from Photocure, 3M, Meda and Genentech for performing clinical trials. Dr Bissonnette has received speakers' honoraria from Galderma and Leo Pharma. He has received financial support from PhotoCure, Graceway, Galderma, Leo Pharma and DUSA Pharmaceuticals for performing clinical trials. Dr Gerritsen has received speakers' honoraria from Galderma, 3M and Medac and joined Galderma advisory board. She has received financial support from PhotoCure, Galderma and 3M, for performing clinical trials. Dr Gilaberte has received speakers' honoraria from Galderma, Astellas and Abbott. She has received financial support from Pfizer for performing clinical studies. Dr Calzavara-Pinton has received speakers' honoraria from Galderma, Pfizer, Schering-Plough, La Roche Posay, Pierre Fabre, Leo and Difa-Cooper. He has received financial support from PhotoCure ASA, Pfizer, Difa-Cooper, Serono and Schering Plough for performing clinical trials. Dr Sidoroff has received financial speakers' honoraria from Galderma. Dr Wulf has received speakers' honoraria from and is a consultant for Galderma and PhotoCure. Dr Szeimies has served as a consultant for, and has received speakers' honoraria from Galderma. He has received financial support from Almirall, Energist, Intendis, 3M, PhotoCure, photonamic, Waldmann Medizintechnik and Wavelight AG for performing clinical trials.

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Introduction

In 1953, Slaughter and coworkers introduced the term 'field cancerization'.[1] They reviewed tumors of the lip, oral cavity and pharynx in 783 patients in 1944 and 1946, having demonstrated that the large majority of oral squamous-cell cancers have much greater horizontal than depth extent and a multicentric origin.[2,3] They concluded that their findings reinforced the concept of multicentric origin and multifocal growth of these tumors, and that the cause probably was a regional carcinogenic activity of some kind. It was known at that time that thermal trauma, sunlight, X-ray and gamma radiation, industrial exposure to hydrocarbons and arsenic ingestion all had carcinogenic effects on the skin.[1] The concept of field cancerization has later been supported by others.[4]

It is generally accepted that sunlight is the main carcinogenic cause of skin cancer and that it is the UVB part of the sunspectrum that is mainly responsible. p53 protects against skin cancer induction caused by UV-B radiation mutations,[5] and UV-induced p53 mutations seem to play an important role in cancer induction. Over 90% of squamous cell carcinomas and more than 50% of basal cell carcinomas from New England patients contain UV-like mutations in the p53 suppressor gene.[6] Furthermore, there are many studies on induction of cancer, actinic keratosis and specific p53 mutations by UVB light in human skin.[7–14] Sunscreens can effectively prevent UV-induced p53 mutations. In a mouse model an 88–92% reduction in the number of p53 mutations was achieved with the use of sunscreens [15]

Dermatologists are frequently consulted by patients with sun-damaged skin. Actinic keratosis (AK) is one of the major problems for these patients, and as AKs have the potential to transform into invasive squamous cell carcinomas they must be treated.[16] Sun-damaged skin of patients does however often suffer from field cancerization, and organ transplant recipients (OTR) are particularly severely affected by field cancerization. Within 5 years about 40% of OTR develop actinic keratosis, and they have a 40–250 fold increase in squamous cell carcinomas (SCC) with a 10-fold increase in mortality because of SCC. The frequency of development of both SCC and BCC in transplant recipients is significantly associated with the duration and level of immunosuppressive therapy, older age at time of transplantation, male sex, outdoor occupation and the presence of AK.[17]

There are a number of treatment options available for AK, the most commonly used are cryotherapy, PDT, topical 5-fluorouracil, topical imiquimod, diclofenac, curettage and electrocoagulation, laser therapy, surgery and radiation therapy.[16] The latter options are more often used by non-dermatologists.

Patients suffering from sun induced field cancerization usually have their lesions on the bald scalp areas, the ears, face and presternal area, the dorsum of the hands and the anterior aspect of the lower legs. Multiple and recurring non-melanoma skin cancers are often seen in these areas. The presence of field cancerization requires treatment options that allow treating large areas without too much discomfort and with a good cosmetic outcome.

The diagnosis of a field cancerization is normally made by clinical inspection and is easy for dermatologists. However, at early stages it is sometimes more difficult. To confirm diagnosis, it is required to perform a biopsy to identify invasive cancer and/or to use fluorescence diagnosis [18] to delineate target areas with incipient lesions. In some patients it can be difficult to distinguish between a non-melanoma skin cancer, Bowen's disease and in particular between hypertrophic AK and an invasive SCC. Examination of p53 mutational status is so far not available on a routine base.

Management of field cancerization

Optimal management of skin field cancerization needs considerable expertise and should ideally be performed by well-trained and experienced dermatologists. It includes correct diagnosis, information to and motivation of the patient respecting important psychological factors, information on treatment options. Finally a consensus about treatment modality must be obtained between patient and dermatologist. The long term care must also be planned in cooperation with the patient.

Information to the patient

When field cancerization is diagnosed patients should be told that the therapeutic approach will require multiple treatments and long term follow-up. Information on the disease, the different treatment options and the potential development into invasive cancer should be discussed to motivate patients to undergo appropriate treatment. Together with the patient, a treatment programme is chosen. It is also important that the programme includes long-term surveillance with multiple visits. New lesions frequently occur as do recurrences in previously treated areas. The frequency of follow-up visits is determined individually based on the severity of the case, the presence or absence of immunosuppression, the number and frequency of previous skin cancers. Frequency of these follow-up visits may vary from every few months to every year. A dermatological follow-up programme with short intervals of follow-up visits (every 2–6 months) is particularly important for organ transplant recipients to detect and treat non-melanoma skin cancers early.

A very important subject to discuss with the patient is the long-term evolution of the disease and in particular the final cosmetic outcome. Although a few patients may not express concern about

cosmetic outcome, given that most lesions are located on visible sites, most patients value a therapy which offers good cosmesis. In addition, skin appearance is becoming more and more important nowadays. For patients who are concerned about the cosmetic outcome the treatment options are relatively restricted.

Besides clinical response and long-term cure rates there are mainly two factors that are important to most patients: side effects including downtime, the appearance of the skin and the discomfort during and after the therapy and the final cosmetic outcome.

Patients usually prefer a treatment which is effective, short-lasting, with as little discomfort as possible and with the best functional as well as cosmetic outcome. All these factors must be discussed with the individual patient to choose the most suitable treatment.

Photodynamic therapy (PDT)

PDT is a relatively new treatment that is based on a phototoxic reaction caused by a photosensitizer that is activated by light to form reactive oxygen species. In dermatology, PDT is mainly performed using topical precursor molecules of the biosynthetic pathway of heme such as 5-aminolevulinic acid (ALA) or its methyl ester methyl aminolevulinate (MAL). In the skin these molecules are then converted into photoactivatable porphyrins, in particular protoporphyrin IX (PpIX).[18] The cell damage and consecutive death is then induced upon illumination of the skin with blue or red light.

PDT is a well-documented therapy for non-melanoma skin cancer and its precursors i.e. AK and Bowen's disease. In addition to high clinical response rates, the cosmetic outcome is also excellent, and in controlled studies patients preferred PDT compared to other therapy options.[18–23]

PDT with ALA applied to hairless mice delays UV photocarcinogenesis,[24] and Sharfaei *et al.*[25] demonstrated that weekly topical application of MAL-PDT followed by light exposure delays the development of UV-induced skin tumors in mice. Even only two sessions of MAL-PDT in a study in mice at day 45 and 90 delayed UV-induced skin cancer formations by about 83 days.[26] In humans, Wulf *et al.*[27] showed prevention of new skin lesions in renal transplant recipients using topical PDT. Thus there is evidence for the concept of PDT as a skin cancer prevention modality even in immunosuppressed organ transplant recipients. For immunocompetent patients, this has also been demonstrated by Apalla and coworkers.[28] They treated in a split face, placebo-controlled design, facial AKs with a field-targeted approach and evaluated the presence of new appearing lesions at 12 months in the control area and the ALA-PDT treated area. They were able to demonstrate a significant delay of about 6 months until new AKs developed in the ALA-PDT treated area.[29]

The advantages of PDT are that it is performed as an office-based treatment within one day and that the period of therapy-induced inflammation is shorter compared to long-term application of drugs like imiquimod, 5-fluorouracil or diclofenac sodium. In some cases there are pustule and crust formations, but these conditions usually resolve in about 10 days. A postinflammatory erythema can however occur and last for a few months in many cases. However, this side effect can also be seen with the other mentioned treatment options but is then usually more intense and lasting.

The major problem of PDT is pain during illumination.[28] Pain usually disappears after stopping the illumination. In rare cases it can continue to the next day, and even longer. The pain is dependent on the location and the size of the treated area and is often pronounced when treating large field cancerized areas on the forehead and the bald scalp in men.[18–23] Based on the size of involvement it is sometimes necessary to divide the PDT treatment into several sessions in order to make it more comfortable to the patient. If multiple light sources are used and large surfaces are treated, anaesthetic procedures like nerve blocks or exceptionally general anaesthesia are of help.[30]

When ALA or MAL is used for cases of field cancerization it is recommended to check for recurrences or treatment failures after a short period especially if the treated areas are quite large. Usually a follow-up visit is scheduled after 3 months but in OTR shorter intervals may be necessary.[16,17,20,21] If there are recurrences or newly developed lesions at the follow-up visits, a retreatment with PDT can be performed. The combination of PDT with 5-FU or imiquimod is another option.[31] In case of a recurrence following a second PDT session a skin biopsy may be required to rule out an invasive squamous cell carcinoma.

In conclusion, PDT is a suitable therapeutic option for patients with multiple AKs and a diagnosis of field cancerization. It may be one of the best options due to the combination of a high and sustained response rate, limited downtime for patients and an excellent aesthetic outcome.

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