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An Evaluation of Photodynamic Therapy in the Management of Cutaneous Metastases of Breast Cancer

Seema A. Khan, Thomas J. Dougherty and Thomas S. Mang

A series of 37 patients with cutaneous metastases of breast carcinoma were treated with photodynamic therapy (PDT) to the chest wall; decreasing doses of photofrin II and increasing light doses were used in order to test drug/light dose reciprocity and determine the lowest effective dose of photofrin II. 5 patients (13.5%) achieved a complete response, 13 (35.1%) demonstrated partial responses and 19 (51.4%) showed no benefit. The extent and type of recurrent disease were strong determinants of the likelihood of response. Minimal and nodular disease responded well to PDT (5/5 complete responses); partial responses were seen in 11/20 (55%) of patients with disease of moderate extent. No patient with extensive erythema derived any benefit (0/5), and only 2/12 (17%) patients with advanced nodularity showed a partial response. Reductions in photofrin dose to 0.75 mg/kg with reciprocal increases in light dose to 182 J/cm^2 did not impair treatment efficacy.
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INTRODUCTION

LOCALLY RECURRENT breast cancer may range in extent from completely asymptomatic skin nodularity to a debilitating encuirasse lesion. Photodynamic therapy (PDT) has emerged as a new form of locally cytotoxic treatment which may have some utility in the local control of this problem. The principle underlying PDT involves excitation of tissue-bound photosensitiser by light, resulting in the production of singlet oxygen, with subsequent cell death [1]. The photosensitiser being used in clinical trials today is photofrin, a purified form of the original hematopophyrin derivative, which consists of about 80% of the porphyrin oligomers selectively retained by tumours [2, 3]. Photofrin is injected intravenously and is retained in malignant tissue and many normal tissues, including skin. It has been shown that there is at least three times more porphyrin in neoplastic skin lesions than in surrounding normal skin [4, 5].

In addition to the photodynamic effect, another property of

Correspondence to S.A. Khan at the Department of Surgery, SUNY Health Science Center at Syracuse, 750 E. Adams Street, Syracuse, NY 13210, U.S.A.; and T.J. Dougherty and T.S. Mang are at the Photodynamic Therapy Center, 666 Elm Street, Buffalo, NY 14263, U.S.A.
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photofrin is its photobleaching during light exposure. Under appropriate conditions this can result in the destruction of the lower levels of drug in the skin before a threshold photodynamic effect sets in. Decreasing the drug dose from 2.0 to 1.0 mg/kg increases the light tolerance of normal skin from seven- to eight-fold [6, 7]. Since the only significant toxicity of photofrin is dermal photosensitivity, a search for the lowest drug dose compatible with cell-kill when excited by a sufficient quantity of light is important.

Over the last 6 years, 37 patients with skin recurrences of breast carcinoma have been treated at Roswell Park Cancer Institute (RPCI). The initial 14 patients have been described previously [8]. This report includes the additional 23 patients in whom the effects of photofrin dose de-escalation on treatment efficacy and photosensitivity were explored.

MATERIALS AND METHODS

Photofrin was obtained from Photomedica (Raritan, NJ, U.S.A.) or Quadra Logic Technologies (Vancouver, BC, Canada) as an aequeous solution of 2.5 mg/ml. The light source used was an argon pumped dye laser emitting light of 630 ± 2 nm at an intensity of 120 to 200 mW/cm^2. This was delivered through a single quartz fiber optic fitted with a micro-lens providing a uniform cone of light for surface illumination. A cylindrical diffuser tip emitting light laterally in all directions was used for interstitial treatments when applicable. Initially, treatment fields extended only a mm or two beyond visible lesions; starting in 1986, light treatment was extended to include 2-cm zones of normal appearance skin around visible lesions. The light doses were 60–75% of those used for visible lesions and were delivered using separate adjoining fields.

Treatment protocols were approved by the RPCI Institutional Review Board and the Federal Drug Administration (FDA), and informed consent was obtained from all patients according to FDA guidelines. Eligibility requirements included the presence of biopsy-proven cutaneous metastases of breast cancer. A minimal interval of 6 weeks was required from the last dose of doxorubicin due to the observed enhancement of phototoxicity by doxorubicin (Mang, Crean and Khan, unpublished results). A 4-week interval was required after the completion of ionising radiation therapy. Treatment methods have been described previously [8]. Photofrin dose ranged from 2.5 to 0.57 mg/kg; drug and light levels are described in Table 1. Light doses for each drug dose were based on experimental data showing drug/light reciprocity [9]. After the first 8 patients it was apparent that the optimal interval from injection to light treatment was 48–72 h. Following the first treatment only, patients were admitted to the hospital in order to monitor the amount of pain, administer parenteral analgesics if necessary, and provide instruction in local wound care. Ninety-five per cent of patients (35/37) returned for at least one follow-up visit 4 weeks after the first treatment session. Further follow-up information was obtained by correspondence and through telephone conversations with the patients and their referring physicians.

Table 1. Drug and light dose schedule

	Drug dose (mg/kg)	Light dose (J/cm^2)
Standard therapy pre 1986	2.0	30–35
Standard therapy 1986 and after	1.0	104–144
Step 1	0.75	140–182
Step 2	0.57	187–244

Light and drug dose scheme used in the treatment of the patients reported. Drug de-escalations were 25% of the previous dose. Light dose escalations were approximately 33% with each drug de-escalation.

Table 2. Previous therapy in 37 patients undergoing PDT

Treatment modality	No. of patients
Chemotherapy	31
Ionising radiation	31
Endocrine therapy	22
Surgical excision	11

Mean number of treatments per patient: 2.4.

Patient characteristics

The patient population involved in this study had disease ranging from very indolent lesions which had progressed over a long period of time to form bulky, ulcerated masses, to newly discovered minimal nodularity or erythema of the chest wall as the first site of relapse. The age ranged from 27 to 88 years with a mean of 44.1 years. The majority had isolated cutaneous metastases; 5 patients had locoregional disease and an additional 2 patients had known distant disease.

In an attempt to relate disease characteristics to probability of response, the extent of disease was retrospectively classified as minimal, moderate or advanced. Minimal disease consisted of 12 or fewer discrete nodules, all under 1 cm in diameter. Moderate disease was considered to be confluent nodularity with the largest nodular diameter being 1–2 cm and/or the presence of spreading erythema on the chest wall occupying less than 25% of the anterior hemithorax. Nodules greater than 2 cm in diameter, or confluent disease occupying 25% or more of the anterior hemithorax was categorised as advanced. Using this classification, there were 5 patients with minimal, 20 patients with moderate, and 12 patients with advanced disease.

As a group, these patients suffered from aggressive disease. The mean number of positive axillary lymph nodes was 7.4, and 7/37 (19%) patients had inflammatory breast carcinoma as their initial lesion. Median disease-free interval was 20 months. Almost all patients had had at least one form of previous therapy, and most were heavily pretreated (see Table 2).

Evaluation of response

A complete response (CR) required an intact (i.e. healed) chest wall *and* no new modules for a minimum period of 4 weeks. This did not imply that healing had to occur within 4 weeks, but once healing was complete, there should be no observable cutaneous metastases for a minimum period of 4 weeks. Partial responses (PR) were defined as patients who developed new nodules between treated areas during the healing period, but treated areas healed without recurrence. Non-responders (NR) were classified as those patients who had recurrences at the site of treatment (including rim recurrences, see below) within 4 weeks of treatment. Patients who had incomplete destruction of

treated nodules and sustained no discernible symptomatic benefit from the treatment were also classified as non-responders.

RESULTS

Clinical course following treatment

Treated lesions followed a predictable course; during light therapy the nodules acquired a bluish hue, and by 24 h most of the treated lesions were dark purple in colour (see Fig. 1). Pain usually began during treatment and analgesic requirements were maximal during the first 3–5 days. Over the next 2 weeks, lesions gradually turned into tough, dry, black eschars. Cellulitis, if it occurred, was seen 3–10 days after light treatment, and was often accompanied by a sharp increase in pain. In patients with small lesions, healing was usually completed before any new lesions were noted on other areas of skin. In some patients the appearance of nodularity at the epithelialising rim denoted recurrence at the edges of the treated area prior to completion of the healing process (rim recurrence). A third possible outcome was the appearance of new nodules between treated areas, with or without healing of the treated areas (*de-novo* recurrence).

Responses

Response to therapy was analysed by extent of disease (minimal, moderate, advanced) and by type of lesion (nodular, erythematous, mass, bleeding surface). These data are presented in Table 3. Complete response was seen in 5 patients, all of whom had minimal nodular disease, without erythema. Of the 13 partial responses 11 had moderately extensive disease, either purely nodular or nodular with a minor erythematous component. 2 patients had advanced lesions, but had distinct palliation of their symptoms (control of bleeding from an extensive velvety tumour in 1 patient, and decrease in bulk and drainage from advanced nodular disease in the other). They are included in the partial responders. There were 19 non-responders (9 with moderate, and 10 with advanced disease) who either had rim recurrences, or had incomplete destruction of tumour with no symptomatic benefit.

Table 3. Response classification by type and extent of disease

	No. of patients	CR	PR	NR
Type of lesion				
Nodular	22	5	8	9
Erythematous	5	0	0	5
Mass	9	0	4	5
Bleeding surface	1	0	1	0
Extent of disease				
Minimal	5	5	0	0
Moderate	20	0	11	9
Advanced	12	0	2	10
Total	37	5	13	19
(%)	(100)	(13.5)	(35.1)	(51.4)

CR = complete response; PR = partial response; NR = no response.

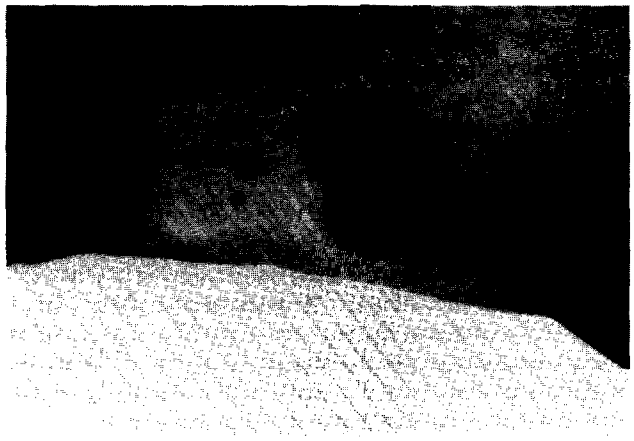
The presence of an erythematous component to the lesions was a predictor of a low likelihood of benefit; purely erythematous lesions showed rapid recurrence at the edges of the treated areas and elsewhere. There were also no responders in the group of 7 patients who presented with inflammatory breast carcinoma as their initial lesion, regardless of the extent and type of chest wall metastases at the time they received PDT. The use of interstitial therapy did not prove beneficial in the 4 patients who were treated in this manner. We feel that PDT is inappropriate therapy for lesions which are too bulky to be treated with superficial illumination.

Duration of complete response ranged from 3 months to 12 months with a median of 5 months. Partial responses lasted from 3 to 20 months, with a median of 6.6 months. Patients who underwent multiple courses of treatment tended to be those with slowly progressing disease, and were also the ones who demonstrated longer partial responses. Duration of survival amongst the 22 patients (59.5%) who have been followed to death ranges from 2 to 36 months, with a mean of 13.5 and a median of 10 months.

Effect of photofrin dose

Experimental evidence of the photobleaching of porphyrins suggested that decreasing doses of photofrin and photodynamically equivalent increases in light dose would allow greater tolerance of normal skin to both therapeutic and incidental light. Since recurrences often occurred in close proximity to treated areas, and doses of 1.0 mg/kg of photofrin achieved adequate tumour necrosis, we began to test the limit of dose reduction of photofrin II, with the addition of zones of grossly normal skin to the treatment fields. 6 patients were treated with 0.75 mg/kg, with light doses as shown in Table 1; 1 of these achieved CR, 3 reached PR and 2 showed no response. Since nodular necrosis

(a)



(b)

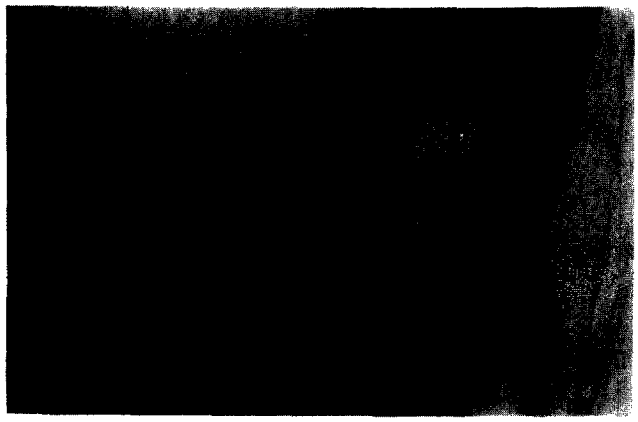
Fig. 1. (a) Cutaneous nodules of metastatic breast cancer, immediately before treatment. (b) 24 h following treatment, showing marked colour change and the beginning of necrosis.

and disease-free healing occurred in 4/6 patients, photofrin dose was again dropped to 0.57 mg/kg. At this dose of photofrin, despite an increase in light dose to a maximum of 244 J/cm^2, 3 out of 4 patients demonstrated incomplete lesional necrosis and recurrences occurred. Further de-escalation in the dose of photofrin was not attempted, since it was concluded that the minimal effective dose of the drug had been reached at the previous dose level of 0.75 mg/kg. It appears (tentatively) that a drug dose of 0.75 mg with light doses of 140–182 J/cm^2 are as effective as drug doses of 1 mg/kg and higher, bearing in mind that higher drug doses in this study were accompanied by lower light doses for a calculated equivalence in photodynamic effect (see Table 1).

Effect of treatment of normal skin surrounding visible lesions

15 patients were given prophylactic light therapy to 2–3 cm zones of normal skin around visible lesions, 2 of whom achieved CR. Light doses used on grossly normal skin were limited to 60–75% of those used for visible lesions. These lower light doses did appear to be cytocidal for as yet invisible tumour deposits in some patients; for example, 1 patient who was treated with 0.57 mg/kg of photofrin and 243 J/cm^2 of light for visible lesions, was also treated with 185 J/cm^2 over a 3-cm zone of surrounding normal skin. Twenty-four hours following treatment, punctate areas of purplish coloration could be seen in the treated zone of normal skin, which was otherwise only slightly pink in colour (Fig. 2). However, within 4 weeks, new lesions had appeared in this prophylactically treated zone, indicating that the tumoricidal effect was incomplete.

(a)



(b)

Fig. 2. Visible metastatic nodules on the chest wall before treatment (a) were treated with light delivery to a zone of grossly normal skin—area between two inked circles in (b). Development of discoloration in this zone (arrow) indicated necrosis of microscopic tumor deposits.

*Table 4. Incidence of complications of PDT in 37 patients**

Pain	
Severe	10
Moderate	48
Eschar	
Requiring operative debridement	6
Requiring office debridement	50
Oedema and blistering of normal skin	4
Diffuser tip dislodgement	1
Osteomyelitis of rib	1
Infection	
Abscess formation	1
Cellulitis	5

*64 treatment cycles including six interstitial implants.

Complications

Drug-induced photosensitivity of untreated skin to natural light has been reduced with progressive reduction of photofrin dose. Forearm skin was tested in sunlight for short periods starting at 2 weeks from injection, without any sunburn noted. Chest wall skin was not specifically tested since we were interested in determining when patients could resume incidental exposure to sunlight. Drug toxicity consisted of two instances of minor sunburn, both in patients who received 2 mg/kg photofrin.

Complications of the drug–light combination consisted of pain, both during and after the treatment, cellulitis or abscess formation following the treatment, eschar formation as an aftermath of the necrosis and sloughing induced by the PDT, one instance of loss of a diffuser tip in the tumour mass during an interstitial implant, and one instance of osteomyelitis of a rib as a result of a deep chest wall echar and slough (Table 4).

A history of chest wall irradiation was accompanied by more severe pain, deeper and more extensive sloughs and slower epithelialisation of granulating areas. The majority (84%) of patients had received prior ionising radiation; severe pain, oedema, blistering and heavy eschar formation were seen in the 9 patients who had been treated with more than one course of radiation therapy. 2 previously irradiated patients required split-thickness skin grafts because of large eschars which would have taken months to separate and heal. The single case of osteomyelitis of a rib mentioned above had also had previous chest wall irradiation. However, it should be noted that patients with heavily irradiated chest walls had also undergone intensive chemotherapy, and tended to have a greater disease burden.

DISCUSSION

An evaluation of PDT in the management of cutaneous metastases of breast cancer has to be undertaken recognising that this is strictly local therapy, undertaken for palliative effect, in patients with a systemic disease. PDT differs from ionising radiation in that it is delivered only to visible lesions, and field treatment of both involved and uninvolved skin is not possible. Patients are symptomatic following therapy, and require local wound care up to the time that complete healing occurs. The period of disease palliation, therefore, is the interval between complete healing and new nodules. Recurrences in untreated

areas do not imply failure of PDT as such, but if they occur before complete healing of treated nodules, the patient does not achieve complete palliation of disease for any period of time. Recurrence at the epithelialising rim of a necrotic lesion may be regarded as failure of PDT, since there was presumably residual microscopic disease despite apparently complete necrosis of the lesion. Our response classification is based on the above observations, so that response to PDT implies lesional destruction and healing without recurrence at the treated site. The distinction between complete and partial response depends on the absence or presence of de novo recurrences during the 4-week period following complete healing. Admittedly, this distinction is based on disease biology rather than treatment effect, but does point out that the category of responders consists of two populations: those who achieved meaningful palliation, and those who did not.

PDT yields the best results in patients with early, minimal, (and therefore asymptomatic) lesions, where we have seen a CR rate of 13.5%. Partial responders constituted 35.1% of the total, and consisted largely of the patients with moderate extent of disease at presentation. PDT was able to destroy treated lesions in this group of patients, but *de-novo* recurrences occurred before healing of treated areas, so that the patients did not have an intact, disease-free chest wall for any period of time. The total response rate (i.e. the proportion of patients in whom treated nodules were destroyed by PDT) is, therefore, 48.6%. These response rates are somewhat lower than those reported by Sperduto *et al.* [10], who observed 20% CR and 45% PR, with the possible explanation that they do not categorise patients by extent of disease, and may have had more patients with less extensive disease. The similarity in response rates is interesting in that Sperduto *et al.* used a standard photofrin dose of 1.5 mg/kg, whereas only 11/37 (29.7%) of patients in our study received this dose or higher.

When cutaneous lesions are already symptomatic at the time of treatment (e.g. pain, foul drainage, ulceration, bulky disease), the results of PDT are disappointing, and palliation of symptoms is, in most cases, minimal. In the present series, only 2 patients who were symptomatic and had advanced lesions at the time of treatment, achieved significant palliation of their symptoms.

PDT failures were classified as such because of the development of rim recurrences, which developed in all cases before complete healing had occurred. In addition, many of these patients also had *de-novo* recurrences. An attempt was made to deal with this problem by treating zones of normally appearing skin around visible nodules. As drug dose was reduced, it became possible to use higher light doses on surrounding normal skin, due to the resultant greater tolerance of normal skin to therapeutic light doses. However, this advantage was limited in patients who had received previous ionizing radiation and/or doxorubicin, since their skin demonstrated greater photosensitivity and light doses to grossly normal skin were only 60–75% of the therapeutic dose delivered to visible lesions. Subsequent experience has shown that in patients with minimal, biologically favourable disease who have not had previous ionising radiation or doxorubicin, full light doses can be used in prophylactic zones, with good results. 4 such patients have been treated recently at RPCI, and are not included in the above report.

No conclusions can be reached regarding the culpability of previous ionising radiation to the local side-effects of PDT based on the data presented in this report since the majority of patients had experienced previous radiation therapy. However, the treatment of cutaneous basal cell carcinoma with PDT at similar drug and light doses [7] has not resulted in the degree of pain, eschar formation, and wound healing difficulty which we have observed in patients with breast cancer, and we surmise that the difference is caused by the radiation history of the breast cancer patients.

Our studies were designed to test the limit of photofrin dose reduction rather than dose reduction of photodynamic effect, with the rationale that decreases in photofrin dose would allow patients to resume normal activity and exposure to sunlight earlier, and would allow the treatment of morphologically normal skin surrounding visible lesions. Therefore, decreasing doses of photofrin were accompanied by increasing doses of light; although we did not find an appreciable difference in response rates by photofrin dose, this has to be interpreted in view of the fact that there was a deliberate attempt to equalise photodynamic effect at each dose level of PDT.

A combination of PDT with systemic therapy was used in 2 patients in whom options for systemic therapy had not been exhausted, with encouraging results. In both, initial treatment with PDT alone led to rim recurrences. Repeat PDT, this time in combination with chemotherapy in one instance and megesterol acetate in the other, led to healing of the treated areas and control of the disease for 4 and 3 months, respectively. The combination of PDT with systemic therapy may enhance local control, but it is unclear whether this has any advantage over the use of systemic therapy alone.

CONCLUSIONS

With the experience gained thus far using PDT as a treatment for cutaneous metastases of breast cancer, the following conclusions can be reached: (1) PDT in its current form has limited utility in the treatment of cutaneous metastases of breast cancer. Further application in this area must await the development of photosensitisers which will allow field treatment similar to ionising radiation, and will allow treatment at greater depths from the skin surface. (2) The optimal dose of photofrin is probably 0.75 mg/kg. This dose of photofrin is efficacious, has the advantage of decreased photosensitivity, and allows prophylactic treatment of surrounding normal skin.

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