A Phase I Study of Foscan-Mediated Photodynamic Therapy and Surgery in Patients With Mesothelioma

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Background. **Photodynamic therapy (PDT) is a light-based cancer treatment that, in the correct setting, can be delivered intraoperatively as an adjuvant therapy. A phase I clinical trial combining surgical debulking with Foscan-mediated PDT was performed in patients with malignant pleural mesothelioma. The purpose of the study was to define the toxicities and to determine the maximally tolerated dose (MTD) of Foscan-mediated PDT.**

Methods. **A total of 26 patients completed treatment. Tumor debulking was accomplished with either an extrapleural pneumonectomy (7 patients) or a lung-sparing pleurectomy–decortication (19 patients). Patients were injected with Foscan before surgery, and 652 nm light was delivered intraoperatively after completion of surgical debulking. Four light sensors were placed in the chest, allowing delivery of light to a uniform measured dose throughout the hemithorax.**

Results. **Four dose levels were explored. The MTD was 0.1 mg/kg of Foscan injected 6 days before surgery in combination with 10 J · cm^{-2} 652 nm light. Dose limiting toxicity at the next higher dose was a systemic capillary leak syndrome leading to death in 2 of 3 patients treated at that dose. Other PDT-related toxicities included wound burns and skin photosensitivity. In all, 14 patients were treated at the MTD without significant complications.**

Conclusions. **Foscan-mediated PDT can be safely combined with surgery at the established MTD. Unlike most other surgery-based multimodal treatments for mesothelioma, Foscan-mediated PDT affords the option, in selected patients, of accomplishing tumor debulking with a lung-sparing procedure rather than an extrapleural pneumonectomy. A phase II study is warranted.**

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Malignant pleural mesothelioma (MPM) is refractory to standard therapies [1]. Typically, the surgical procedure of choice for most patients with early stage MPM has been extrapleural pneumonectomy (EPP) [2, 3]. Despite apparently "complete" resections, high local recurrence rates and low survival rates are the rule [1]. These poor results have led to the investigation of combining adjuvant therapies such as radiation, chemotherapy, or photodynamic therapy (PDT) with surgery [2, 4–7].

Photodynamic therapy is a cancer treatment that involves the use of a photosensitizer, oxygen, and laser light [8]. Preclinical studies demonstrate greater retention of photosensitizers in tumor compared to normal tissues, potentially providing an improved therapeutic gain [9, 10]. Photodynamic therapy is a superficial treatment that can be delivered intraoperatively and is potentially ideal for surface malignancies such as MPM.

The first-generation photosensitizer, hematoporphyrin derivative (HPD), is a mixture of porphyrins that is partially purified to produce the commercially available product, Photofrin [11]. The second-generation photosensitizer, tetra (m-hydroxyphenyl) chlorin (Foscan), is a synthetic chlorin compound that is activated by 652 nm light [9]. We chose to perform a phase I study of Foscan-mediated PDT because: 1) PDT, as opposed to external beam radiation, preserves the option of performing a lung-sparing procedure; 2) Foscan confers several advantages including a high singlet oxygen yield and a shorter duration of cutaneous photosensitivity; and 3) there is a need for new adjuvant therapies for mesothelioma [12, 13]. The primary objectives of this trial were to define the toxicities and MTD of Foscan-mediated PDT.

Material and Methods

The clinical protocol was approved by the University of Pennsylvania Institutional Review Board on November

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26, 1997, and was conducted under an Investigational New Drug Application with the United States Food and Drug Administration. Written informed consent was obtained from all patients.

The eligibility criteria for patients were a diagnosis of mesothelioma limited to one hemithorax, 30 days since any previous cancer treatment, Eastern Cooperative Oncology Group performance status of 0 to 2, medical suitability for resection, and age 18 years or more. Patients were excluded for distant metastases, T4 tumors, coexisting malignancy, pregnancy or lactation, reactive human immunodeficiency virus test, or inadequate hematologic, renal, and hepatic function.

Patient evaluation included imaging studies of the chest (computed tomography or magnetic resonance imaging), pulmonary function tests, quantitative ventilation-perfusion scans, and laboratory studies. Imaging studies of the brain, abdomen, pelvis, and bones were performed as clinically indicated. Preoperatively, all patients underwent an upper endoscopy, bronchoscopy, and diagnostic laparoscopy with peritoneal lavage and biopsies. Initially, the diagnostic laparoscopy was performed in the operating room on the same day as the thoracotomy. However, after 2 patients who had already received Foscan were found to have subdiaphragmatic disease, a decision was made to perform the laparoscopy as a separate outpatient procedure before Foscan administration. All patients were clinically staged (14). preoperatively and pathologically staged postoperatively by two investigators (J.S.F. and S.M.H.). Patients were seen for outpatient visits 1 month and 2 months after surgery and PDT. Thereafter, patients were seen and computed tomographic scans were obtained every 3 months for 2 years and then every 6 months thereafter. Clinical evaluation and computed tomographic scans were used to document recurrence.

Patients were enrolled in cohorts of 3 patients in which the dose of 652 nm light and the drug–light interval were altered. The Foscan dose was fixed at 0.1 $mg \cdot kg^{-1}$. Four PDT dose cohorts were evaluated, who received the following drug–light intervals and light doses: 5 $J \cdot cm^{-2}$ for 6 days; 5 $J \cdot cm^{-2}$ for 4 days, 10 $J \cdot cm^{-2}$ for 6 days; and 10 $J \cdot cm^{-2}$ for 4 days. The light doses and time intervals were based upon a review of the clinical literature [5] as well as discussions held with European investigators who had used Foscan in similar clinical trials.

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Toxicity was scored using the National Cancer Institute Cooperative Group Common Toxicity Criteria, version 1.0. All 37 patients who were enrolled in this trial were followed for toxicity until they were taken off study. Dose escalation proceeded without delay from one cohort to the next if 3 of 3 patients had only grade II toxicity or less. Dose escalation was permitted if no patient within a dose group had grade II treatment-related toxicity during the first 30 days after treatment. In instances in which grade II treatment-related toxicity was encountered, enrollment to the next dose cohort was delayed until an additional 2 weeks had elapsed.

The maximally tolerated dose (MTD) was defined as the highest PDT dose level that resulted in fewer than two instances of dose-limiting toxicity (DLT) among 6 treated patients (defined by grade III nonhematologic or grade IV hematologic toxicity). Once the MTD was determined, no patients were treated above that dose. If only one of the first 3 patients at a dose level experienced DLT, then an additional 3 patients were treated at that level. If none of the additional 3 patients experienced DLT, then the dose was escalated to the next dose level. If one or more of the additional 3 patients experienced DLT, then the dose of PDT for all subsequent patients was reduced to the previous dose level thereby defining the MTD. Once the MTD had been established, the protocol was amended to allow enrollment of additional patients at the MTD. A careful review of toxicities was performed at each dose level to determine whether dose escalation should proceed. An attempt was made to separate out PDT-related toxicities from typical surgery or disease-related toxicities.

The operating room lights and the surgeon's headlamp were covered with yellow filter paper (Roscoe, Hollywood, CA) to reduce unwanted activation of the photosensitizer. After the first procedure, which was complicated by an incisional burn, all subsequent incisions were shielded from light with blue towels sewn to the skin edges. The pulse oximeter was rotated between fingers every 15 to 30 minutes to avoid nail bed burns.

All thoracotomies were performed under the direction of the attending thoracic surgeon (J.S.F.). The protocol allowed for delivery of light if tumor could be resected to a thickness of 5 mm or less (as assessed by the attending surgeon). Although the protocol allowed for light delivery with minimal residual tumor, the goal was that all patients would be debulked to the point where there was no visible or palpable tumor remaining. To avoid tumor spillage into other body cavities, every effort was made to preserve the natural boundaries between the diseased hemithorax and the contralateral pleura, pericardium, and peritoneum.

In each case the chest was entered through the bed of the resected seventh rib. Visceral pleural tumor was removed by performing a pneumonectomy in 7 patients. The remaining 19 patients underwent decortications that ranged from partial pleural stripping to denuding the entire surface of the lung. In the lung-sparing procedures, all fissures were also debulked to whatever extent required, occasionally exposing the pulmonary artery.

It should be noted that there was a learning curve involved with this trial as the debulking technique evolved. Initially, patients with all but the slightest visceral pleural involvement underwent debulking with a standard EPP. As the trial progressed, and older patients were enrolled, a greater emphasis was placed on parenchymal preservation. By the conclusion of the trial, it was found that the majority of patients, with even extensive

visceral pleural involvement, could be debulked with decortications using a split ventilation technique. In this technique, the operative lung was kept on positive end-expiratory pressure (5 to 40 cm of water) during the majority of the decortication, and it was found that in almost all cases the tumor could be stripped from the parenchyma. This technique almost always mandated resection of the visceral pleura, which resulted in large postoperative air leaks but full pulmonary expansion. In all but 1 case, the air leaks rapidly resolved in the postoperative period. (One patient was discharged with a chest tube and Heimlich valve that was removed as an outpatient 2 weeks after discharge.) In addition, as opposed to EPP, the first plane of dissection that was developed in the lung-sparing procedures was the plane between the lung and tumor. The extrapleural plane was developed only after the lung had been fully liberated.

In lung-sparing procedures, the parietal pleura was then separated from the bony hemithorax following natural cleavage planes. In patients who underwent debulking with EPP, the parietal pleura overlying the bony hemithorax was resected en bloc with the lung. In both cases, the tumor overlying the mediastinum and diaphragm were separately addressed. In almost all cases, it was possible to strip tumor from the mediastinum but to preserve at least partial thickness of the pericardium. The pericardial fat was routinely resected. In some cases, portions of the fibrous pericardium were resected with preservation of the serous pericardium. Occasionally there was a small portion of pericardium that could not be debulked. In these situations, the area of involved pericardium was tented outward and undercut with a stapling device to effect immediate closure. Every attempt was made to preserve the pericardium as a natural barrier.

Debulking the diaphragm without entering the abdomen was commonly the most challenging portion of the procedure. If the tumor had not grossly invaded the diaphragm or was well into the diaphragmatic muscle, the diaphragm could be debulked by either leaving or resecting the underlying muscle. Commonly there was a partial thickness invasion of the diaphragm. In these cases, a CO_2 laser was used to debulk the diaphragm to the point of no visible or palpable remaining tumor. In any case in which a substantial portion of the diaphragmatic muscle remained, the phrenic nerve was preserved. This commonly required a neurolysis.

The diaphragm was reconstructed at the completion of light delivery with a 2-mm Gore-Tex (W.L Gore & Associates, Flagstaff, AZ) patch in any patient in which the majority of the diaphragmatic muscle had been resected. Any inadvertent full thickness transgression of the pericardium or into the abdomen was immediately oversewn with 4-0 Vicryl (Ethicon, Somerville, NJ) suture. A mediastinal lymphadenectomy was performed at the conclusion of the debulking. Before light delivery, the chest was irrigated and hemostasis was achieved. Argon beam electrocautery was frequently used to achieve hemostasis on the chest wall.

The technique of light delivery was similar to the procedure previously described by Pass and colleagues [7] and by Baas and associates [5]. The light dosimetry system was the same that used by Baas and associates [5, 15]. The distribution and total dose of light delivered was monitored with isotropic light detectors (Rare Earth Medical, West Yarmouth, MA) with an accuracy of +15%. The detectors were connected to photodiodes (Photop UDT-455, Graseby Electronics, Orlando, FL), the output of which was converted, displayed, and stored on a PC. The software (Clinical Physics Department, Daniel den Hoed Cancer Center, Rotterdam, the Netherlands) allowed real-time fluence rate measurements and integrated fluence measurements. The probes measured both direct incident and scattered light as previously described [15]. The probes were calibrated in air in an integrating sphere with a diffuse light field. The probes were then placed in sterile polyethylene lockable extension tubes and filled with saline to match the refractive index of the surrounding medium. Four probes were then placed in the thoracic cavity at the following locations: in the apex of the chest, on the mediastinum adjacent to the mainstem bronchus, in the diaphragmatic sulcus (either posterior or anterior), and on the lateral chest wall, adjacent to the incision.

In some patients who underwent an EPP, a transparent sterile plastic bag (Steri-Drape, 3M Corporation) was placed in the thoracic cavity and filled with saline warmed to body temperature. This allowed a more homogeneous distribution of light. The light source was a spherical diffusing fiber (Rare Earth Medical) which was placed in the center of the plastic bag. The surgical wound was then approximated during the illumination to maximize back scattering of light due to reflections from the cavity. In some patients treated in this manner, the light dose in the diaphragmatic sulcus was low necessitating separate treatment to this region with a microlens fiber (Rare Earth Medical).

For patients who had an intact lung (pleurectomy) or for some patients who had undergone an extrapleural pneumonectomy, a different method of light delivery was used. In these patients, the chest cavity was filled with a dilute intralipid solution (0.01%). An end-cut fiber placed within an endotracheal tube was used to deliver light to all surfaces of the chest cavity and lung. In all instances, the light fiber was manipulated to obtain uniform light exposure as determined by the real-time light dose measurements from the dosimetry system.

Laser light was generated using the KTP/532 Laser System–model 630 XP Dye Module (Laserscope, San Jose, CA). After completion of light administration, the detectors and optical fibers were removed and passed from the table. Patients were instructed to avoid direct sunlight for 14 to 18 days after Foscan administration.

All observed toxicities were tabled and were summarized by frequencies. Progression-free survival and overall survival were estimated by the Kaplan-Meier method for the 20 patients treated at the MTD. Progression-free survival was defined as the time from study entry to documented disease progression, death from any cause, or last patient contact. Overall survival was defined as the

time from study entry to death from any cause or last patient contact. An intent-to-treat analysis was used. All 20 patients entered at the MTD dose level and who received Foscan, regardless of ability to receive intraoperative PDT, were included in the analysis of progression-free survival and overall survival.

Results

A total of 36 patients, who constituted 37 registrations, were enrolled between December 1997 and January 2001 (Table 1). The characteristics of the 36 patients are shown in Table 1. Of the patients, 34 were male and 2 female. The mean age was 63 years (range, 39 to 79 years).

Epitheloid was the most common histology (64%), followed by biphasic type (25%). Two patients did not have mesothelioma. One patient was enrolled in the study with a pathologic diagnosis of mesothelioma but between the time of Foscan administration and surgery, he was found to have new liver lesions. The surgery was cancelled and workup of the liver lesions revealed them to be metastatic adenocarcinoma. This resulted in review and revision of his original diagnosis and it was concluded that his pleural disease was also metastatic adenocarcinoma and he was taken off study. A second patient had a clinical and radiographic presentation that was believed by the investigators to be most consistent with mesothelioma. Multiple biopsies were taken preoperatively but were nondiagnostic. The case was presented at a multidisciplinary conference, and it was the collective opinion of the independent panel that the patient most likely had mesothelioma and that therapy directed against mesothelioma was appropriate. The FDA was contacted and allowed that the patient be enrolled in the study, but mandated that light not be delivered unless a frozen section showed mesothelioma. The patient went to surgery, but multiple frozen sections as well as the patient's final pathology material did not demonstrate mesothelioma and he did not receive light treatment. This patient was also taken off study.

The majority of patients had clinical T1 tumors (64%) and N0 nodal status (83%). Pathologic staging, however, demonstrated that most patients had T2 or T3 tumors (60% and 27%, respectively) and that 33% of patients had documented nodal metastases.

The flow of all 37 subjects through this trial is shown in Figure 1. In 5 patients who received Foscan, it was determined that the planned thoracotomy was not indicated. One patient received Foscan but, on arrival in the operating room, developed electrocardiographic changes before the induction of anesthesia and surgery was aborted. After further cardiac workup, he was enrolled a second time. Two patients received Foscan but were found to have intrabdominal disease on diagnostic laparoscopy before performing the thoracotomy. They were taken off study. Two patients received Foscan and were found to have distant metastatic disease. One patient developed new liver metastases and was subsequently diagnosed as having metastatic adenocarcinoma and not mesothelioma, and 1 patient was found to have a contralateral endobronchial mesothelioma metastasis on preoperative bronchoscopy.

Table 1. Patient Characteristics (N = 36)[a]

Characteristic	n	%
Sex		
Male	34	94
Female	2	6
ECOG Status		
0	1	3
1	35	97
Cell type		
Epitheloid	23	64
Biphasic	9	25
Sarcomatous	2	6
Adenocarcinoma	1	3
N/A[b]	1	3
Clinical stage		
T stage		
T1	23	64
T2	9	25
T3	4	11
N stage		
N0	30	83
N1	2	6
N2	4	11
M stage		
M0	33	92
M1	3	8
Pathologic stage (n = 30)		
T stage		
T1	4	13
T2	18	60
T3	8	27
N stage		
N0	16	53
N1	1	3
N2	9	30
Nx	4	13
M stage		
M0	30	100
M1	0	–
Prior therapy		
None	34	94
Chemotherapy	1	3
Gene therapy	1	3

	Mean ± SD	Min	Max
Age (y)	63 ± 10	39	79

[a] Data are for 37 registrations in 36 patients. One patient was enrolled twice at dose level 4.
[b] Tumor biopsy did not confirm malignancy

A total of 32 patients met the eligibility criteria for proceeding with the planned thoracotomy. Six of these patients did not undergo intraoperative PDT (Fig 1). One patient had a myocardial infarction at the time of anesthesia induction. Four patients had unresectable disease

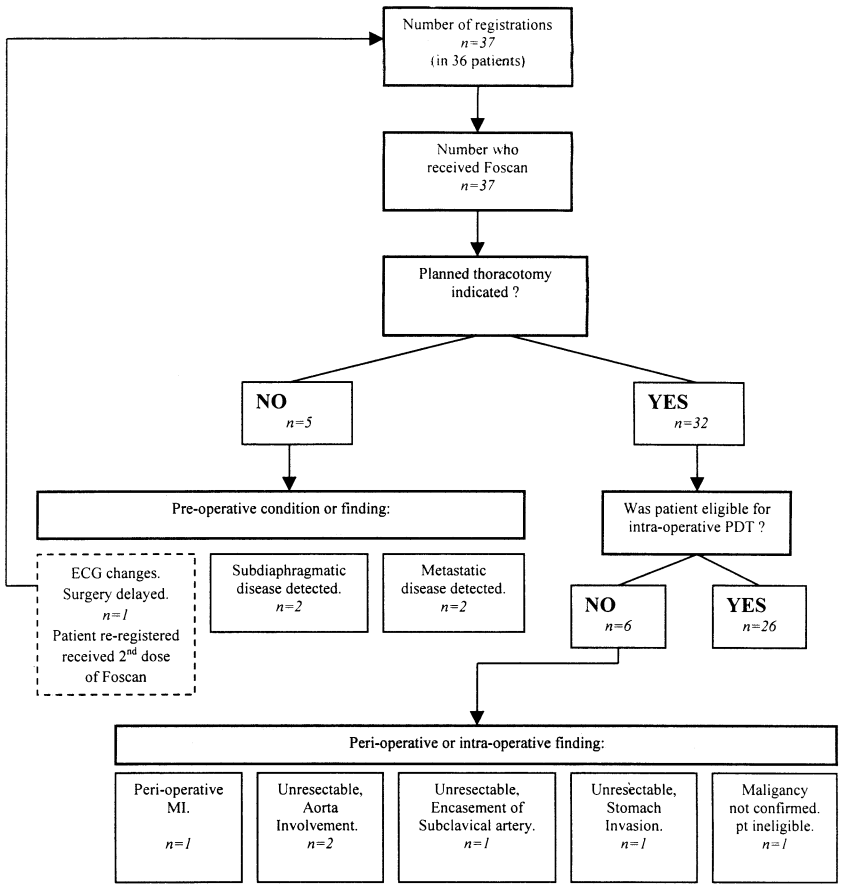

*Fig 1. Flow of patients on study. A total of 36 patients constituting 37 study subjects were enrolled. Five patients were not surgical candidates; 1 patient had electrocardiographic changes leading to cancellation of surgery; 2 patients were found to have subdiaphragmatic disease on diagnostic laparoscopy; 2 patients were found to have distant metastatic disease. In all, 32 patients were surgical candidates. Six of these patients did not undergo light delivery: 1 patient had a myocardial infarction at the time of anesthesia induction; 4 patients had unresectable disease (aorta involvement, 2 patients; encasement of the subclavian artery, 1 patient; and invasion of the stomach, 1 patient); and 1 patient did not have malignancy confirmed at the time of thoracotomy (see text). (*ECG = *electrocardiographic;* MI = *myocardial infarction;* PDT = *photodynamic therapy;* pt = *patient.)*

(aortic involvement, 2 patients; encasement of the subclavian artery, 1 patient; and invasion of the stomach [hiatal hernia], 1 patient). One patient did not have malignancy confirmed at the time of thoracotomy. In all, 26 patients underwent surgery and received intraoperative PDT (Fig 1 and Table 2). The distribution of patients according to dose level is shown in Table 2.

The combination of PDT with surgery complicated the process of evaluating which toxicities were the result of PDT (Foscan, light delivery, and the photochemical effect) versus which were the result of the surgical procedure. Table 3 shows all grade III to V toxicities observed in the 26 patients who were treated with surgery and PDT regardless of whether these toxicities were attributed to PDT.

One of the first 3 patients treated on the first dose level developed a third-degree incisional burn that required excision and grafting. The wound subsequently healed without incident. The operating room lights and surgeon's headlamp were identified as the causative factors,

Table 2. Dose Level and Treatment Information

Dose Level	Drug/Light Interval (days)	Light Dose ($J \cdot cm^{-2}$)	Received Foscan	Thoracotomy Indicated	Received Intraoperative PDT
1	6	5	9[a]	7	6
2	4	5	4	4	3
3 (MTD)	6	10	10[b]	8	6
4	4	10	4[c]	3	3
5 (MTD)	6	10	10	10	8
Total			37	32	26
Total at MTD			20	18	14

[a] Two patients were found to have subdiaphragmatic disease and did not undergo surgery.
[b] Two patients were found to have metastases (1 liver metastasis, 1 endobronchial metastasis) and did not undergo surgery.
[c] One patient was registered twice at dose level 4. At the first registration, the patient received Foscan and was scheduled for surgery but due to electrocardiographic changes, the surgery was delayed. At the second registration, the patient received Foscan, underwent surgery and PDT.

MDT = maximally tolerated dose; PDT = photodynamic therapy.

Table 3. Dose-Limiting Toxicity by Dose Level

Dose Level	No. of Patients	Grade III Toxicities (no. of patients)	Grade IV or V Toxicities (no. of patients)	No. of DLTs
1	6	Atrial dysrythmia (3) Neurologic (3) Hyperglycemia (1) Wound (1) Prerenal azotemia (1) Bilirubin (1) Hemorrhage (1)	Atrial dysrythmia (1) Hypotension (2) Bilirubin (1) Fever (1) Pulmonary (1)[a]	1
2	3	Anemia (1) Bilirubin (1)		0
3 (MTD)	6	Hyperglycemia (1) Hypocalcemia (3) Atrial dysrhythmia (2)		0
4	3	Neurologic (1) Thrombocytopenia (2) Hyperglycemia (2) Hypocalcemia (1) Prerenal azotemia (1) Transaminases (1)	Edema (1) Volume (1) Hypotension (2) Ischemia (1) Anemia (2) Acidosis (2) Hyperkalemia (1) Bilirubin (1) Pulmonary (1)	2
5	8	Anemia (1) Hypocalcemia (1) Esophageal perforation (1)	GI hemorrhage (1) Chest hemorrhage (1)[a]	0

[a] Grade 5 toxicity, not treatment-related

and for all subsequent patients the skin was shielded from light with blue towels sewn to the edges. This toxicity was considered a DLT. Three additional patients were then treated at the first dose level and none developed wound burns or other DLT.

Two other patients treated on the first dose level had serious complications postoperatively. The first patient underwent a pneumonectomy followed by PDT. He developed refractory rapid atrial fibrillation and pneumonia. Subsequently he developed adult respiratory distress syndrome and multiorgan failure that resulted in his death. The second patient developed a high fever toward the end of the operation and in the immediate postoperative period. There was no evidence of infection and the patient stabilized after being placed on a calcium channel blocker. It was determined that the patient most likely had a form of malignant hyperthermia. A review of the toxicities in these 2 patients on dose level 1 suggested that they were most likely complications of the surgery and anesthesia and not related to PDT. After a careful review, it was decided to proceed with dose escalation.

No serious PDT-related toxicities were observed at the second or third dose levels. DLT were observed in 2 of 3 patients treated at the fourth dose level. Two patients who underwent a pleurectomy and PDT developed an acute capillary leak syndrome resulting in hypotension, acidosis, multiorgan failure, and death. As a result of these toxicities, the next 3 patients were enrolled at the third dose level of PDT and none experienced DLT. The third dose level was then declared the MTD based on 6 patients treated in that cohort. Ten additional patients, 8 of whom received PDT, were entered at the MTD. Thus, a total of 20 patients were enrolled at the MTD.

Complications of wound healing and infection were observed in 7 patients. Temporary erythema at the wound site was often observed for several weeks after treatment and was possibly related to PDT. The incisions appeared to be mild wound infections and responded to local wound care and antibiotics, typical of this type of complication. It should be noted, however, that incisional erythema was seen more frequently than would be expected and, thus, may have been PDT related.

Grade III or IV elevations in total bilirubin and liver function studies were observed in 2 patients at dose level 1, 1 patient at dose level 2, and 2 patients at dose level 4 during the immediate postoperative period. The majority of these laboratory abnormalities were observed in the setting of adult respiratory distress syndrome/multiorgan failure, malignant hyperthermia, and acute capillary leak syndrome. Serious bilirubin and LFT abnormalities were not observed at the third dose level, suggesting that there was no clear relationship of these toxicities to PDT dose.

Atrial dysrhythmias were observed in 13 of 26 patients during the immediate postoperative period. Transient ventricular dysrhythmias were observed in 2 patients.

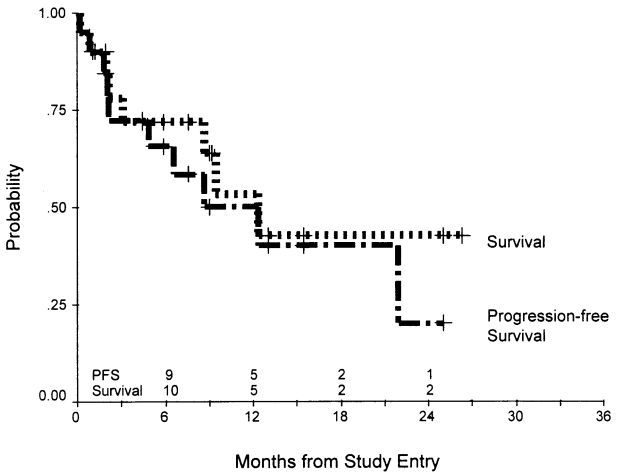

*Fig 2. Progression-free survival (*PFS*) and overall survival in the 20 patients enrolled at maximally tolerated dose. The number of patients at risk is shown.*

There was no clear relationship between PDT dose and the development of cardiac dysrhythmias. Other grade III or IV toxicities that were not clearly related to PDT included transient mental confusion, anemia, transient thrombocytopenia, transient hypocalcemia, and prerenal azotemia.

Two patient deaths occurred in the postoperative period among the 20 patients enrolled at the MTD. One patient was diagnosed with a pulmonary embolism and received anticoagulation treatment. He was discharged to home in stable condition and subsequently expired at home from gastrointestinal bleeding. A second patient developed upper gastrointestinal bleeding and experienced an iatrogenic esophageal perforation during an endoscopy. Despite prompt diagnosis and treatment, including an esophageal exclusion procedure, the patient expired as a result of this complication. Neither death was believed to be directly related to PDT.

Progression-free survival and overall survival were calculated for the 20 patients treated at the MTD. The median follow-up for the patients currently alive is 8.3 months and 8 of 20 patients enrolled at the MTD have died. The progression-free survival rate at 8 months was 72% and the overall survival at 8 months was 58%. The median progression-free survival was 12.4 months (95% confidence interval, 3.9 to 20.9 months) and overall survival was 12.4 months (95% confidence interval, 7.4 to 17.4 months). Six patients developed recurrent disease; 3 patients developed distant metastatic disease and 3 had local progression of disease (within the ipsilateral lung). Figure 2 shows the progression-free survival and overall survival for patients treated at the MTD.

Comment

Several investigators have evaluated HPD-mediated PDT in mesothelioma [7, 16]. Pass and colleagues [7] performed a phase III randomized trial of chemoimmunotherapy and surgery with and without HPD-mediated PDT. This trial showed no survival or local control benefit from PDT.

Ris and colleagues [17] were the first investigators to evaluate Foscan in the treatment of MPM. In this pilot study, 7 of 8 patients had local control of their disease but all developed distant metastases. A pilot study of 5 patients by Baas and colleagues [5] evaluated PDT in patients after EPP using Foscan and 652 nm light. The patients received Foscan 0.1 $mg \cdot kg^{-1}$4 days before surgery with a light dose of 10 $J \cdot cm^{-2}$. Four patients were alive with no signs of recurrent tumor with a follow-up of 9 to 11 months. There was no postoperative mortality, although 1 patient experienced a diaphragmatic rupture and hemopericardium in the immediate postoperative period.

The primary objective of this phase I study was to determine the DLT and MTD of Foscan and 652 nm light delivered immediately after surgical resection in patients with malignant pleural mesothelioma. The MTD of PDT was determined to be Foscan 0.1 $mg \cdot kg^{-1}$, 10 $J \cdot cm^{-2}$ 652 nm light with a drug–light interval of 6 days. The DLT was determined to be an acute capillary leak syndrome in 2 patients who had undergone a pleurectomy and decortication followed by PDT. Although it cannot be proved that PDT caused the capillary leak syndrome, 2 of 3 patients treated at the highest dose level developed this same lethal toxicity. This is not a complication that would be anticipated as a result of the surgical procedure alone, pleurectomy, and decortication. This DLT has not been described by others who have investigated Foscan-mediated PDT [5, 17]. One potential reason for this is that, unlike other studies of Foscan in mesothelioma, the majority of patients in our series underwent a debulking of the lung with a decortication rather than a pneumonectomy. Our hypothesis is that the presence of the lung and its inclusion in the PDT treatment field may have led to the release or activation of factors that precipitated a systemic inflammatory syndrome [18]. An evaluation of serum cytokine levels in a subset of patients treated on this trial is currently underway.

We have not observed clear evidence of PDT-related toxicity to other intrathoracic organs. One reason for this may be the measurement of light doses within the thoracic cavity. The light delivered in this protocol was based upon real-time measured light dose collected from isotropic light detectors that were placed intraoperatively before initiating the light treatment. Thus, the administered light dose was measured, not estimated as in some PDT treatments, and included all photons registered by the detectors, direct and scattered [15]. This approach ensured that the same amount of light energy was deposited in the tissues of all patients treated at a given dose level.

The rationale for combining adjuvant treatments with surgery for mesothelioma is to kill the microscopic disease organisms that likely remain after surgical debulking. The advantage of PDT over other current adjuvant treatments such as external beam radiation is that it is a superficial treatment and, as a result, it does not mandate

removal of the lung. The ability to perform lung-sparing debulking procedures in most patients is a potential advantage of PDT over other adjuvant treatments in this setting.

In summary, the MTD of Foscan-mediated PDT, in combination with surgery, for malignant pleural mesothelioma has been established in this study. We have demonstrated the feasibility and safety of delivering PDT in the intraoperative setting immediately after either a pleurectomy or a pneumonectomy. The median progression-free survival and overall survival of 12.4 months for all 20 patients enrolled at the MTD is comparable to other treatments for mesothelioma, particularly in light of the fact that patients were enrolled in this phase I trial regardless of tumor subtype or nodal status. One potential advantage of Foscan-mediated PDT, in this setting, is that it offers the option of performing a lung-sparing procedure as was performed in the last 17 of 19 patients enrolled. The preliminary results of this study support the continued development of Foscan-mediated PDT and progression to a phase II trial.

References

1. Antman KH, Pass HI, Schiff PB. Benign and malignant mesothelioma (Chap). Cancer, Principles and practice of oncology, 5th ed, DeVita VT, Hellman S, Rosenberg SA (Eds). Philadelphia: Lippincott-Raven, 1997:1853–78.
2. Ho L, Sugarbaker DJ, Skarin AT. Malignant pleural mesothelioma. Cancer Treat Res 2001;105:327–73.
3. Sugarbaker DJ, Norberto JJ, Swanson SJ. Extrapleural pneumonectomy in the setting of multimodality therapy for diffuse malignant pleural mesothelioma. Semin Thorac Cardiovasc Surg 1997;9:373–82.
4. Sterman DH, Kaiser LR, Albelda SM. Advances in the treatment of malignant pleural mesothelioma. Chest 1999; 116:504–20.
5. Baas P, Murrer L, Zoetmulder FA, et al. Photodynamic therapy as adjuvant therapy in surgically treated pleural malignancies. Br J Cancer 1997;76:819–26.
6. Pass HI, Tochner Z, DeLaney T, et al. Intraoperative photodynamic therapy for malignant mesothelioma. Ann Thorac Surg 1990;50:687–8.
7. Pass HI, Temeck BK, Kranda K, et al. Phase III randomized trial of surgery with or without intraoperative photodynamic therapy, and postoperative immunochemotherapy for malignant pleural mesothelioma. Ann Surg Oncol 1997;4:628–33.
8. Dougherty TJ, Gomer CJ, Henderson BW, et al. Photodynamic therapy [Review]. J Natl Cancer Inst 1998;90:889–905.
9. Berenbaum MC, Akande SL, Bonnett R, et al. Meso-tetra(hydroxyphenyl)porphyrins, a new class of potent tumour photosensitisers with favourable selectivity. Br J Cancer 1986;54:717–25.
10. Young SW, Woodburn KW, Wright M, et al. Lutetium texaphyrin (PCI-0123): a near-infrared, water-soluble photosensitizer. Photochem Photobiol 1996;63:892–7.
11. Oleinick NL, Evans HH. The photobiology of photodynamic therapy: cellular targets and mechanisms. Radiat Res 1998; 150:S146–56.
12. Ma L, Moan J, Berg K. Evaluation of a new photosensitizer, meso-tetra-hydroxyphenyl-chlorin, for use in photodynamic therapy: a comparison of its photobiological properties with those of two other photosensitizers. Int J Cancer 1994;57: 883–8.
13. van Geel IP, Oppelaar H, Oussoren YG, van der Valk MA, Stewart FA. Photosensitizing efficacy of MTHPC-PDT compared to photofrin-PDT in the RIF1 mouse tumour and normal skin. Int J Cancer 1995;60:388–94.
14. American Joint Committee on Cancer. Cancer staging manual, 5th ed. 1997.
15. Vulcan TG, Zhu TC, Rodriguez CE, et al. Comparison between isotropic and nonisotropic dosimetry systems during intraperitoneal photodynamic therapy. Lasers Surg Med 2000;26:292–301.
16. Takita H, Dougherty TJ. Intracavitary photodynamic therapy for malignant pleural mesothelioma. Semin Surg Oncol 1995;11:368–71.
17. Ris HB, Altermatt HJ, Inderbitzi R, et al. Photodynamic therapy with chlorins for diffuse malignant mesothelioma: initial clinical results. Br J Cancer 1991;64:1116–20.
18. Kim PK, Deutschman CS. Inflammatory responses and mediators. Surg Clin North Am 2000;80:885–94.