Guidelines on the use of photodynamic therapy for nonmelanoma skin cancer: An international consensus

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Topical photodynamic therapy (PDT) is used to treat nonmelanoma skin cancers, such as actinic keratoses, Bowen's disease, and basal cell carcinoma (superficial and nodular). This article presents up-to-date, practical, evidence-based recommendations on the use of topical PDT using 5-aminolevulinic acid or methyl aminolevulinate for the treatment (and prevention) of nonmelanoma skin cancers. A systematic literature review was conducted (using MEDLINE), and recommendations were made on the basis of the quality of evidence for efficacy, safety/tolerability, cosmetic outcome, and patient satisfaction/preference. Topical PDT is highly effective in the treatment of actinic keratoses, Bowen's disease, superficial and thin nodular basal cell carcinomas, with cosmesis typically superior to that achieved with existing standard therapies. PDT may also be a means of preventing certain nonmelanoma skin cancers in immunosuppressed patients. (J Am Acad Dermatol 2007;56:125-43.)

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The recommendations set forth in this article have been prepared for dermatologists on behalf of the International Society for Photodynamic Therapy in Dermatology and reflect the best data available at the time this report was prepared. Caution should be exercised in interpreting the data; the results of future studies may require alteration of the conclusions or recommendations of this report. It may be necessary or even desirable to depart from the recommendations in the interests of specific patients or special circumstances. Just as adherence to these recommendations may not constitute a defense against a claim of negligence, so deviation from them should not necessarily be deemed negligent.

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Photodynamic therapy (PDT) involves the use of light to activate a photosensitizer, localized in diseased tissues, resulting in the formation of cytotoxic reactive oxygen species. Topical PDT is effective in treating certain nonmelanoma skin cancers (NMSCs), and there are several studies suggesting its potential in nononcologic indications, including the treatment of acne, photoaging, viral warts, and morphea.[1,2]

Topical PDT is currently mainly used to treat actinic keratosis (AK) and superficial NMSCs in an increasing number of countries, with many recent publications providing new evidence in this field. There is now a need for up-to-date practical evidence-based recommendations to guide clinicians in the use of PDT for NMSCs.

Abbreviations used:

AK:	actinic keratosis
ALA:	5-aminolevulinic acid
BCC:	basal cell carcinoma
BD:	Bowen's disease
MAL:	methyl aminolevulinate
nBCC:	nodular basal cell carcinoma
NMSC:	nonmelanoma skin cancer
PDT:	photodynamic therapy
sBCC:	superficial basal cell carcinoma
SCC:	squamous cell carcinoma

METHOD

These recommendations were developed during a meeting of the International Society for Photodynamic Therapy in Dermatology in January 2005. A systematic literature review was conducted (using MEDLINE), and recommendations were made based on the quality of evidence for efficacy, safety/tolerability, cosmetic outcome, and patient satisfaction/preference. Cosmetic outcome and patient preference are important considerations when treating superficial NMSCs, which generally respond well to treatment and have a good prognosis. Health economics were not considered, since differences in national health systems and pricing makes it difficult to form general conclusions that are relevant at an international level. Quality of evidence and strength of recommendations were scored according to the system shown in the Appendix, which appears after the references.

LITERATURE REVIEW

Epidemiology of NMSCs

NMSCs are the most common malignancies in the Caucasian population, accounting for more than one third of all adult cancers in the United States, with approximately 900,000 to 1,200,000 new cases per year,[3] up to 18- to 20-fold more than malignant melanoma.[4] The incidence of NMSC has been steadily increasing worldwide at a rate of 3% to 8% per year since 1964,[5] with greater increases nearer the equator.[6] In Australia, the incidences of squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) rose by 133% and 35%, respectively, between 1985 and 2002.[7] Immunosuppressed transplant patients have an even higher incidence of NMSC (eg, after kidney transplantation, 1-year incidence of SCC is 7%, increasing to 70% after 20 years[8]).

There is wide geographic variation in the incidence of NMSCs (eg, in Australia, incidences of NMSCs are much higher than in Europe [2% vs 0.12%]), mainly because of differences in climate and the skin type of local populations. The link between sun exposure, skin type, and NMSC is well established and supported by a large body of epidemiologic data. In addition, a patient with an NMSC lesion is much more likely to have additional lesions, particularly in the first year after diagnosis of the first lesion (in 36.39% of patients, additional lesions develop in the first year).[9,10]

NMSCs have a generally favorable prognosis, when treated early. BCCs do not, or rarely, metastasize but can be locally invasive if left untreated. SCC can be life threatening. It is therefore important to treat Bowen's disease (BD, SCC in situ), and AK.[11]

Topical PDT: Mechanism of action

Methyl aminolevulinate (MAL), marketed as Metvix in Europe, Australia, and New Zealand and 5-aminolevulinic acid (ALA), marketed in the United States and Canada as Levulan, are topical photosensitizer precursors used to treat NMSC. When applied, ALA and MAL are converted by the neoplastic tissue into photoactive porphyrins. There is preferential production of photoactive porphyrins in neoplastic relative to nonneoplastic cells after ALA and MAL application, with evidence of greater selectivity for neoplastic tissue with MAL.[12-15] After topical application of MAL or ALA, sufficient time must be left to allow for production and accumulation of porphyrins before activation with light. For the treatment of both AK and BCC, MAL needs to be applied for 3 hours under occlusion. For the treatment of AK with ALA, US and Canadian monographs stipulate an incubation time of 14 to 18 hours.

It is important to choose an appropriate light source for PDT to ensure optimal photosensitizer excitation and tissue penetration. The spectral output of the light source should match one of the excitation peaks of the photosensitizer. The depth of light penetration in the skin increases with longer wavelengths. Although blue light may allow sufficient