Optimized Photodynamic Therapy with Systemic Photosensitizer Following Debulking Technique for Nonmelanoma Skin Cancers

Cacilda S. Souza, MD, PhD,* Ana B. S. Neves,* Lília A. B. Felício, MD,* Juliana Ferreira, MD,† Cristina Kurachi, MD, PhD,† and Vanderlei S. Bagnato, MD, PhD†

BACKGROUND The thickness and depth of invasion of skin tumors may be limiting factors for topical photosensitizer-based photodynamic therapy (PDT). The use of PDT with systemic photosensitizer needs to be further explored as a modality of treatment for nonmelanoma skin cancer (NMSC).

OBJECTIVE The objective was to present six patients with multiple, nodular, and/or pigmented NMSC treated successfully with purified hematoporphyrin derivative (PHD) and PDT using prior debulking.

METHODS After 24 hours of systemic PHD (1.5 mg/kg), 12 lesions of NMSC were selected for PHD-PDT alone and 6 nodular/elevated lesions for PHD-PDT following a debulking procedure. The tumor area was illuminated in one single-dose session of 300 J/cm^2, at an intensity range of 130 to 150 mW/cm^2, with a 630-nm-wavelength diode laser.

RESULTS The prior curettage provided significant reduction in volume and/or pigmentation of lesions. After the session of PHD-PDT with prior curettage and additional topical 20% ALA-PDT in two lesions or PHD-PDT alone, 83% (5/6) of lesions and 58% (7/12) of lesions, respectively, maintained a complete clinical response, 22.2 $\pm$ 8.9 months of follow-up.

CONCLUSIONS The combination of prior debulking with systemic agents-PDT appears to be a good option for multiple, pigmented, and/or nodular lesions of NMSC and can allow the improvement of clinical results.

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Photodynamic therapy (PDT) is a treatment method that involves the activation of a photosensitizer agent by visible light to produce cytotoxic oxygen species and free radicals, which promote selective tumor destruction. The interaction of an appropriate nonionizing light in the visible wavelength and a photosensitizer substance applied, either systemically or topically, is used to induce a photodynamic reaction. Red light from laser or narrow-band nonlaser source is usually employed to optimize depth of light penetration in tissue.[1] With current techniques of light delivery and doses, the red light may penetrate up to 0.6 to 1 cm, depending on the tissue and the light scatter.[2] The thickness and depth of invasion of the tumors may be a critical factor, because deep dermal or subcutaneous projections may be inadequately reached by light.[3] PDT using topical 5-aminolevulinic acid (ALA), a precursor of the highly photosensitive protoporphyrin (PpIX), induces complete response (CR) rates, ranging from 79 to 100%, in superficial basal cell carcinomas (BCC).[4] For nodular BCC lesions, a CR rate lower than 50% after a single treatment has been reported.[4] In depth of tumor, little or no fluorescence is induced by topically ALA applied alone in nodular BCCs.[5,6] The methyl-5-aminolevulinate (m-ALA) is an ester derivative of ALA with increased lipophilicity. Preliminary studies suggest deeper penetration into tumor tissue than is achieved with topical ALA and have indicated that this drug is safe and effective

*Division of Dermatology of the School of Medicine of Ribeirão Preto and †Institute of Physics of São Carlos, University of São Paulo, São Carlos, São Paulo, Brazil.

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as a treatment for nonmelanoma skin cancer (NMSC).[7] In addition, this option of treatment for "difficult-to-treat" BCC resulted in 78% of estimated sustained CR rate at 24 months.[8]

The systemic agents presently being investigated in clinical use would be potentially more efficient compared to ALA-PDT for the treatment of nodular lesions.[4] The agents initially approved for systemic use in cancer treatment were hematoporphyrin derivative (HpD) and its purified successor, generic name, porfimer sodium (Photofrin II, Photosan, and Photogem). However, as with many other porphyrin compounds administered systemically, HpDs lead to transient skin photosensitivity for at least 4 weeks. From the first-generation development, HpD and purified hematoporphyrin derivatives (PHD), a second generation of photosensitizers has been developed and is now under trial. The porfimer sodium is now used widely and remains the most common photosensitizer for tumor treatment.[7] In agreement with the first work of Dougherty and his group,[3,4,9] high rates of CRs, ranging from 72% to 100%, were observed in successive clinical reports concerning use of HpD or PHD-PDT in NMSC.[3,4,9] In contrast, poor clinical results were associated with low light or drug doses.[3] In addition, elevated lesions, deeply invading ones, and heavy pigmentation of pigmented BCCs, and fibrous stroma of morpheaform BCCs represent additional obstacles to PDT. We report six patients with nodular and/or pigmented tumors treated successfully with PHD-PDT using prior debulking.

Patients and Methods

Six Brazilian patients, three man and three women, aged 44 to 84 years (mean, 66.8 ± 14.4 years), with a diagnosis of NMSC treated at the University Hospital of the School of Medicine at Ribeirão Preto, University of São Paulo, were enrolled after informed consent, according to the approved protocol by the institutional ethics committee. The study protocol conformed to the guidelines of the 1975 Declaration of Helsinki. Most of the patients had several previous surgical excisions in common as well as other multiple primary and/or recurrent NMSC. Two patients each had two lesions, and four patients each had a mean of four lesions all located on the head and neck. The previous skin biopsy and/or subsequent curettage fragments confirmed the histopathologic diagnosis of NMSC: Bowen's disease, BCC, and well-differentiated squamous cell carcinoma/keratoacanthoma (SCC-KA). Twelve lesions were selected for PHD-PDT alone. Six nodular lesions were selected for PHD-PDT after debulking: nodular pigmented BCC on the scalp (01; Figure 1A); nodular BCC, in the nose (02) and in the auricle of the ear (01); and well-differentiated nodular SCC-KA, on the forehead (01; Figure 2A) and in mandible (01; Table 1).

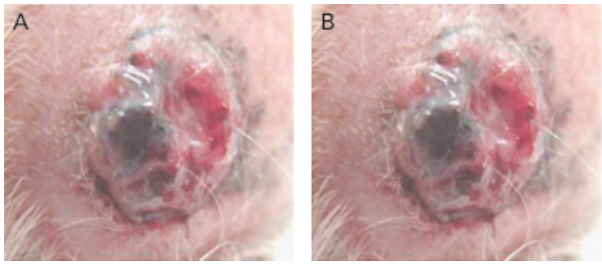

Figure 1. (A) Nodular-ulcerative and pigmented BCC in scalp. (B) After 60 days of the PHD-PDT following prior debulking technique, pigmented residual borders were observed along superior part of the lesion periphery.

The patients were injected intravenously with 1.5 mg/kg sodium salt and PHD (Photogem, Moscow, Russia). After 24 hours, immediately before the PDT session, a simple debulking procedure was performed under local anesthesia on the visible parts of nodular/elevated lesions by using a small surgical

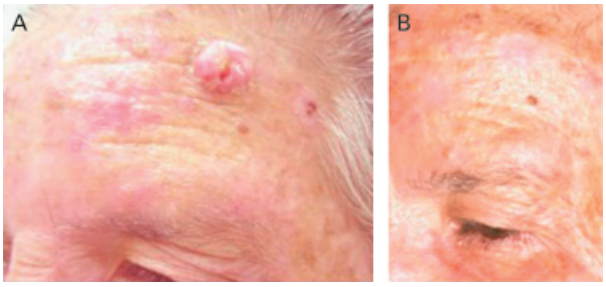

Figure 2. (A) Well-differentiated nodular SCC-KA. (B) After 30 days of the PHD-PDT following prior debulking technique area with mild hypochromic scar.

TABLE 1. Clinical Data, Outcome, and Follow-Up Time of Six Patients with NMSC Lesions Treated with Different Procedures Based on Purified Hematoporphyrin Derivative-Photodynamic Therapy

		Outcome		
Patient/sex/age (years)	*Tumor type/ location*	*PHD-PDT with prior curettage (n = 6)*	*PHD-PDT alone (n = 12)*	*Follow-up time (months*
1/F/75	n-u and pigmented BCC/scalp	CR*		
	superficial pigmented BCC/temporal		PR	29
2/F/65	well-differentiated SCC-KA/lateral forehead	CR		16
	BD/preauricular-malar		CR	
	BD/supralabial		CR	
	recurrent BCC/zygomatic		PR	
3/M/75	n-u BCC/nose left side	PR		7
	n-u BCC/malar		PR	
	n-u BCC/supralabial		CR	
	n-u BCC/nose right side		PR	
4/M/84	well-differentiated SCC-KA/mandible	CR		25
	n-u BCC/preauricular left		PR	
	n-u BCC/temporal left		CR	
	n-u BCC/forehead		CR	
	n-u BCC/preauricular right		CR	
	n-u BCC/temporal right		CR	
5/M/58	n-u BCC concha auricular	CR		27
6/F/44	n-u BCC/nose	CR*		29

*After the second session with ALA-PDT
M, male; F, female; n-u, noduloulcerative; PHD-PDT, purified hematoporphyrin derivative-photodynamic therapy; SCC-KA, squamous cell carcinoma-keratoacanthoma; BCC, basal cell carcinoma; BD, Bowen's disease; CR, complete response; PR, partial response.

curette (Richter, Brazil). The ferric chloride solution was used to hemostasis when there was a minimum bleeding. The field containing tumor area and security margin (~1.0 cm) was illuminated in one single-dose session of 300 J/cm^2, at an intensity range of 130 to 150 mW/cm^2, with a 630-nm-wavelength diode laser (CeramOptec-GmbH, Bonn, Germany). Avoiding exposure to sunlight was recommended for 30 days. Two patients (Cases 1 and 6) were submitted to second session with an occlusive topical application of 20% 5-ALA (Alasens, Moscow, Russia) with 0.5% dimethylsulfoxide (DMSO) and 3% ethylenediaminetetraacetic acid in oil–water emulsion on the affected area for 6 hours and later illuminated with similar parameters used in PHD-PDT.

Results

In the first 24 hours, the patients reported moderate edema and exudation, occasional blister formation, and mild local pain that progressively diminished over the period of one week, giving rise to a crusted ulcer. None of the patients presented manifestations of cutaneous photosensitivity. The healing occurred within 4 to 6 weeks; only local mild erythema or hypochromia was observed on treated areas.

The clinical details of the patients, tumor type, location, outcome, and follow-up are given in Table 1. After the session of PHD-PDT with prior curettage and additional ALA-PDT in two lesions or PHD-PDT alone, 83% (5/6) and 58% (7/12) of the lesions, respectively, maintained a complete clinical response, 22.2 ± 8.9 months of follow-up. In general, the cosmetic results were considered excellent or good in all patients. The prior curettage provided significant reduction in volume and/or pigmentation in nodular-pigmented BCC in scalp (Case 1, Figure 1) and SCC-KA tumors (Case 2, Figure 2; Case 4), respectively. In Case 1, an area with alopecia, mild hypochromia, and atrophy delimited by pigmented

borders as a result of the single session of PHD-PDT (Figure 1B). The presence of pigmented (Case 1) or translucent (Case 6) residual borders was an indication for a second session of topical 20% ALA-PDT, to simplify the procedure and avoid substantial systemic toxicity.

Discussion

Choosing an optimal therapy for a tumor depends mainly on the location, size, histologic subtype, the condition of the primary or recurrent lesion, age, and general health of the patient.[10] The life table 5-year cumulative recurrence rates for primary and recurrent BCC treated with excision, cryotherapy, curettage, or radiotherapy range from 7.5% to 40.0%. Mohs micrographic surgery appears to have the lowest recurrence rate[11] and it is the treatment of choice for lesions with high risk of recurrence, such as larger, morphea-type BCCs located in danger zones.[12]

All these treatment procedures are followed by variable degrees of scarring with fibrosis tissue defects, dysfunction, and even some disfigurement. PDT may prove advantageous where site or number of lesions limits the efficacy and acceptability of conventional therapies.[13] The cases reported here all had scars resultant of several previous surgical excisions, recurrent NMSC, and/or lesions in sites, such as auricle of the ear where surgical treatment is limited. PDT was used to treat a large number of lesions in only one session, minimizing the surgical trauma and new scar formation or disfigurement. Adjunctive therapy with prior curettage or use of penetration enhancers or fractionated treatment may improve the results of topical ALA-PDT.[13] Soler and coworkers[14] achieved a maintenance of cure rate of 95% for the 119 nodular BCCs up to 17 months (range, 12–36 years) after ALA-PDT, which included an initial debulking procedure and topical application of DMSO as penetration enhancer.[14] Prior debulking curettage 3 weeks before ALA-PDT performed by Thissen and colleagues[15] obtained a 92% clinical and histologic response rate in 24 nodular BCCs.[15] Soler and coworkers[16] used m-ALA-based PDT with prior curettage of all nodular lesions of BCC.[16] Instead, we performed the previous curettage after PDT using systemic photosensitizer, PHD, to reduce the mass of the tumor and to allow the penetration of light into the base of the tumor with the intention of optimizing the PDT efficacy.

Another obstacle was that pigment contained in tumors became resistant to PDT therapy because melanin competes and absorbs the photoactivating light delivered for PpIX, even if there is sufficient accumulation of the PpIX in the tumor cells. In agreement with Itoh and colleagues,[17] our report showed that the debulking followed by PDT induced the reduction of almost all pigmented nodular BCC on scalp, while leaving only superficial pigmentation along the border of scar (Case 1, Figure 1B). The second session with topical 20% ALA-PDT resulted in a CR in this case.

PDT can be a selective and curative therapy with many potential advantages over available alternatives. A single treatment can eradicate disease and can have an excellent cosmetic result. Particular advantages are obtained with the treatment of tumors located in poor healing sites or in which surgical intervention is restricted by local or systemic conditions or for patients with multiple tumors.[13,18] Despite the cutaneous photosensitivity, which could be minimized with the advent of the new photosensitizers, the use of topical or systemic agents-PDT is an attractive modality of oncologic therapy.

With the exception of porfimer sodium, the only other PDT drug currently approved for systemic use in cancer treatment is temoporfin (chlorine derivative).[7,19] Initially used for age-related degeneration macular, verteporfin, a benzoporphiryn derivative, has been indicated for NMSC treatment. It is cleared rapidly and does not induce a generalized skin photosensitivity that lasts longer than 24 hours. Lui and coworkers[20] obtained 95% of clinical response rate with a single course of PDT with verteporfin and

180 J/cm^2 red light (688 $\pm$ 10 nm) for the treatment of NMSC, which indicates promising use of verteporfin PDT.[20]

The prior curettage of primary BCC may help to increase the cure rate by more accurately defining the true borders to excision procedure of BCC[21] and improving the results of topical agents-PDT, ALA-PDT,[13–15,17] and m-ALA-PDT.[16] In summary, the cases reported here reinforce the advantages of treating multiple tumors with PHD-PDT. In addition, the combination of prior debulking with PHD-PDT, systemic agent-PDT, appears to be a good option for pigmented and/or nodular BCCs and well-differentiated SCC-KA and can allow the improvement of clinical results.

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Address correspondence and reprint requests to: Cacilda S. Souza, MD, PhD, School of Medicine of Ribeirão Preto, University of São Paulo, Av. Bandeirantes 3900 CEP 14048-900, Ribeirão Preto, São Paulo, Brazil, or e-mail: cssouza@fmrp.usp.br.