Original article

PHOTODYNAMIC THERAPY IN THE MANAGEMENT OF NONMELANOMA SKIN CANCERS

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Photodynamic therapy involves the use of light to activate a photosensitizer, localized in the diseased skin, resulting in the formation of cytotoxic reactive oxygen species. Topical photodynamic therapy (PDT) is used to treat nonmelanoma skin cancers, such as actinic keratoses, Bowen's disease, and basal cell carcinoma, superficial as well as nodular. This article presents up-to-date, practical recommendations on the use of topical PDT using 5-aminolevulinic acid or methyl aminolevulinate for the treatment as well as 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, tolerability and cosmetic outcome. Most authors concluded that topical PDT was highly effective in the treatment of actinic keratoses, Bowen's disease, superficial and thin nodular basal cell carcinomas, without cosmetic defects usually seen in standard therapeutic procedures. Photodynamic therapy may also be a means of preventing certain nonmelanoma skin cancers in immunosuppressed patients. *Acta Medica Medianae 2008;47(2):28-32.*

Key words: *photodynamic therapy, nonmelanoma skin cancers, methyl aminolevulinate, 5-aminolevulinic acid*

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Introduction

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

Topical PDT is currently mainly used to treat actinic keratosis (AK) and superficial nonmelanoma skin cancers (NMSCs). There is now a need for up-to-date practical evidence-based recommendations to guide clinicians in the use of PDT for NMSCs.

Epidemiology of nonmelanoma skin cancers

Nonmelanoma skin cancers are the most commom malignancies 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 (2) up to 18-to 20-fold more than malignant melanoma (3). The infcidence of NMSCs has been steadily increasing wordwide at a rate of 3% to 8% per year since 1964 (4) with greater increases nearer the equator (5). In Australia, the incidences of squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) rose by 133% and 35%, respectively, between 1985 and 2002 (6). 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 (7).

There is a wide geographic variation in the incidence of NMSCs, mainly because of differences in climate and 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, particulary in the first year after diagnosis of the first lesion (in 36,39% of patients, additional lesions develop in the first year) (8).

Topical PDT: Mechanism of action

Methyl aminolevulinate (MAL), marketed as MetvixR in Europe and 5-aminolevulinic acid

(ALA), marketed in United States as LevulanR, are topical photosensitizer precursors used to treat NMSC. When applied, ALA and MAL are converted by the neoplastic tissue into photoactive phorphyrins. There is preferential production of photoactive porphyrins in neoplastic reactive to nonneoplastic cells after ALA and MAL application, with evidence of greater selectivity for neoplastic tissue with MAL (9,10). 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 BCC, MAL needs to be applied for 3 hours under occlusion.

It is important to choose an appropriate light source for PDT to ensure optimal photosensitizer excitation and tissue penetration. The depth of light penetration in the skin increases with longer wavelengths. So, red light penetrates deeper and may be more effective for the treatment of thicker lesions such as BCC. After illumination, photoactive porphyrins are excited to their higher energy state. Energy is then transferred to oxygen molecules, resulting in the formation of cytotoxic free radicals and singlet oxigen. The precise mechanisms, at a cellular level, underlying the efficacy of topical PDT in the treatment of NMSC are not fully known. Both apoptosis (11) and necrosis (12) have been described as occuring after topical PDT, and the importance of each phenomenon may be influenced by intracellular localization of the photosensitizer and illumination parameters.

Superficial basal cell carcinoma (sBCC)

BCC is the most common malignant skin cancer, presenting as ulcerative (uBCC), nodural (nBCC), superficial (sBCC) and morpheic (mBCC). BCCs are locally aggressive tumors that very rarely metastasize. Guidelines have recently been developed to orient treatment choice according to tumor characteristics (histology, size, location, and evolution, ie, primary or recurrent lesion (13,14). Primary sBCC outside the H zone of the face can be classified as low risk, where cosmetic outcome can be considered together with antitumor efficacy. Cosmetic outcome is also a particularly important consideration for sBCC since this disease is more frequent in younger patient, often appearing as multiple lesions localized on body sites susceptible to dystrophic scarring after surgery.

PDT is a noninvasive option for sBCC that has been specifically evaluated for efficacy and cosmetic outcome (15-19). There is now much supportive evidence for the use of PDT in sBCC, including large phase III studies of MAL-PDT. Three month clearance rates with this therapy range from 80% (in complex cases, with recurrent or large lesions, or H-zone lesions) to 97% in primary sBCC (16). New therapies for BCC are required not only to demonstrate high efficacy, but also long-term responses that are at least equivalent to standard therapies. Four-year follow-up of a phase III study (17,20) suggest that recurrence with MAL-PDT is comparable with cryotherapy (22% for MAL-PDT vs 19% for cryotherapy at 48 months (17). PDT was generally well tolerated in these patients, with some pain and erythema experienced by most patients. Wang et al. (19) found that BCC patients experienced similar levels of pain with PDT and cryotherapy.

Electrodesiccation and curettage has been used for the treatment of BCC lesions, especially in past years. A systematic review by Thissen et al.(21) based on available studies found higher cumulative recurrence rates after 5 years with electrodesiccation and curettage (5,7%-18,8%) than has traditionally been considered to be "gold standard" treatment for BCC. However, patients may not be appropriate for surgery in certain situations (eg, large lesion, unsuitability for invasive therapy, poor ability for wound care, high risk of disfigurement, poor vasculature, concomitant use of anticoagulants, immunosuppression, diabetes, or inadequate prior response to standard therapies). In this respect, PDT may offer significant advantages over surgical or other destructive technicues. In a randomized comparator strudy of MAL-PDT, cosmetic outcome was superior to cryotherapy at 3 months (89% vs 50% of patients rated as having "good" or "exellent" cosmetic outcome) (20). High cure rates with superior cosmetic outcome makes PDT particularly well suited for the treatment of large, extensive, and multiple lesions. Horn et al.(16) found that cosmetic outcome improved over time in "difficult-to-treat" populations (complex cases, with recurrent or large lesions, or H-zone lesions) who might be expected to have poor cosmetic outcomes. In "difficult-to-treat" patients with either nBCC or sBCC (or both) treated with MAL-PDT, 76% of patients had "exellent" or "good" cosmetic outcome, rising to 94% after 24 months (16).

In conclusion, PDT is an effective and reliable treatment option for sBCC that offers exellent or good cosmetic outcome. PDT offers an advantage in the treatment of large, extensive, and multiple lesions. MAL-PDT has demonstrated long-term efficacy in sBCC, with 5-year follow-up.

Nodular basal cell carcinoma (nBCC)

Topical MAL has been shown to effectively penetrate into thick nodular BCC lesions (22). MAL has superior tissue penetration over ALA because of its decreased charge and increased lipophilicity (22), although these agents have not been compared directly in clinical studies of nBCC. In PDT for nBCC lesions larger than 2 mm, response may be optimized by debulking the tumor before treatment, with the re-treatment of lesions also possible if necessary.

The strongest evidence for topical PDT in nBCC comes from 5 phase III studies with MAL-PDT, in which a total of 220 nBCC lesions were treated (16, 23-26). Efficacy is consistently high, with 3-month complete response rates of 73% to 94% with MAL-PDT. Histologically controlled studies have confirmed the reliability of efficacy data (73% and 79%)(24,25). Horn et al.(16) and Vinciullo et al. (23) specifically examined MAL-PDT in "difficult-to-treat" as well as in "high-risk" cases and still found impresive 3-month response

rates of 94% and 87%, respectively. Studies with ALA report variable efficacy, eg, 92% (26,27), 61% (28), and 64% (29). Lower rates may be due to differences in lesion preparation and use of nonstandard light sources, such as laser or red light (30). In addition, the poorer penetration of ALA into nBCC lesions may also contribute to lower efficacy compared with MAL.

A 5-year recurrence rate of 14% has been found in patients who took part in a phase III study of MAL-PDT for nBCC (26). This rate is the same as at 36 months (ie, there were no further recurrences between 36 and 60 months after treatment), showing that MAL-PDT appears to remain effective in the longer term. For "difficult-to-treat" nBCC, recurrence rates at 48 to 60 months of follow-up vary from 18% to 30% (16,23). In a retrospective study of patients receiving MAL-PDT for the treatment of nBCC, recurrence rates of 7% and 14% for thin and thick nBCC lesions, respectively, were reported at a median 35-month follow-up (15). This suggests that thin nBCC may be particularly responsive to MAL-PDT, althought thickness of nBCC has not specifically been assessed in other studies (30). Thin nBCCs are also likely to require less lesion preparation and may be best suited to treatment by topical PDT.

MAL-PDT has been compared with the "gold standard" approach of surgery for nBCC (26). MAL-PDT provided a 3-month response rate that was not inferior to that achieved with surgery (91% compared with 98% for surgery, and a 60-month recurrence rate 14% compared with 4% for surgery (30). ALA has compared favorably with cryotherapy for nBCC, with 1-year recurrence rates of 13% and 21%, respectively. However, cryotherapy is not an ideal treatment for nBCC, and therefore this is not the best comparator (30).

PDT for nBCC is generally well tolerated, with predictable, transient, and manageable pain and erythema in most patients.

Cosmetic outcome with PDT in nBCC are generally very impressive, quoted as "exellent" or "good" in 82% to 95% patients (15,16,19,23-27). Cosmetic outcome with PDT was found to be superior to cryotherapy (19) and surgery (23). Cosmetic outcome with MAL-PDT was impressive even when the populations specifically included patients with lesions in cosmetically sensitive areas (16,23) with continued improvements seen over the long term. nBCC lesions less than 2 mm thick located outside the risk zone are considered low-risk tumors and their treatment should offer both optimal efficacy and cosmetic outcome.

Squamous cell carcinoma (SCC)

SCC lesions are potentially metastatic and can be life treatening. The standard treatments for SCC include surgery, curettage, cryotherapy, or radiation therapy. Three open-label studies have described the use of ALA-PDT in SCC, with initial complete response rates of 54% to 100% for superficial (confirmed to the papillary dermis) SCC, but with recurrence rates of up to 69% (31), mean 24% after 3-47 months (28,31,32).

Thus, although ALA-PDT has shown efficacy in some small studies of superficial SCC, the relatively high recurrence rates and metastatic potential of this serious condition have restricted further development. There are no published reports of the use of MAL-PDT for SCC. Therefore PDT cannot be recommended for the treatment of SCC at present (30).

PDT for NMSC prevention in immuno-suppressed patients

An area of strong interest in PDT is the potential prevention of NMSCs, including premalignant lesions, in high risk patients such as those who are immunosuppressed, after organ transplantation. Transplant patients have a 10-fold increased risk of BCC and a 40- to 150-fold increased risk of developing SCC, with a higher risk of AK lesions rapidly progressing to SCC (33). These cancers also result in higher mobidity as patients often develop multiple tumors, and SCC in these patients is more aggressive with an increased metastatic potential (34).

Furthermore, patients with a history of pre-transplant NMSC have a greatly increased incidence of NMSC after transplantation (35). Heart transplant patients are more susceptible because of their older mean age and the requirement for aggressive immunosuppressant therapy (36).

Experimental research has demonstrated that multiple topical MAL-PDT can delay the appearance of skin tumors in hairless mice exposed over the long term to UV radiation (37). To date there are relatively limited human data to back up these early studies. In an ongoing multicenter, randomized study in immunosuppressed transplant recipient (n=81), the occurence of new NMSC lesions on a 5 x 10 cm2 area of skin treated with MAL-PDT was compared with that on a contralateral area treated with standard therapy, mainly cryotherapy. After 3 months, a significantly lower number of new AK lesions occurred in the MAL-PDT-treated area compared with the area treated with standard therapy (n=44 vs 80; p=.009) (38). Dragieva G, et al (39) found that MAL-PDT for AK was similarly effective in immunosuppressed and nonimmunosuppressed patients.

Conclusion

PDT is an effective and reliable treatment option for sBCC that offers exellent or good cosmetic outcome. PDT offers an advantage in the treatment of large, extensive, and multiple lesions. MAL-PDT has demonstrated long-term efficacy in sBCC, with 5-year follow-up.

MAL-PDT is an effective treatment option for nBCC less than 2 mm in depth, when compared with surgery, but offering the advantage of superior cosmetic outcome. It has demonstrated long-term efficacy in nBCC, with 5-year follow-up.

There is currently insufficient evidence to support the rutine use of topical PDT for SCC.

PDT may be considered as a mean of preventing new AK lesions, SCC and BCC in immunosuppressed transplant patients.

NMSCs are not imminently life treatening, and a variety of treatmnts show good efficacy. Therefore, patient option should be a consideration in determining therapy choice. Up-to-day patients showed a marked preference for PDT over previous therapies when asked.

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FOTODINAMSKA TERAPIJA U LEČENJU NEMELANOMSKIH KARCINOMA KOŽE

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Fotodinamska terapija podrazumeva primenu svetlosti u cilju aktivacije fotosenzitajzera koji je nanet na predeo obolele kože, što dovodi do formiranja reaktivnog kiseonika koji ima citotoksične efekte. Lokalno primenjena fotodinamska terapija (FDT) koristi se u lečenju nemelanomskih karcinoma kože, kao što su aktinične keratose (actinic keratoses), Bowenova bolest i bazocelularni karcinom, kako superficijalni tako i nodularni. U radu su izneti najnoviji podaci i praktične preporuke za lokalnu primenu FDT sa 5-aminolevulinskom kiselinom (aminolevulinic acid) ili metil-aminolevulinatom (mathyl amininolevulinate) u lečenju, ali i prevenciji nemelanomskih karcinoma kože. Sistematičan pregled literature izvršen je uz pomoć MEDLINE, a preporuke su date na osnovu kvaliteta dokaza o efikasnosti, toleranciji i kozmetskim efektima. Zaključak većine do sada objavljenih saopštenja je da je lokalno primenjena FDT veoma efikasna u lečenju aktinične keratoze, Bowenove bolesti, kao i superficijalnog i nodularnog bazocelularnog karcinoma kao i da ne izaziva kozmetske defekte koji se viđaju kod standardnih terapijskih procedura. Ovaj vid terapije može da spreči pojavu nemelanomskih karcinoma kože kod osoba sa imunosupresijom. *Acta Medica Medianae 2008;47(2):28-32.*

Ključne reči: *fotodinamska terapija, nemelanomski karcinomi kože, metil aminolevulinat, 5-aminovevulinska kiselina*