Photodynamic Therapy Using Mono-L-aspartyl Chlorin e$_6$ (Npe6) for the Treatment of Cutaneous Disease: A Phase I Clinical Study$^1$

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**ABSTRACT**

The activity of a new photosensitizer, mono-L-aspartyl chlorin e$_6$ (Npe6), was assessed in an ascending dose Phase I study for patients with superficial tumor. Eleven patients, with a total of 14 tumor sites, were treated with photodynamic therapy (PDT) using Npe6. Lesions included recurrent adenocarcinoma of the breast, basal cell carcinoma, and squamous cell carcinoma. The phototherapy protocol consisted of a single i.v. injection of 0.5–3.5 mg/kg Npe6, followed 4 h later by 25–100 J/cm$^2$ at 664 nm of light. PDT using Npe6 caused no significant toxicity with the exception of temporary generalized skin photosensitivity. In all cases, light treatment caused immediate tissue blanching, followed by a marked necrosis of the tumor mass. Regression of tumor occurred over 24–48 h after the light treatment and was followed by the formation of a heavy eschar over the tumor site. Tumor regression was short-lived at Npe6 doses of 1.65 mg/kg and below. In two of three patients, tumor regression was either incomplete or tumors recurred within the 12-week observation period. Increasing the Npe6 dose to 2.5 or 3.5 mg/kg combined with 100 J/cm$^2$ of light energy resulted in better control of tumor regrowth with 66% (6/9) of sites remaining tumor-free through 12 weeks observation. This increased tumor response came at the expense of the tissue selectivity observed at Npe6 doses of 1.65 mg/kg and below. There was no apparent selectivity for destruction of tumor compared with normal skin at Npe6 doses of 2.5 mg/kg and above. These data demonstrate that Npe6 is both an effective and safe photosensitizer for use in PDT and provide the impetus for continued study in Phase II clinical trials.

**INTRODUCTION**

PDT$^3$ is an evolving cancer treatment shown highly successful for treatment malignant neoplasms. The relative simplicity and cost effectiveness of the administration of PDT make it a very promising modality in both the curative and palliative treatment of a variety of solid tumors. PDT has been used for treatment of a wide range of malignancies including skin (1, 2), breast (3), head and neck (4, 5), esophageal (6), lung (7, 8), and gastric cancers (8, 9). Complete understanding of the mechanisms by which PDT destroys tumor has not yet been attained.

PDT is a two-step process. Light sensitive dyes or photosensitizing agents are injected i.v. and allowed to circulate and be taken up by tissues including tumor (10). Tissues are then illuminated with exposure to nonthermal light at a wavelength specific to the photosensitizing agent. The activation of the photosensitizer by light is an oxygen-dependent process that results in the generation of highly cytotoxic species including singlet oxygen (11). The release of these reactive molecules results in damage to both tumor cells and to the tumor microenvironment. There are several photosensitizers presently under clinical investigation, and Photofrin (QLT Phototherapeutics, Vancouver, BC), a first-generation agent, has been approved recently for use against esophageal cancer (12) and early lung cancer (13). Npe6 is a new photosensitizer that has been shown to be effective in preclinical and clinical studies (14–16). Npe6 has a strong absorption peak at 664 nm and produces high yields of triplet oxygen when excited. This absorption peak allows activation at long wavelengths and provides deeper penetration of the light into the target tissue, thereby increasing the volume of tissue that can be ablated (17). Npe6 is cleared rapidly from tissues and in preliminary studies appears to offer a reduced duration of cutaneous photosensitivity (18, 19). This article reviews an 18-month clinical study of PDT using Npe6 as the photosensitizing agent. The design of this investigation was a single ascending dose, open-label study of 11 patients with a variety of solid tumors.

**MATERIALS AND METHODS**

PDT therapy with Npe6 was used in the treatment of superficial malignancies in five women and six men ranging in age from 51 to 91 years. The objectives of this study were to determine the safety and tolerance of i.v. administration of single ascending doses of Npe6 and the effectiveness of PDT using Npe6. Tumor palliation and/or cure were secondary objectives.

Patients with superficial malignancies were asked to enroll

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3 The abbreviations used are: PDT, photodynamic therapy; NPe6, mono-L-aspartyl chlorin e$_6$; ECG, electrocardiogram.
into the study if they had either failed or refused conventional treatments for their disease and met specific criteria. Inclusion criteria included superficial malignancies, either primary or metastatic that were accessible to treatment, including primary skin cancers, metastatic or recurrent cutaneous tumors, soft tissue sarcomas, and primary head and neck cancers. Subjects who met one of the above criteria were enrolled into the study if they had: a life expectancy of at least 12 weeks, a Karnofsky Performance Status Score of \( \geq 40\% \), the ability to tolerate regional anesthesia, adequate renal function with no prior history of renal disease, adequate hepatic function with a serum total bilirubin of \( \leq 1.5 \text{ mg/dl} \), the ability to give informed consent, and the willingness to be institutionalized with close monitoring for 48 h after treatment and to return for regular follow-up visits.

Exclusion criteria included: the failure to meet any of the above inclusion criteria; a history of porphyria; a patient history or family history of seizure disorders; an abnormal coagulation profile; a history of sun hypersensitivity or photosensitive dermatitis; significant gastrointestinal, cardiovascular, hematological, endocrine, neurological, respiratory, or psychiatric diseases; a history of significant allergies; previous treatment with doxorubicin or related products (due to production of skin photosensitivity); concurrent administration of any other medications affecting skin sensitivity; systemic or localized cancer treatment within 30 days prior to PDT; and a positive serology for hepatitis or HIV. Subjects were also excluded if they had a history of ongoing alcohol or narcotic abuse. All subjects signed the informed consent in compliance with the Institutional Review Board of the University of Louisville School of Medicine.

Doses of Npe6 and the timing between photosensitizer injection and light treatment were based on data from preclinical studies. The initial dose of the protocol (0.5 mg/kg) was 1/50th the dosage that had no measurable effect in dogs. The Npe6 doses used were 0.5, 1.0, 1.65, 2.5, and 3.5 mg/kg with no dose-limiting toxicity reported. Light treatment was administered 4 h after the i.v. injection of Npe6.

Of 15 patients enrolled in the study, all were eligible to participate. Three patients withdrew prior to receiving Npe6. Eleven of 12 patients completed 4 weeks on the study. The data from these 11 patients were analyzed. Lesions treated included recurrent adenocarcinoma of the breast, adenocarcinoma of the colon, basal cell carcinoma of the chest wall, squamous cell carcinoma of the hypopharynx, shoulder, and parotid, and epidermoid cancer of the urethra. More than one lesion per patient was treated if separation of the lesions was adequate to insure proper shielding.

Npe6 was supplied as a lyophilized powder by Beckhoff Associates, Inc. (Overland Park, KS)/Nippon Petrochemicals Co., Ltd. (Tokyo, Japan), study monitor and study sponsor, respectively. It was stored at a temperature of 25\(^\circ\)C and was protected from light. The Npe6 was reconstituted with sodium chloride injection USP to a concentration of 25 mg/ml immediately before use. A single i.v. dose of Npe6 was given 4 h before light treatment.

For photosensitizer activation, either a Spectra-Physics (Mountain View, CA) Model 171 or a Laserionics (Orlando, FL) model 1400–12A argon ion laser was used to pump a Spectra-Physics model 375B dye laser. The wavelength of activating light was adjusted to 664 nm for activation of Npe6 and was verified by a monochromator (model DMC1–02; Optometrics, Inc., Ayer, MA). A fiberoptic delivery system was used and was terminated with either a single-use microlens or a cylindrical diffusing fiber [PDT Systems (now Mirivant, Santa Barbara, CA)]. The fiberoptic tip was examined for defects, function, and power output before treatment. Power output was monitored before and after light treatment with a calibrated meter [PDT Systems (Mirivant) model 2015]. A flat tumor or raised tumor <1.5 cm in thickness was irradiated superficially with a microlens. A raised tumor >1.5 cm and \( \leq 2.0 \text{ cm} \) in thickness was irradiated interstitially with a cylindrical diffuser. A raised tumor >2.0 cm in thickness was not treated in this study. The tumor and a perimeter of normal tissue (0.5 cm) were irradiated at power densities ranging between 35 and 100 mW/cm\(^2\) for total light doses classified as low (25 J/cm\(^2\)), intermediate (50 or 100 J/cm\(^2\)), or high (200 J/cm\(^2\)). All treatments using cylindrical diffusing fibers were at a power density of 200 mW/linear cm for total doses of 100 J/linear cm.

Cutaneous photosensitivity/phototoxicity testing was accomplished using a solar simulator (Oriel Corporation, Stratford, CT). A small circular area was outlined on the patient’s lower back and irradiated at a light intensity of 80 mW/cm\(^2\) for 5 min (24 J/cm\(^2\)). Phototoxicity was graded as: 0, no visible reaction; 1, minimal erythema; 2, deep, clearly defined erythema; or 3, intense erythema and edema. Skin photosensitivity/phototoxicity testing was done prestudy and at frequent intervals after dosing through week 1 and then at weeks 2, 3, 4, and 6 if a moderate or greater skin reaction persisted.

Patients given Npe6 were instructed to wear protective sunglasses for 6 weeks from the time of Npe6 injection (or longer if photophobia was experienced). Protective clothing was also to be worn until testing with the solar simulator showed no reaction. Patients were still required to report any cutaneous photosensitivity for the duration of the study.

Study patients were evaluated prestudy during treatment, including 48 h in the hospital, and during a 4-week period posttreatment. Additional assessments were made at 6 and 12 weeks after treatment. The prestudy evaluation included a comprehensive medical history, physical examination with vital signs, neurological examination, ECG, chest X-ray, clinical laboratories, skin photosensitivity testing, and ophthalmological examination. A positive biopsy was required within 3 months of study enrollment. A posttreatment biopsy of the treated area could be performed at the discretion of the investigator.

During the 48-h hospitalization, evaluation included cardiac monitoring for 24 h, beginning just before NPe6 injection, an ECG at 48 h, frequent clinical laboratories (complete blood count, liver function tests, and serum electrolytes) and daily photosensitivity testing. Physical and neurological examinations were conducted immediately predosing and daily thereafter. Tumor assessments, which graded erythema, edema, firmness, and the reaction of adjacent skin, were recorded, and photographs were taken at designated intervals.

The close follow-up of each study patient over a 4-week period after PDT treatment with NPe6 consisted of the same examinations, labs, testing, and assessments conducted during hospitalization with the exception of the 24-h cardiac monitoring. Ophthalmological examination was repeated at 12 weeks after NPe6 injection.
Tumor response was evaluated at designated study intervals with the final evaluation at 12 weeks after PDT treatment. A complete response was defined as the absence of visual or histopathological evidence of tumor within the area treated. A >50% decrease in the size of the lesion treated was considered a partial response. Failure was defined as a <50% decrease in the size of the lesion treated.

Adverse experiences observed by the investigator or elicited from the patient were recorded throughout the study. A WHO scale was used to grade toxicity.

RESULTS

Tumor Response. Of the 15 tumors in 12 patients treated with PDT, 14 were evaluated for response (Table 1). Patient UL1-15 died of metastatic disease at 2.5 weeks posttreatment. Tumor response could not be adequately assessed in this patient, and the patient was thus excluded from analysis. A dosage of 0.5 mg/kg NPe6 combined with 100 J/cm² light was considered too low to produce an effectual tumor response. The one patient treated with this dose combination showed only minimal regression of the tumor mass. NPe6 doses of 1.0–3.5 mg/kg combined with 100 J/cm² light were effective in producing tumor regression in the patient groups studied. In all cases, there was marked blanching of the tissue by the completion of light treatment, followed by edema and tissue discoloration. Regression of tumor occurred over 24–48 h with gradual formation of a heavy eschar over the tumor site. After eschar formation, the tissue blanching of the tissue by the completion of light treatment, Tumor response could not be adequately assessed in this patient, X 5.6 was variable but usually occurred by 8–12 weeks after phototherapy.

Tumor regression was often transient when NPe6 doses of 1.65 mg/kg or below were used. Exceptions were the successful treatment of a large basal cell carcinoma (7.4 cm × 5.6 cm) in one patient (UL1-2) and an unclassified malignant skin neoplasm in a second patient (UL1-3). The response of tumor to PDT was relatively selective with only minor damage to normal tissues exposed to light during treatment. Increasing the NPe6 dose to 2.5 or 3.5 mg/kg combined with 100 J/cm² light resulted in better control of the tumor with 66% (six of nine) of the sites remaining free of tumor throughout the completion of the study. This increased response came at the expense of the tissue selectivity observed at lower NPe6 doses. There was no apparent selectivity of destruction to tumor compared with normal skin at doses of 2.5 mg/kg or higher; both the tumor and the surrounding normal tissues responded to light treatment with similar degrees of tissue damage and necrosis. Phototherapy at doses of 3.5 mg/kg showed no apparent increase in long-term tumor cure compared with NPe6 doses of 2.5 mg/kg (five out of six with complete response at 2.5 mg/kg versus one out of three with complete response at 3.5 mg/kg). One of the failures at 3.5 mg/kg NPe6 and 100 J/cm² light was a breast adenocarcinoma that was refractory to previous PDT treatment at 2.5 mg/kg NPe6 and 100 J/cm² light (UL1-11). In both treatment failures, the tumor and surrounding tissue did not show the characteristic heavy necrosis and eschar formation seen in other patients. A second patient with an invasive epidermal carcinoma that extended to a depth of 2 cm was treated with a surface illumination of 50 J/cm² light combined with 100 J/cm linear light from a single cylindrical diffuser that was implanted along the major axis of the tumor growth. The absence of complete tumor regression in this patient was believed to result from incomplete light delivery to the tumor. Subjects were not treated with the high (200 J/cm²) light dosage.

Pain. Pain was a frequent reaction to light treatment of photosensitized tissues both within and adjacent to the area or areas treated. Pain was related to PDT treatment rather than to NPe6 alone. The levels of pain experienced during and/or immediately after PDT with NPe6 varied from no pain to moderate pain, with no definitive correlation between the dosages of NPe6 and light and the degree of pain experienced.

Pain experienced during treatment was managed with mor-
phene sulfate administered i.v. by patient-controlled anesthesia pump as a continuous infusion and/or a bolus infusion. Post-treatment, during the 48-h hospitalization, any pain experienced at the treatment site was treated with oral or i.v. analgesics. If pain persisted after hospitalization, it was effectively managed with oral analgesics.

**Localized Cutaneous Reactions.** Erythema and edema were common findings within or adjacent to sites of photodynamic therapy. At doses of 0.5 mg/kg of NPe6 (one patient) and 1.0 mg/kg (one patient), mild erythema was seen immediately posttreatment and resolved within 2–3 weeks. Increased erythema and edema was observed after treatment in one patient who received 1.65 mg/kg NPe6 but was not observed in other patients given the same NPe6 dose.

Of the three patients injected with 2.5 mg/kg of NPe6, moderate to severe erythema was noted in one patient. Mild to moderate erythema was observed in the two patients. And mild to moderate edema was observed in all patients.

One of the four patients injected with 3.5 mg/kg of NPe6 developed moderate to severe erythema, whereas the other three patients showed only mild to moderate erythema. Moderate edema was observed in this patient group.

**Photosensitivity/Phototoxicity.** Reactions to skin photosensitivity testing were scored immediately after the completion of the 24 J/cm² light exposure and at 24- and 48-h intervals thereafter. Table 2 shows the maximum skin photosensitivity score at each test site over the study period. A reaction at the test site was usually apparent immediately after the completion of the light exposure and was sustained at that site through 24 h. In one patient, a transient wheal and flare reaction was noted that extended into the untreated skin surrounding the test area. Test sites that initially showed minimal erythema (category 1) or erythema (category 2) subsided within 48 h; test sites that produced intense erythema (category 3) and edema in the first 24 h showed only minimal erythema at 48 h.

Test sites for patients given NPe6 dosages of 0.5 and 1.0 mg/kg produced only minimal erythema when testing was done in the first week after NPe6 injection. Subsequent photosensitivity testing in these patients showed no reaction. The treatment groups that received NPe6 at doses of 1.65 and 5.5 mg/kg exhibited phototoxicity scores that returned to baseline values with 7–14 days.

One patient given NPe6 at the 3.5 mg/kg dose exhibited intense erythema and edema at the test sites when measured 24 h after NPe6 injection. The patient developed erythema at test sites through 96 h after injection and minimal erythema at test sites to week 6 after injection. A second patient showed the development of only minimal erythema at the test site, but that minimal reaction persisted through week 4 of observation. A third patient showed no apparent cutaneous photosensitivity at any time before or after NPe6 injection.

**Adverse Experiences.** The physical and neurological examinations of patients given PDT using NPe6 were essentially unchanged from the pretreatment evaluation through posttreatment week 4. Clinical laboratory testing of blood revealed no changes related to NPe6 alone or PDT with NPe6 treatment. An elevation in results from liver function tests was noted in four patients. This was considered to be unrelated to PDT with NPe6 but rather to the general diminishing health of these patients. One patient (UL1-12) presented with elevated bilirubin and alkaline phosphatase levels during the study, but this was felt to be secondary to the onset of metastatic disease in the liver. Results from ECG and Holter monitoring after NPe6 injection and PDT treatment revealed no changes from pretreatment evaluation. Ophthalmological examinations of the patients were performed before NPe6 injection and PDT treatment revealed no changes from pretreatment evaluation. Ophthalmological examinations of the patients were performed before NPe6 injection and 12 weeks after PDT treatment. No clinically significant changes were observed. Three patients did not receive an ophthalmological examination 12 weeks after phototherapy because they died of metastatic disease (UL1-2 and UL1-12) or were lost to follow-up (UL1-14).

The only adverse event among the study patients that was considered “definitely related” to PDT with NPe6 was the discharge of serosanguineous fluid at the treatment site. No side effects were considered “probably” related to PDT with NPe6. Other isolated complaints of nausea, pruritis, vomiting, headache, diarrhea, dizziness, and heartburn were reported and classified as possibly related to the combination of NPe6 administration with light treatment.

**Multiple Treatment with NPe6.** A patient not listed above (UL1-16) was selected for treatment in a special protocol.
designed to assess the effect of multiple NPe6 injections and PDT treatments over a short time span. This patient had extensive breast carcinoma that encompassed 60% of her chest wall and extended around the left side to the back. The total treatment area was divided into four sites that would be treated at designated intervals based on the previous treatment results. A total of four NPe6 treatments was given over a period of 12 weeks, each involving injection of photosensitizer and light treatment 4 h later. The first NPe6 dose given was 3.5 mg/kg. Subsequent NPe6 doses were given at 1.65 mg/kg. The plasma levels of NPe6 were carefully recorded from the time of initial NPe6 injection through the completion of the fourth treatment. Light treatment was 50 or 100 J/cm², 4 h after NPe6 injection. PDT using NPe6 produced tumor regression at all sites treated over the four courses of therapy. Tissues containing tumor showed necrosis followed by the formation of a heavy eschar. The treated areas showed evidence of reepithelization and healing 2–4 weeks after treatment. The response of all areas, irrespective of the NPe6 dose administered, was classified as complete at 12 weeks observation. Additional areas of tumor growth were noted outside the light treatment fields during this study. We did not observe any cumulative effects of the multiple NPe6 administration for skin photosensitivity. Cutaneous photosensitivity in this patient was similar to that observed in other patients given the same photosensitizer doses. Plasma levels of NPe6 showed the expected decay profile observed when patients received a single photosensitizer dose (data not shown). Repeated injections of NPe6 at 4-week intervals did not alter the baseline for photosensitizer retention.

**DISCUSSION**

This Phase I clinical study demonstrates that PDT using NPe6 is an effective and safe treatment for recurrent breast cancer and specific skin cancers. No side effects from i.v. administration of NPe6 were observed at doses up to and including 3.5 mg/kg with the exception of a generalized cutaneous photosensitivity.

Light treatment was delivered 4 h after injection of NPe6 and was based on preclinical studies (15). The tumor response and cure in these studies was found to be greatest when light treatment was given when the plasma level of NPe6 was high (19) and decreased rapidly as the time between NPe6 injection and light treatment progressed from 2–12 h. Phototherapy under conditions when plasma levels of photosensitizer are high implies a vascular mechanism of tissue destruction. Several recent investigations have concluded that tumor destruction after PDT using NPe6 is dependent on vascular damage and blood flow stasis (20, 21).

Tissue blanching and discoloration were the first signs of response of photosensitized tissues treated with 664 nm of light in the clinical study. Shrinkage of tumor and formation of eschar followed this. Phototherapy with NPe6 doses of 1.65 mg/kg or less produced a highly selective response. Tumor shrinkage and necrosis were observed without significant damage to the surrounding skin within the light treatment field. Slight edema and erythema were observed on the normal skin within the treatment field, but this did not lead to necrosis. This subsided after light application ended. In our small study treatment, NPe6 doses of 1.65 mg/kg and 100 J/cm² light produced tumor regression through 12 weeks of observation in one of three patients. The recurrent growth of tumor appeared to originate from the edges of the original tumor site, suggesting that there was incomplete destruction of tumor cells at the interface between tumor and normal tissue. These observations are similar to findings of failure in tumor response and cure noted in preclinical experiments using Photofrin (22). Long-term tumor regression and cure were found only if damage occurred to both the tumor and the perimeter of normal skin surrounding the tumor (23, 24). Cells at the periphery of the tumor mass appear to survive PDT treatment due to either maintained tissue oxygenation or reoxygenation of the cells by the microvasculature of the surrounding skin.

Escalation of the NPe6 dose to 2.5 and 3.5 mg/kg and light treatment with 50–100 J/cm² light caused necrosis of both tumor and normal tissue within the treatment area. No apparent selectivity for damage to either tumor or normal skin was observed. The increase in relative damage to both of these tissues did result in complete tumor regression in six of nine patients through 12 weeks of observation after PDT (i.e., NPe6 and light). It remains unclear whether this response is a result of increased damage within the tumor or as a result of the destruction of the normal skin surrounding the tumor and presumed destruction of the vasculature at the periphery of the tumor mass.

It remains unknown whether the destruction of the normal tissue surrounding the tumor is a necessary condition for tumor cure. The use of different NPe6 or light dose conditions that may have maximized the destruction of tumor compared with normal tissue was not investigated in this Phase I clinical study. Studies under Phase II should investigate the effect of increasing the light dose above 100 J/cm² at NPe6 doses where tissue selectivity was seen in this Phase I trial (1.65 mg/kg NPe6).

A significant advantage of PDT using NPe6 is the reduced duration of cutaneous photosensitivity as compared with other photosensitizers. Photosensitivity testing of patients given NPe6 doses of up to 3.5 mg/kg generally showed only minimal or mild erythema within the first 96 h after NPe6 injection and no significant skin photosensitivity after that time. Two patients were exceptions to this finding and exhibited mild cutaneous photosensitivity at 4 weeks after NPe6 injection. Because of the wide range in results from photosensitivity testing, no direct correlation of NPe6 dosage to the degree of cutaneous photosensitivity was established in the present study. None of the groups given a dose of NPe6 <3.5 mg/kg showed prolonged photosensitivity. This, however, represents a small number of patients and further testing for photosensitivity would need to be performed.

The short duration of photosensitivity corresponds to animal studies by Roberts et al. (18), who found no skin phototoxicity 24 h after NPe6 injection in mice and guinea pigs. These findings coincide with the rapid clearance of NPe6 from plasma and tissues seen by other groups (15, 19). The effect of NPe6 on skin photosensitivity is different from that observed with Photofrin, which can be associated with some degree of photosensitivity for periods of 6 weeks or longer after injection (24, 25).

The rapid clearance of NPe6 from tissues permits additional PDT treatments to be given over a relatively short time
period. Our experience with one patient given four sequential PDT treatments over 12 weeks indicates that this therapy can be delivered safely and effectively with no accumulation of residual photosensitizer. Multiple treatments of single tumors may allow smaller and less damaging NPe6 doses and light doses to be used. This could be useful to preserve the surrounding normal tissues or vital structures and to treat large areas or invasive tumors that cannot be satisfactorily managed in a single treatment.

NPe6 appears to offer a practical and safe alternative to other presently available photosensitizers used in PDT. A limited duration of photosensitivity is the only expected and significant side effect. The addition of NPe6 as a photosensitizer for use in PDT provides the clinician with an additional tool for the delivery of phototherapy and treatment of solid tumors. The potential of this photosensitizer for use in PDT provides an important motivation for continued investigation of NPe6 in Phase II studies.

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