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Photodynamic Therapy by Topical meso-Tetraphenylporphinesulfonate Tetrasodium Salt Administration in Superficial Basal Cell Carcinomas[1]

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ABSTRACT

The efficacy of an originally developed photodynamic approach, using topical administration of tetraphenylporphinesulfonate as the photosensitizer, was evaluated in a series of 292 basal cell carcinoma lesions (<2-mm thick) in 50 treated patients. The lack of indication for conventional therapies was the main selection criterion. The photosensitizing agent (2% solution) was topically applied at 0.1 ml/cm², followed by light irradiation with a dye laser emitting at 645 nm (120 or 150 J/cm²). After initial treatment, all lesions responded, with 273 (93.5%) complete responses. Recurrences were observed in 29 (10.6%). A second application of photoradiation was performed in 15 persistent lesions and 11 relapsed lesions, producing 19/26 complete responses. Our results suggest that this technique can be considered a promising alternative treatment modality in selected cases of superficial basal cell carcinomas.

INTRODUCTION

Photodynamic therapy is a new technique proposed for selective local destruction of malignant tumor cells (1, 2). This approach is based on the systemic administration of photosensitizing agents. Most studies have used an HpD (a complex mixture of porphyrins), which may be retained selectively in tumors relative to surrounding tissue. Drug can be activated by dye laser to produce local cytotoxic effect (3, 4).

The principal adverse effect of i.v. injection of HpD is cutaneous photosensitization, manifested as erythema, edema, and burns, which last 4–6 weeks after drug administration. The complication is due to prolonged retention of the photosensitizer in the skin, and patients, therefore, must avoid both sunlight exposure and bright, artificial lights for this period of time (5). Experimental studies on the possibility to exploit topical use of HpD were reported by McCullough *et al.* (6).

Since 1985 we have evaluated the effectiveness of topical application of TPPS[3] to reduce side effects in the treatment of superficial skin tumors. Experimental studies in mice (7) showed that optimal photosensitizing effects in topical PDT were critically dependent on drug dose, number of treatments, light intensity, and irradiation of the peripheral margins of the tumor. Preliminary clinical experiences (8) confirmed these issues and emphasized specific advantages over conventional therapies in selected conditions. In January 1987, a new therapeutic approach was tested on flat BCC and Bowen's disease. A lack of indication for conventional treatments was considered the main criterion to enter the pilot study (Table 1).

This report aims to analyze and define the role of topical PDT in the management of skin tumors in addition or alternatively to conventional therapies and systemic PDT.

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[3] The abbreviations used are: PDT, photoradiation therapy; TPPS, tetrasodium-meso-tetraphenylporphinesulfonate; HpD, hematoporphyrin derivative; BCC, basal cell carcinoma; CR, complete response; PR, partial response.

MATERIALS AND METHODS

Photosensitizer. TPPS was obtained as a dark green powder from Porphyrin Products (Logan, UT). A 2% solution was obtained by dissolving the drug in a mixture composed of isopropyl alcohol:water:azone (50:48:2). Azone (*N*-dodecylazacycloheptane-2-one), a penetration enhancer (9), was kindly supplied by Nelson Research (Irvine, CA).

Patients. From February 1987 to December 1988, 50 patients, with a total of 292 BCC, were selected for topical photodynamic therapy at the Istituto Nazionale Tumori of Milan, Italy. Their median age was 67 years (range, 32–92 years). Treatment was performed on an outpatient basis; an inpatient procedure was necessary only in two cases, due to the patient's age (92 years) in one case and to geographic inaccessibility in the other one.

Of the 292 lesions, 276 were untreated BCC, 6 were persistent lesions after 5-fluorouracil topical treatment, and 8 were recurrences after radiation therapy and 2 after surgery. Multiple lesions were present in 39 patients (with a maximum of 26 lesions per patient and a maximum diameter of 6 cm), whereas 11 patients had wide single lesions (4 cm maximum diameter). Of the 292 lesions, 262 (89.7%) were located in flat skin areas. Patients bearing lesions in the lumbosacral area (111 lesions) were all irradiated in that site 20–30 years before for arthrosis (10). The remaining lesions were distributed in the head and neck (6.8%) and in the limbs (3.5%).

A biopsy specimen was taken in all cases for the histological diagnosis of the lesions. However, the tumor thickness in the biopsy specimen was not considered representative of the entire lesion, due to the irregular pattern of skin involvement (11). The thickness of the lesions, estimated clinically by measuring the swelling over the skin surface, was <1.5 mm in 233 lesions, whereas in 59 lesions it was ≥1.5 mm but <2 mm. Response to treatment was evaluated as tumor necrosis at 1, 7, and 30 days after treatment. Subsequent follow-up examinations were conducted every 4 months during the first year and then every 6 months.

Procedure. TPPS solution was painted at 0.1 ml/cm² onto the tumor surface by a micropipette, 24, 6, and 3 h before light irradiation. Before each administration and before irradiation, the skin surface was cleaned with ether to increase TPPS penetration by dissolving skin lipid content of the upper layer of the epithelium and to remove excess TPPS. The time required for TPPS application was mainly dependent on the lesion's diameter and, then, on individual skin characteristics: approximately 5 min/cm² was necessary in most cases.

An argon-pumped dye laser (MDS90; MEDITEC, Heroldsberg, Germany), emitting at 645 ± 1 nm, coupled with a 600-μm quartz optical fiber was used for irradiation. The optimal wavelength for tissue irradiation is still to be determined. TPPS in aqueous solution (pH 7) has an excitation peak in the red region, at about 635 nm, whereas when it is bound to cellular structures the excitation peak shifts toward longer wavelengths, at about 645 nm. The optical fiber was fixed to a mechanical support and directed orthogonally to the treated area.

Total energy fluences of 120 and 150 J/cm² were delivered for lesions with a clinical thickness of <1.5 mm and between 1.5 and 2 mm, respectively. Light irradiance varied between 20 and 200 mW/cm², depending on the diameter of the field. Initially, in a few cases in the series, irradiation fields covering several lesions were used for multiple lesions, whereas subsequently single irradiation fields were preferred for each lesion. The irradiation field extended 5 mm out from the margin of the lesion.

Postreatment wound care consisted of frequent surface cleaning and dry dressing.

Table 1 *Indications for topical PDT*

Multiple lesions
Wide single lesion
Recurrence after radiation therapy
Radio-induced lesions
Contraindications for surgery
Clinical thickness <2 mm

Table 2 *Tumor response after first treatment*

Lesions thickness (mm)	Lesions	CR	PR
≤1.5	233	218/233	15/233
>1.5 ≤ 2	59	55/59	4/59
Total	292	273/292	19/292

Statistical Analysis. The pattern of relapse-free survival in lesions with a CR was estimated by means of the product limit method (12). Tumor recurrence was taken as the end point, and time to this event was measured from the date of PDT.

RESULTS

Response to Treatment. The lesion area appeared progressively darker after each painting, presenting as dark purple and reproducing the tumor shape after the third TPPS application. After irradiation a local response was apparent within the light field in most cases. Initially, it was manifested as erythema and edema in the tumor area, progressing to necrosis within 24 h. However, the sites with partial necrosis at 24 h had an almost CR by day 30. Complete reepithelialization was apparent within 10–15 days after treatment in small lesions, whereas the healing process required 30–40 days in larger tumor sites (>3 cm in diameter). Erythema was often evident even in the healthy skin surrounding the treatment field at the end of the light exposure, and it disappeared in a few hours. Cosmetic results were generally satisfactory: pale pink areas were usually evident at the lesion sites 1 month after treatment. Two patients died of cardiovascular disease 6 months after PDT, without evidence of BCC and 1 patient was lost to follow-up due to geographic inaccessibility. The distribution of the follow-up period of the 273 lesions in the remaining 47 patients was: 79 (29%) <12 months, 103 (38%) >12 months, 37 (13%) >18 months, and 54 (20%) >24 months.

CR, defined as eradication of the lesion by the time of evaluation at 4 months, or PR, defined as a reduction by at least 50% in the greatest tumor diameter, was observed in all cases (Table 2). The overall incidence of CR after the first treatment was 93.5%. CR was obtained in 218 of 233 lesions (93.6%) with clinical thickness of <1.5 mm (first group); whereas in the group of sites with a clinical thickness between 1.5 and 2 mm (59 lesions), a CR was obtained in 55 (93.2%). PR was observed in the remaining 19 cases. Tumor recurrence, with a disease-free interval of 6 months, was noted in 29 lesions: 19 of the first group (8.7%) and 10 of the second one (18.2%). Fig. 1 shows the relapse-free survival curves of the two groups. The probability of tumor recurrence was 0.06 and 0.18 at 12 months and 0.18 and 0.20 at 24 months, respectively.

Clinical results and treatment procedures for persistent and relapsed lesions are illustrated in Fig. 2. A second application of photoradiation was performed in all cases of marginal persistence and in 11 of 13 marginal recurrences and produced a CR in 19 of these cases (73.1%). Of the 22 remaining cases, 13 underwent surgical excision or 5-fluorouracil topical application, since they were single and/or small lesions, and 9 lesions (4 central persistence and 5 central recurrence) were submitted to radiation therapy or surgery.

Side Effects. No significant complications were observed in any case. Most patients, especially those bearing ulcerated or wide lesions, experienced mild to severe itching during the first minutes of irradiation. Anesthesia was required in only 3 patients because of intense pain during light irradiation. Since a temperature increase of a few degrees centigrade (maximum 7°C) was expected only at the highest dose rate during light irradiation (11), the burning sensation does not reflect a thermal effect but presumably the photochemical reaction. No analgesics were necessary in the posttreatment period.

Some patients with facial lesions developed marked edema the day after treatment. This complication was easily controlled by corticosteroid administration (30 mg prednisone daily for 3 days). Infection at the site of treatment was observed in 8 lesions (2.8%) and was resolved by daily applications of streptomycin powder. Neither hemorrhage nor spiking fever was noted in our series.

DISCUSSION

The present study confirms our previous preliminary results (8). Nevertheless, some methodological aspects deserve detailed analysis to stress the main problems to be resolved in the near future. One of the most important points is careful patient selection. Surgery and radiotherapy are effective (curative in most cases) in skin tumors. However, inpatient plastic restoration or large irradiation fields are required to obtain complete control of the disease in particular conditions, *i.e.*, multiple and/or wide lesions. In addition, most of the elderly patients treated had had general problems in undergoing surgical procedures or long-lasting radiation therapy. In contrast, topical PDT is applied on an outpatient basis, lasts 2 days, offers a comparable cure rate to conventional therapies, and assures an excellent cosmetic result. In particular, eradication of lesions of the face or in anatomic sites with difficult access (*i.e.*, external ear canal) can be achieved with satisfying results.

Most relapses could be interpreted in terms of inadequate extension of the irradiation field (an effective second course of

Table 3 *Partial remission and relapses, according to dose rate*

	Dose rate (W/m²)				
	0-500	501-1000	1001-1500	1501-2000	Total
PR	2/18	4/46	1/20	12/208	19/292
R	4/18	9/46	5/20	11/208	29/292
Total	6/18	13/46	6/20	23/208	48/292

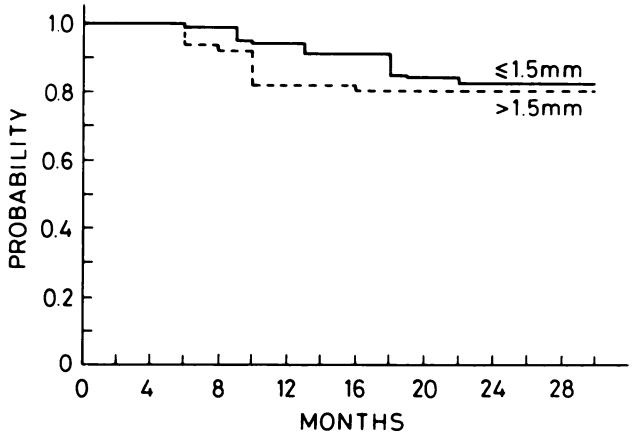

Fig. 1. Relapse-free survival curves of the two groups of patients with BCC lesions. The two groups are derived on the basis of lesion thickness as indicated in Table 2.

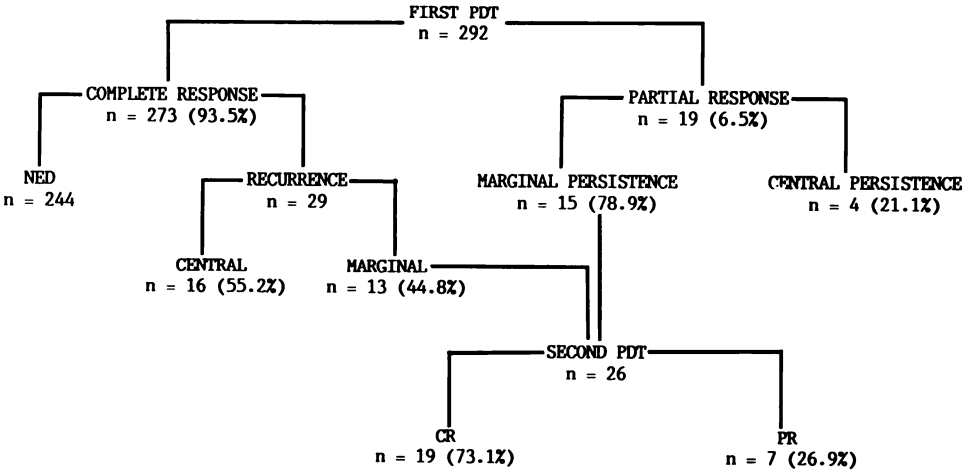

Fig. 2. Clinical results and treatment procedures for persistent and relapsed lesions. All lesions with central persistence, central recurrence, two marginal recurrences, and all partial response lesions following a second course of PDT had traditional treatments. *NED*, no evidence of disease.

PDT could eventually be supplied in such cases) or insufficient TPPS and/or light penetration. Previous fluorescence measurements (7) demonstrated that TPPS penetration in the skin was dependent on time elapsed from painting. A few hours after application, TPPS was concentrated in the upper layers of the epithelium, whereas 24 h after painting it was found even in deep dermis. To obtain a homogeneous drug distribution, three applications, at the mentioned intervals, therefore, were considered the optimal administration schedule. Nevertheless, clinical observations seem to suggest that TPPS lesion saturation could be complete in two applications (at 24 and 6 h). Currently, we are evaluating the results after reducing the number of paintings. Topical application of TPPS is time consuming: the hydroalcoholic solution needs to be painted very slowly to avoid going beyond the treatment area. To overcome this limitation other ways of TPPS topical administration and/or semisolid vehicles will be evaluated.

When large and multiple lesions are involved, a relevant limitation is the time required for dye laser irradiation. As an example, in the case of a thin lesion of 6 cm in diameter (*i.e.*, an irradiation field of about 50 cm^2), 50 min is needed to deliver the required dose, since the maximum dye laser power is 2 W. In the case of deeper lesions, >60 min is necessary to administer the required dose. These limitations justify splitting the treatment into two separate sessions when more than 10–12 lesions or very large lesions have to be treated.

Even though clinical results seem to show different responses according to irradiance (Table 3) (13), statistical analysis does not reveal a significant linear correlation between dose rate and PR ($P = 0.088$) or relapse ($P = 0.33$).

The reflectance spectrum of the skin of the patients was evaluated by using an integrating sphere coupled by fiber optics to a spectrophotometer. Measurements performed on the lesion site revealed typical absorption peaks of TPPS at about 647, 593, 555, and 517 nm. When reflectance was measured between 1–2 cm from the border of the lesion, only the absorption peaks of hemoglobin, at about 540 and 580 nm, were evident. Nevertheless, between 645 and 650 nm, a shallow peak was observed that could be related to the absorption peak in the red of TPPS, since the other peaks were masked by skin blood content. At distances >4 cm, the reflectance measurements did not show any evidence of the presence of TPPS. Moreover, blood content of TPPS was measured to evaluate whether the presence of TPPS near the painting area was due to a diffusion process through the skin or to blood flow. Spectrofluorimetric analysis in plasma of several patients revealed the presence of small amounts of TPPS: about 1% of the administered skin dose was present in the plasma. This finding is in contrast to previous measurements when no evidence of the drug was found (8). Nevertheless, previous data referred to patients bearing small lesions: in those cases spectrofluorometer sensitivity did not allow detection of TPPS concentrations <0.01 μg/ml of serum.

In conclusion, the results reported in this study support the therapeutic potential of topical PDT as a primary means of treating selected cutaneous neoplasms. Careful estimation of long-term responses and further optimization of treatment parameters are expected to improve the efficacy of this new approach.

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