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PHOTODYNAMIC THERAPY (PDT) USING HPPH FOR THE TREATMENT OF PRECANCEROUS LESIONS ASSOCIATED WITH BARRETT'S ESOPHAGUS

Hector R Nava, M.D., Shyam S Allamaneni, M.D., Thomas J Dougherty, Ph.D., Michele T Cooper, RN., Wei Tan, MA., Gregory Wilding, Ph.D., and Barbara W Henderson, Ph.D.
Roswell Park Cancer Institute, Buffalo, NY, 14263

Abstract

Background and Objectives—Photodynamic therapy (PDT) with porfimer sodium, FDA approved to treat premalignant lesions in Barrett's esophagus, causes photosensitivity for 6-8 weeks. HPPH (2-[1-hexyloxyethyl]-2-devinyl pyropheophorbide-a) shows minimal photosensitization of short duration and promising efficacy in preclinical studies. Here we explore toxicity and optimal drug and light dose with endoscopic HPPH-PDT. We also want to know the efficacy of one time treatment with HPPH-PDT.

Study Design/Materials and Methods—Two nonrandomized dose escalation studies were performed (18 patients each) with biopsy-proven high grade dysplasia or early intramucosal adenocarcinoma of esophagus. HPPH doses ranged from 3 to 6 mg/m². At 24 or 48 hours after HPPH administration the lesions received one endoscopic exposure to 150, 175 or 200 J/cm of 665 nm light.

Results—Most patients experienced mild to moderate chest pain requiring symptomatic treatment only. Six patients experienced Grade 3 & 4 adverse events (16.6%). Three esophageal strictures were treated with dilatation. No clear pattern of dose dependence of toxicities emerged.

In the drug dose ranging study (light dose of 150 J/cm at 48 h), 3 and 4 mg/m² of HPPH emerged as most effective. In the light dose ranging study (3 or 4 mg/m² HPPH, light at 24 h), complete response rates (disappearance of high grade dysplasia and early carcinoma) of 72% were achieved at 1 year, with all patients treated with 3 mg/m² HPPH plus 175 J/cm and 4 mg/m² HPPH plus 150 J/cm showing complete responses at 1 year.

Conclusions—HPPH-PDT for precancerous lesions in Barrett's esophagus appears to be safe and showing promising efficacy. Further clinical studies are required to establish the use of HPPH-PDT.

Keywords

Esophageal cancer; High Grade Dysplasia; Photosensitizer; Ablative Therapies

Corresponding Author: Barbara W Henderson Ph.D., Director of the PDT center, Roswell Park Cancer Institute, Elm & Carlton streets, Buffalo, NY - 14263. bararahenderson@roswellpark.org, Tel: 716 845 4429, Fax: 716 845 8920.

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INTRODUCTION

There will be an estimated 16,640 new cases and 14,500 deaths of esophageal cancer in the United States in 2010 [1, 2]. Adenocarcinoma of esophagus arises from its precursor lesion, Barrett's esophagus (BE), and progresses through stages of low and high grade dysplasia to invasive cancer [3]. While the risk of cancer arising from BE is ~0.5 % per year, that risk in BE with high grade dysplasia (HGD) is >10% per year, and cancer is present, often undetected, in up to ~50% (25-73%) of patients with HGD [4]. Given the dismal prognosis of invasive cancer (5-year survival of ~5-20%), treatment of the precursor lesions has been emphasized, especially when HGD is present [3, 5-7]. HGD is considered a criterion for esophagectomy in many medical centers. However, given the high rates of mortality (2-12%), and morbidity (40-50%) of esophagectomy and co-morbidities [5, 6, 8], local endoscopic ablation techniques have been explored. These include laser therapy, multipolar electrocoagulation, argon-plasma coagulation, cryoablation, radiofrequency ablation (RFA), endoscopic mucosal resection (EMR) and photodynamic therapy (PDT). While RFA and cryoablation have gained favor in recent years, Menon et al. concluded after an extensive analysis of the published data that it is yet impossible to determine comparative effectiveness of each modality due to shortcomings in published studies [9]. Therefore, attempts to improve PDT as presented here are still valid.

PDT is a minimally invasive treatment of solid tumors employing a photosensitizing drug (photosensitizer) and laser light [10]. Photosensitizers accumulated in malignant tissues remain inactive until exposed to a specific wavelength of visible, non-thermal light. PDT has been used to treat carcinomas in many organs and porfimer sodium (Photofrin) -PDT has regulatory approval in the United States to treat early and advanced stage endobronchial and esophageal cancers, and HGD associated with BE [11,12]. The generally accepted mechanism of action of PDT is the generation of singlet oxygen, which causes irreversible oxidation of essential cellular components [13, 14]. In addition to tumor cell destruction, vascular disruption and activation of anti-tumor immunity aid in PDT anti-tumor activity [10, 15].

PDT with porfimer sodium has minimal invasiveness and systemic toxicity, and offers opportunities for re-treatment without cumulative toxicities. PDT with curative intent is currently restricted to local treatments and cancers that are accessible to delivery of visible light and that are no more than ~3-6 mm in depth, i.e. HGD in BE, are a potential indication for PDT. Indeed, 5-year follow-ups are available for non-randomized studies with porfimer sodium, as well as for a multi-center randomized trial that led to regulatory approval [12].

Porfimer sodium PDT causes prolonged skin photosensitivity, which requires avoidance of sun and bright lights for 4-8 weeks. To mitigate this problem the photosensitizer HPPH (2-[1-hexyloxyethyl]-2-devinyl pyropheophorbide-a) has been developed that has demonstrated minimal photosensitization of short duration in preclinical and clinical studies [16-20]. HPPH strongly absorbs light at 665nm, allowing deeper light penetration into tissue. The primary objective of this study was to identify toxicity and optimal drug and light dose with endoscopic HPPH-PDT. Our secondary objective was to measure the efficacy of a one time-treatment of HPPH-PDT in the microscopic disappearance of HGD and early intramucosal adenocarcinoma.

METHODS

This report is comprised of results from two nonrandomized dose escalation studies (drug dose and light dose). All studies were carried out at Roswell Park Cancer Institute (RPCI) between the years 2000 and 2004. A total of 36 patients received endoscopic HPPH-PDT.

The studies were approved by the RPCI Institutional Review Board and overseen by the RPCI Data and Safety Monitoring Board.

Patient eligibility

Patients referred with a diagnosis of BE with HGD were enrolled and had to meet the following criteria: biopsy-proven HGD or early intramucosal adenocarcinoma, 18 years of age or older, and a signed consent. Lesions could be primary or recurrent and patients could have received prior treatment of any kind, if that treatment had occurred at least one month or more prior. Patients who had prior cancer other than non-melanoma skin cancer must have been deemed disease-free. Patients had to have a Karnofsky status of 50 or above and could not have any contraindications to endoscopy. Patients had to be either ineligible for surgical resection or had refused surgery and other forms of treatment. Patient exclusion criteria were as follows: porphyria or hypersensitivity to porphyrin or porphyrin-like compounds; blood cell count $<4,000$; platelet count $<100,000$; normalized ratio of prothrombin time >1.5 upper normal limit; serum bilirubin >3.0 mg/dl; serum creatinine >3 mg%; alkaline phosphatase or SGOT >3 upper normal limits.

Patients provided consent prior to treatment. Inclusion/exclusion criteria were applied, based on medical history and physical examination, electrocardiogram, laboratory tests, chest radiograph, chest and abdominal CT scan, esophagogram, endoscopy, EUS (when appropriate), mapping and assessment of Barrett's mucosa (BM) and biopsies.

HPPH dose escalation design

This study was designed to examine toxicity (HPPH alone and HPPH plus light) and lesion response at four HPPH doses (3, 4, 5, 6 mg/m²) and a fixed light dose of 150 J/cm delivered 48 hr after infusion of HPPH.

Light dose escalation design

This study was designed to determine the range of safe and effective light doses at two HPPH doses, 3 and 4 mg/m². A light dose of 150, 175 or 200 J/cm was delivered 24 hr after infusion of HPPH.

HPPH - PDT treatment

HPPH was administered as a single, slow intravenous infusion over 1 hour. The BE was exposed endoscopically to 665 nm light from an argon dye laser-pumped tunable dye laser through a freely placed cylindrical diffuser fiber (length 1-5 cm). The fiber length was chosen to cover the involved area with 5 mm margins at the distal and proximal ends of the BE mucosal length. Treatment fields longer than 4 cm were treated with multiple fiber placements. Patients received conscious sedation during the endoscopic procedure. Each patient received only 1 course of treatment (HPPH+light).

Two days after laser therapy, patients' initial mucosal response was assessed by endoscopy, and photographed (Figs. 1 & 2). Endoscopy and 4-quadrant biopsies covering the initial length of the BM were done on follow-up at 2, 4 and 6 months, and every 6 months thereafter up to 5 years. In addition, an esophagogram was done at the 2 month follow-up and a thoracic CT scan was done at the 6 month follow-up. Patients were allowed only one HPPH course with laser. All patients received concomitant acid suppression therapy with omeprazole (20 mg twice a day).

Safety measures

Patients were instructed to avoid exposure to sunlight or bright indoor light for at least 7 days by wearing protective clothing and specific sunglasses provided by RPCI PDT Center. Patients were instructed to expose a small area of skin to sunlight on Day 8 for 10 minutes to determine any remaining photosensitivity.

Patients were monitored for systemic toxicity at the time of HPPH administration, laser treatment and at each follow-up. All patients were admitted until the follow up endoscopy 48 hrs after laser treatment, allowing the accurate capture of all complications. Laboratory tests were carried out when indicated. Adverse events were documented as to onset and resolution date, classification of intensity, relationship to treatment, action taken and patient outcome.

Outcome measures

All AEs were recorded per MedDRA coding (Medical Dictionary for Regulatory Activities). Microscopic disappearance of HGD and early intramucosal adenocarcinoma was taken from pathology reports on 4-quadrant jumbo biopsies. Although complete ablation of BM was not expected with a single PDT exposure, BM responses were also recorded. The outcome was considered as complete response (CR) if there was total disappearance of HGD or early intramucosal carcinoma. Persistence of foci of HGD in spite of significant resolution of BM was considered as no response.

RESULTS

Pretreatment patient characteristics

Table 1. One patient had received prior treatment (esophagectomy, chemotherapy, radiation) with recurrence of disease in the remaining esophagus. None of the other patients had received any prior treatment.

Adverse events (AE) profile

No clear pattern of dose dependence was observed in either study. There were total of 6 (16.6%) grade 3 & 4 adverse events out of which one (diabetic acidosis) is unrelated to the PDT. In addition, most patients (94%) reported at least one transient AE. The majority of these events were mild to moderate chest pain (in 86% of patients), with one patient reporting grade 3 chest pain (Table 2). In every case, chest pain was reported during the 48 hours of hospitalization following laser light exposure; none of the patients needed to extend their stay in the hospital due to this adverse event. Gastrointestinal AEs (in 53% of patients) included mild to moderate dysphagia, nausea and odynophagia. Three esophageal strictures definitely related to PDT (1 grade 3, Table 3) were treated with dilatation, with one patient requiring repeated dilatation. Weight loss (grade 1) and dysphagia (grade 2) were associated with the grade 3 esophageal stricture. Of the 4 pleural effusions (three grade 3, Table 3), 2 were treated medically, while 2 required thoracentesis. All patients recovered uneventfully. Two grade 1 unexpected AEs were attributed to HPPH alone (1 injection site extravasation, 1 unexpected headache, Table 3). Four unexpected events (diabetic acidosis grade 4, bradycardia grade 2, shortness of breath grade 2 and respiratory depression grade 2) were unrelated to PDT and were attributable to underlying disease and surgery (anesthesia), respectively.

Two photosensitivity reactions (6% of patients) were observed; one patient experienced mild photophobia and another patient experienced grade 1 sunburn due to HPPH.

HPPH dose escalation study responses

After one patient was treated at 3 mg/m² HPPH, the study was amended to change the starting dose to 4 mg/m² because we observed that the patient treated with 3 mg/m² did not respond as rapidly to treatment as had been observed with porfimer sodium. The patient eventually had a CR. In retrospect this amendment was not required as 3 mg/m² HPPH was found as effective as 4 mg/m² in subsequent studies. Eleven patients were treated with 4 mg/m² of HPPH. The 1-year CR rate for the combined 3 and 4 mg/m² treatments (7 patients) was 39%. Interestingly, there were no complete responses with HPPH doses of 5 and 6 mg/m². Eight patients experienced good responses with significant decreases in length of BM, but because some residual HGD was found in biopsies, these patients were placed in the “no response” category as per study criteria.

Two patients were diagnosed with invasive cancer on the 48 hr post-treatment endoscopy. One patient was diagnosed with invasive cancer at the time of the 3-month follow-up endoscopy. Because of short interval from PDT and to diagnosis of invasive cancer, it is assumed that these 3 patients had preexisting invasive cancer that was missed on initial biopsies. Of 7 patients who had CR at 1 year, only 2 continued to show CR at the end of 5 yrs. Of 4 patients who developed recurrence of focal HGD, 3 subsequently received porfimer sodium-PDT and one received Nd-YAG laser ablation. One patient was lost to follow-up. All 8 patients who were categorized as no response under this study criterion had significant responses in the form of decrease in the length of BM but had remaining areas of HGD. Of these, 6 went on to receive porfimer sodium-PDT, while 2 patients received Nd-YAG laser ablation to an area of focal HGD.

Light dose escalation study responses

All of the 6 patients who received 3 mg/m² HPPH and 175 J/cm or 4 mg/m² and 150 J/cm showed CR at 1 year post treatment. Over the range of doses applied, there was no clear dose dependence in this study. The 1-year CR rate across all treatment regimens was 72% (13/18) after only one treatment course. Of 13 patients with CR, 7 (54%) patients did not show any recurrence of the disease on follow-up at 5 years, with one patient lost to follow-up. Of 5 patients who developed recurrence, 2 subsequently received porfimer sodium-PDT and 2 patients underwent EMR. Of 5 patients who were PR, 2 subsequently received porfimer sodium-PDT and 3 patients underwent EMR.

Although complete regression of BM with just one exposure to PDT treatment was not expected, a detailed breakdown of responses of BM across all PDT doses was analyzed; 7/18 patients showed complete resolution of BM. Barrett's mucosa resolution was 50-99% in 5 patients and less than 50% in 5 patients. One patient did not show any BM response.

DISCUSSION

This study presents for the first time the results of ablation with HPPH-PDT of precancerous lesions and early intramucosal cancer associated with BE.

Despite the relatively small number of patients, the results allow some conclusions to be drawn. First, HPPH-PDT appears to be safe in patients with early esophageal lesions. The AE profile in the two related studies reported here is similar to that of the published randomized clinical trials with porfimer sodium-PDT [11, 21], with some notable exceptions. The major rationale for the clinical development of HPPH was the much reduced time of general photosensitivity observed in preclinical and clinical studies [18]. Only two study patients (6%) reported mild photosensitivity reactions. This is markedly lower than reported for the randomized porfimer sodium-PDT trial [11] and the experience with porfimer sodium-PDT at Mayo Clinic published by Prasad et al [22], which reported

69% and 60%, respectively, of patients experiencing general photosensitivity. We attribute our results to the short plasma half-lives of HPPH in patients (α and β half-lives 7.77 h and 596 h, respectively) [17]. In a study evaluating cutaneous photosensitivity, patients injected with 3 or 4 mg/m² had no skin reaction following exposure to artificial solar-spectrum light; one of 2 patients injected with 5 mg/m² HPPH and 2 of 3 patients receiving 6 mg/m² HPPH had skin reactions limited to very minimal erythema [18].

By far the most common AE associated with HPPH-PDT was non-cardiac chest pain. It was mostly mild to moderate, ascertained through rigorous questioning of the patients by clinical staff. Only one patient reported severe chest pain. As pointed out by Wang et al., chest pain is common in most ablative techniques, including porfimer sodium PDT [23]. Grade 3 & 4 adverse events are noted only in 6/36 (16.6%) patients and one of them is unrelated to HPPH-PDT. In the current studies, 3 patients (8%) developed stricture requiring dilatation in response to one HPPH-PDT exposure. The reported stricture rate after up to three porfimer sodium-PDT exposures is 36% and 27%, respectively [11,22,24,25]. One porfimer sodium-PDT treatment resulted in a 12% stricture rate [11,21], comparable to the stricture rate in this study.

Overholt et al. [25] reported pleural effusions in 11/14 patients, detected by routine CXR within 48 h after porfimer sodium PDT. Pleural effusions, noted *via* routine use of chest x-rays for chest pain and shortness of breath, occurred in 4/36 (11%) of patients in the current study. There were no occurrences of bleeding or perforation, and no death were recorded. Panjehpour and Overholt [21] mention a small risk of atrial fibrillation after PDT. In a series of 100 patients with porfimer sodium PDT, 3 patients developed this AE [25]. In the current study, 1/36 patients developed a grade 1 atrial fibrillation that was possibly attributable to HPPH-PDT.

The second tentative conclusion to be drawn from our studies is that HPPH-PDT is effective. After only one PDT treatment, all patients showed initial responses which ranged from significant reductions in BE to downgrading of HGD, to complete ablation of HGD and cancerous lesions. Interestingly, the HPPH dose finding study revealed that increasing the HPPH dose above 4 mg/m² does not seem to improve outcomes. Similar trends were observed in studies in rodent tumor models [26, 27] where they were explained based on the concept of photochemical oxygen depletion [28]. The depletion of oxygen can occur during the process of rapid and extensive singlet oxygen generation that exceeds the rate at which oxygen can be resupplied by diffusion from the vasculature. High photosensitizer dose and irradiance (irradiance ranged from 100-400 mW/cm² in our studies) are major determinants for photochemical oxygen depletion. Under such conditions PDT becomes self-limiting because the PDT response depends critically on the availability of molecular oxygen and production of singlet oxygen for cell injury. This explanation, however, is not entirely convincing when one considers the difference in the drug/light time interval in the two studies, 48 hours in the HPPH escalation study and 24 hours in the light dose escalation study. Given the clearance kinetics of HPPH [17], drug levels in the circulation at 48 hours after an HPPH dose of 5 or 6 mg/m² can be expected to be very similar to those at 24 hours after an HPPH dose of 3 or 4 mg/m². This speaks against oxygen depletion alone influencing outcomes and rather suggests possible differences in HPPH distribution.

Having determined the optimal range of HPPH doses, with 3 and 4 mg/m² appearing effective, the light dose finding study focused on these drug doses. It achieved 100% initial CR rates with the drug/light combinations of 3 and 4 mg/m² HPPH plus 175 and 150 J/cm, respectively. The 1-year CR rate across all drug/light combinations, which showed no clear dose dependence, was 72%. Importantly, 39% of patients (54% of patients with 1 year CR) achieved lasting (5-year) CR upon the one course of HPPH-PDT. This compares well with

the results from the Phase III porfimer sodium trial, where 32% of patients did not require a second treatment course, thus presumably achieved CR with one treatment course [11].

As in the other studies, partial responses and HGD recurrences, which were usually restricted to small disease foci, were treated successfully with EMR and/or porfimer sodium-PDT. Repeated courses of treatment would no doubt further improve the here reported treatment outcomes. Multiple HPPH-PDT treatment courses with a treatment interval of at least 6 weeks have been carried out in other trials without any cumulative toxicity (unpublished data).

The gold standard treatment for the indications addressed here still appears to be esophagectomy for avoiding cancer development and prolonging survival, although it is associated with considerable mortality and morbidity. While the emphasis here has been on HPPH PDT vis a vis porfimer sodium PDT, this study design, allowing only one PDT exposure, does not permit any direct comparison with either porfimer sodium PDT or other ablative techniques such as RFA, multipolar electrocoagulation (MPEC) or cryoablation, as these have included numerous (up to 4) exposures [9, 29].

Gross and Wolfsen have reviewed the use of EMR, as well as the various approaches of PDT in BE [30]. While EMR appears highly effective for the removal of localized lesions of BM or HGD, a high percentage of dysplasia has been detected in resection margins. EMR has, however, proven effective in this and other studies in removing small islands of disease that sometimes remain after PDT or other ablative techniques. EMR was applied, if necessary, after PDT to allow assessment of HPPH PDT efficacy for treating thicker lesions.

HPPH is one of several new photosensitizing agents under investigation. The pro-drug ALA (5-aminolevulinic acid), which leads to high intracellular levels of the photodynamically active protoporphyrin IX, has generated uneven results in the treatment of early esophageal disease [9, 31-34]. Attractive because of the absence of prolonged general photosensitivity, this agent, when light-activated (630 nm), has given initial response rates ranging from as high as 97-100% to as low as 67%. Recurrence rates may be high, likely due to limited tissue penetration. Also, ALA given orally at effective doses is associated with nausea and vomiting, and has caused one death due to vascular instability [33].

The photosensitizer m-tetrahydroxyphenyl chlorine (mTHPC, Foscan®; 652 nm) has been evaluated in a small number of patients with HGD and BM, and was found to be a highly potent [30, 35]. Because of its high activity it has been associated with a high incidence of stricture formation, full thickness tissue necrosis, and in one case tissue perforation. Cutaneous photosensitivity has been observed up to 3 weeks. Optimal treatment parameters have yet to be defined.

While other ablation techniques have gained favor in recent years, attempts to improve PDT are still valuable. First, data so far have not convincingly proven the superiority of RFA or any other ablative technique [9]. Second, as argued by Wang et al., PDT is easy to perform, which ensures that it can be performed without much variation in response due to endoscopic skill [23]. These authors further argue that this relative simplicity and cost-effectiveness will allow translation into practice, not only in the US, but also in countries with limited health care resources. They also pointed out the still existing challenges of this modality: the high stricture rate, prolonged cutaneous photosensitivity and acute morbidity, especially severe chest pain. The study presented here addresses at least two of these challenges; it describes the use of a new PDT agent that causes minimal cutaneous photosensitivity and has mostly mild to moderate acute morbidity. The stricture rate was low in the present study, but it is yet unknown whether it may increase upon repeated treatments.

The results from our studies need to be interpreted in a cautious manner when comparing to the published studies. The major limitation of our study is small sample size in some groups as we examined multiple variables. Other important issues, which may be concealing the full potential of HPPH, are single course treatment and light delivery technique. Here a freely placed cylindrical diffuser fiber was used to deliver the light rather than the balloon catheter employed in the randomized porfimer sodium-PDT trial [11]. Although this decision was made because no balloon catheter was available, several other considerations may support that choice, including the possible compression of mucosa and thus possible decrease in blood flow and oxygen supply, and the slippage of the balloon due to esophageal mobility. No comparative data for the different light delivery approaches are available.

From the present studies we conclude that HPPH-PDT for precancerous lesions and early intramucosal cancer in BE appears to be safe with promising efficacy, justifying more extensive controlled studies to establish its use for this disease.

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Figure 1.
Endoscopic view of the esophagus before HPPH photodynamic therapy showing extensive Barrett's changes.

Figure 2.
Endoscopic view of the esophagus 48 h after HPPH photodynamic therapy showing extensive necrosis.

TABLE 1
Pretreatment patient characteristics

PATIENT CHARACTERISTICS	HPPH DOSE ESCALATION STUDY	LIGHT DOSE ESCALATION STUDY
No. patients	18	18
No. men	16	16
No. women	2	2
Age range (y)	54-86	50-82
Age median (y)	69	70
Length of BE, range (cm)	2-15	1-7
Length of BE, median (cm)	5	5
HGD	18	17
Intramucosal carcinoma	0	1

TABLE 2

Combined adverse events (AEs)

	EVENT	DISEASE (%)	HPH ¹ (%)	PDT ² (%)	SURGERY (%)
At Least 1 AE		3 (8)	4 (11)	34 (94)	1 (3)
CARDIAC DISORDERS				4 (11)	
	Atrial fibrillation			3 (8)	
	Bradycardia sinus			1 (3)	
GASTROINTESTINAL DISORDERS		3 (8)		19 (53)	
	Fullness abdominal / bloated			4 (11)	
	Heartburn			1 (3)	
	Hiccups			1 (3)	
	Nausea			6 (17)	
	Vomiting			2 (6)	
	Dysphagia	1 (3)		7 (19)	
	Odynophagia			5 (14)	
	Stricture esophagus	2 (6)		3 (8)	
GENERAL DISORDERS			1 (3)	31 (86)	
	Fatigue			1 (3)	
	Injection site extravasation		1 (3)		
	Pain chest			31 (86)	
METABOLIC AND NUTRITIONAL DISORDERS		1 (3)		6 (17)	
	Weight loss			4 (11)	
	Appetite decreased			2 (6)	
MUSCULOSKELETAL DISORDERS		1 (3)			
	Diabetic acidosis				
	Joint range of motion decreased		1 (3)		
NERVOUS SYSTEM DISORDERS			1 (3)		
	Headache				

EVENT	DISEASE (%)	HPPH ¹ (%)	PDT ² (%)	SURGERY (%)
RESPIRATORY DISORDERS				
Cough			4 (11)	1 (3)
Pleural effusion			3 (8)	
Respiration depressed			4 (11)	
Shortness of breath				1 (3)
PHOTOSENSITIVITY DISORDERS				
		2 (6)		
Photophobia		1 (3)		
Sunburn		1 (3)		
VASCULAR DISORDERS				
			2 (6)	
Elevated blood pressure reading			1 (3)	
Hypertension			1 (3)	

¹Toxicity related to HPPH only

²Toxicity related to HPPH + light

TABLE 3
Unexpected & Grade 3 & 4 Adverse Events

DRUG DOSE ESCALATION STUDY					
Unexpected	Event	Grade	HPPH #Events/Attribution (Dose)	PDT ² #Events/ Attribution (Dose)	Unrelated To PDT ³
	Injection site extravasation	2	1/ definite (4 mg/m ²)		
	Headache	2	1/ possible (4 mg/m ²)		
	Dyspnea	1		1/ possible (6 mg/m ² HPPH, 150 J)	
	Hypertension	1		1/ possible (5 mg/m ² HPPH, 150 J)	
	Diabetic acidosis	4			1

LIGHT DOSE ESCALATION STUDY					
Expected	Event	Grade	HPPH #Events/Attribution (Dose)	PDT #Events/Attribution (Dose)	Unrelated To PDT
	Esophageal stricture	3		1/ definite (3 mg/m ² HPPH, 200 J)	
	Pleural effusion	3		3 / definite (3 mg/m ² HPPH, 200 J; (4 mg/m ² HPPH, 150 J)	
	Chest pain	3		1/ definite (3 mg/m ² HPPH, 200 J)	
Unexpected					
	Elevated blood pressure	1		1/ definite (3 mg/m ² HPPH, 200 J)	
	Bradycardia	2			1
	Shortness of breath	2			1
	Respiration depressed	3			1

¹Toxicity related to HPPH only

²Toxicity related to HPPH+Light

³Toxicity related to neither HPPH or HPPH+light.