A Phase II Trial of Intraperitoneal Photodynamic Therapy for Patients with Peritoneal Carcinomatosis and Sarcomatosis

Stephen M. Hahn,[1] Douglas L. Fraker,[2] Rosemarie Mick,[1,3] James Metz,[1] Theresa M. Busch,[1] Debbie Smith,[1] Timothy Zhu,[1] Carmen Rodriguez,[1] Andreea Dimofte,[1] Francis Spitz,[2] Mary Putt,[3] Stephen C. Rubin,[5] Chandrakala Menon,[2] Hsing-Wen Wang,[1,4] Daniel Shin,[1] Arjun Yodh,[1,4] and Eli Glatstein[1]

Abstract

Purpose: A previous phase I trial of i.p. photodynamic therapy established the maximally tolerated dose of Photofrin (Axcan Pharma, Birmingham, AL)-mediated photodynamic therapy and showed encouraging efficacy. The primary objectives of this phase II study were to determine the efficacy and toxicities of i.p. photodynamic therapy in patients with peritoneal carcinomatosis and sarcomatosis.

Experimental Design: Patients received Photofrin 2.5 mg/kg i.v. 48 hours before debulking surgery. Intraoperative laser light was delivered to the peritoneal surfaces of the abdomen and pelvis. The outcomes of interest were (*a*) complete response, (*b*) failure-free survival time, and (*c*) overall survival time. Photosensitizer levels in tumor and normal tissues were measured.

Results: One hundred patients were enrolled into one of three strata (33 ovarian, 37 gastrointestinal, and 30 sarcoma). Twenty-nine patients did not receive light treatment. All 100 patients had progressed by the time of statistical analysis. The median failure-free survival and overall survival by strata were ovarian, 2.1 and 20.1 months; gastrointestinal cancers, 1.8 and 11.1 months; sarcoma, 3.7 and 21.9 months. Substantial fluid shifts were observed postoperatively, and the major toxicities were related to volume overload. Two patients died in the immediate postoperative period from bleeding, sepsis, adult respiratory distress syndrome, and cardiac ischemia.

Conclusions: Intraperitoneal Photofrin-mediated photodynamic therapy is feasible but does not lead to significant objective complete responses or long-term tumor control. Heterogeneity in photosensitizer uptake and tumor oxygenation, lack of tumor specificity for photosensitizer uptake, and the heterogeneity in tissue optical properties may account for the lack of efficacy observed.

Photodynamic therapy is a treatment modality using a photosensitizing agent and light to kill cells in the presence of oxygen. Clinical use of photodynamic therapy requires a photosensitizing agent, oxygen, and light of a wavelength specific to the absorption characteristics of the photosensitizer. One appeal of photodynamic therapy in oncology has been the longer retention of some photosensitizers in malignant, relative to normal tissues (1–3). The potential for effective treatment of cancer with minimal normal tissue toxicity has prompted an interest in studying photodynamic therapy as a cancer treatment.

Despite a large body of data exploring the basic biology of photodynamic therapy in animal models, photodynamic therapy has been used infrequently in the intraoperative setting. Early phase clinical studies are important both to determine whether the therapy shows sufficient efficacy to proceed to randomized trials, as well as to determine whether the results from animal models have relevance in a clinical setting. A phase I study of surgery in combination with photodynamic therapy with laser light and Photofrin (Axcan Pharma, Birmingham, AL) was conducted by the Surgery and Radiation Oncology Branches of the National Cancer Institute for disseminated i.p. malignancies (4, 5). Fifty-four patients with peritoneal carcinomatosis who underwent debulking surgery were treated on the study. The photodynamic therapy dose was sequentially escalated by increasing the sensitizer dose from 1.5 to 2.5 mg/kg, by shortening the interval between sensitizer injection and the surgery, and by increasing the light dose. With the use of 630 nm red light, photodynamic therapy induced small bowel edema and resulted in three small bowel perforations. Because of this transmural penetration by red light, less penetrating 514-nm green light was used for the large field exposures to the bowel and mesentery thereafter. This allowed further light dose escalation, and no additional small bowel complications were seen. Dose-limiting toxicity was encountered in two of three patients at the highest dose (5.0 J/cm^2) of green light with boost. These two patients both developed pleural effusions that required thoracentesis and postoperative respiratory support for 7 to 9 days. The maximally tolerated dose of

Authors' Affiliations: [1]Departments of Radiation Oncology, [2]Surgery, [3]Biostatistics and Epidemiology, [4]Physics and Astronomy and [5]Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of Pennsylvania, Philadelphia, Pennsylvania

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Requests for reprints: Stephen M. Hahn, 3400 Spruce Street, 2 Donner, Philadelphia, PA 19104-4283. Phone: 215-662-7296; Fax: 215-349-5445; E-mail: hahn@xrt.upenn.edu.

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photodynamic therapy 48 hours after i.v. administration of Photofrin (2.5 mg/kg) was determined to be 3.75 J/cm^2 of 514-nm green light to the entire peritoneal surface with boosts 5.0 to 7.5 J/cm^2 of green light or 10 to 15 J/cm^2 of red light to areas of gross disease. Subsequent modifications to the light doses have been made since the initial report was published.

The follow-up of these patients has been updated (5). An overall peritoneal cytologic response rate of 76% was reported in evaluable patients. More importantly, long-term disease-free survivors were reported in the subgroup of patients with ovarian cancer. Three of 25 ovarian cancer patients were disease-free >36 months after treatment. These results are especially impressive when one considers that this was a phase I trial. It should also be emphasized that many of the patients received what in retrospect was an inadequate light dose. Based upon the encouraging results of the phase I study and the lack of curative therapy for patients with peritoneal carcinomatosis and sarcomatosis, we initiated a phase II study of Photofrin-mediated i.p. photodynamic therapy.

Materials and Methods

Trial design. The primary objectives of this study were to determine the efficacy and rate of toxicities of Photofrin-mediated i.p. photodynamic therapy in patients with peritoneal carcinomatosis and sarcomatosis. Secondary objectives were to determine Photofrin uptake in normal and malignant tissues and to assess the optical properties of peritoneal tissues. Efficacy variables included complete response rate as well as failure-free and overall survival. A total of 100 patients were enrolled in this phase II study. All patients were treated with the same photodynamic therapy regimen as defined in the previously reported phase I study (4, 5). Photofrin (porfimer sodium) 2.5 mg/kg was administered i.v. ~48 hours before the planned laparotomy. Surgical resection and light delivery were done as described below. The protocol permitted light administration to any patient whose peritoneal disease was resected to a thickness of ≤5 mm. Toxicity was scored using the National Cancer Institute Cooperative Group Common Toxicity Criteria, version 1.0. Operative mortality was defined as death within 30 days of patients leaving the hospital. The patients were seen by the investigators or primary oncologists every 3 months after surgery until disease progression.

Patient selection. Patients were selected based upon the following eligibility criteria: biopsy-proven peritoneal carcinomatosis or sarcomatosis who had exhausted curative therapies, age > 18 years, signed informed consent, and absence of distant metastatic disease. Patients were entered into one of three strata: ovarian cancer, sarcoma, and gastrointestinal cancers.

Patients were excluded based on the following criteria: borderline tumors of low malignant potential; ulcerative colitis; regional enteritis; inability to tolerate general anesthesia; HIV positivity; white count <2,000 per mm^3 or platelet count <100,000 per mm^3; serum creatinine ≥2.5 mg/dL; severe liver disease, including cirrhosis, grade 3 to 4 elevations in liver function studies, or bilirubin in excess of 1.5 mg/dL, and pregnant or lactating patients. Patients who in the opinion of the attending surgeon could not be debulked to a thickness of ≤5 mm on preoperative evaluation were also excluded.

Patients underwent a preoperative evaluation that included a history and physical examination, imaging studies of the abdomen and pelvis (computerized tomography and/or magnetic imaging resonance), a chest radiograph and laboratory studies including an HIV antibody test. Other tests, including tests to exclude distant metastases, were done as clinically indicated.

The protocol was conducted under an investigator-sponsored Investigational New Drug Application with the U.S. Food and Drug Administration. This study was done in accordance with the Declaration of Helsinki and had approval from the Institutional Review Board of the University of Pennsylvania and the University of Pennsylvania Clinical Trials Scientific Review and Monitoring Committee. The trial opened in February 1997 and closed in March 2004.

Surgical procedure. Surgery was done at the Hospital of the University of Pennsylvania. The operating room lights and the surgeons' headlamps were covered with amber filter paper (Roscoe, Inc., Hollywood, CA) to reduce unwanted activation of the photosensitizer. The pulse oximeter, which uses a red light probe capable of activating the photosensitizer, was rotated to a different finger every 15 to 30 minutes to avoid burns to the nail bed. A laparotomy was done on all patients under the direction of the attending surgeon. The goal was to have all tumor resected to a thickness of ≤5 mm at the conclusion of the surgical resection. Normal tissues were resected only as necessary to debulk the tumor. The abdominal cavity was irrigated, hemostasis was achieved, and the light delivery portion of the procedure was then initiated.

Intraoperative photodynamic therapy. The light delivery and dosimetry system were similar to the technique previously described (6). Light doses were monitored with fixed peritoneal diodes located in the right upper quadrant, left upper quadrant, left peritoneal gutter, right peritoneal gutter, and in the midline pelvis anteriorly. One to two mobile photodiodes were also employed to measure dose in other regions. Laser light was generated using the KTP/532 Laser System manufactured by Laserscope, Inc. (San Jose, CA). The KTP laser pumped a model 630 XP Dye Module manufactured by Laserscope. The power density of the light did not exceed, on average, 150 mW/cm^2. Eye protection in the form of goggles was used to attenuate the wavelength used to 10^{-4} of incident intensity.

The light doses were determined previously in a phase I trial (4, 5). The mesentery, the large bowel, and the small bowel were treated with 532-nm green light at a dose of 2.5 J/cm^2 using a flat-cut optical fiber. The bowel was positioned under a circular beam of light and was treated in segments sequentially. After delivery of green light to the bowel and before 630-nm light delivery to the rest of the peritoneal surfaces with 630-nm red light, the abdomen was filled with a dilute solution of intralipid (0.01%) in sterile normal saline. This was used to enhance scattering of the light. The 630-nm light to the peritoneal cavity was delivered with an optical fiber sheathed within a modified endotracheal tube. The balloon cuff was inflated and filled with a 0.1% intralipid solution. The stomach received 5.0 J/cm^2; the diaphragms, liver, and spleen received 7.5 J/cm^2, whereas the pelvis and abdominal gutters received 10 J/cm^2. Sites of gross disease on the right diaphragm, on the abdominal gutters, and in the pelvis were treated with a boost treatment up to 15 J/cm^2. Patients received one course of light therapy at the time of surgery. Following the completion of light administration, the sterile photodiodes were removed from the abdomen. In the immediate postoperative period and after discharge, patients were instructed to avoid direct sunlight for 30 to 60 days after Photofrin administration.

Patients were transferred to the intensive care unit immediately after surgery and were, in general, intubated for at least 24 hours after the procedure. Significant fluid shifts were observed postoperatively, which necessitated massive fluid resuscitation as previously described (7).

Patient follow-up. Patients were seen 1 month after their discharge either in the outpatient clinics at the Hospital of the University of Pennsylvania or by the primary referring physician to assess treatment-related toxicities. The patients were then seen 3 months after the procedure and every 3 months for the first 24 months. A computerized tomography scan of the abdomen and pelvis was done every 3 months during the first year after treatment, every 6 months the second year, and then as clinically indicated thereafter. Other tests were done as clinically indicated. At the 6-month follow-up visit, if the patient had no clinical evidence of disease, a minilaparotomy or a laparoscopy was done for pathologic restaging. Biopsies, if clinically indicated, were taken from all regions that could be safely exposed at the time of laparoscopy/minilaparotomy. A laparoscopy was done in five patients, and a minilaparotomy was done in seven patients.

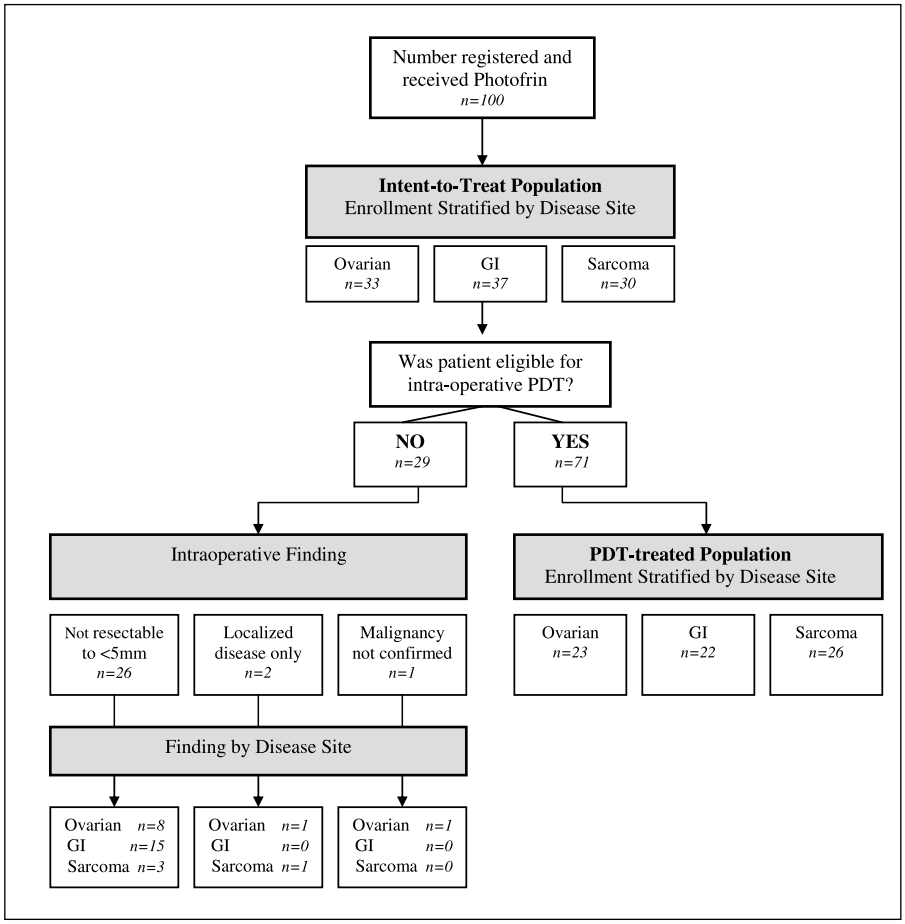

Fig. 1. Patient enrollment and treatment course on the study. Enrollment was stratified by disease site: ovarian cancer, gastrointestinal (*GI*) cancers, and sarcoma. Reasons why intraoperative photodynamic therapy was not done are indicated for the 29 patients who did not receive light treatment.

Photosensitizer concentration in tissue samples. Portions of tumor and resected normal tissues were placed in specimen containers, protected from visible light, and frozen at −70°C. The assay for porfimer sodium quantitation was based on a previous report (8). Tissue samples were thawed to room temperature and weighed and, depending on the amount available, ~10 to ~50 mg of tissue was placed in a vial with 0.150 to 0.500 mL, respectively, of the tissue solubilizer Solvable (Packard, Meriden, CT). The vial was capped and heated at 50°C overnight (20 ± 2 hours) in the dark. The solution was cooled to room temperature, an equal volume of distilled water was added and, after thorough mixing, it was transferred to a quartz cuvette of 0.2 mL (10-mg samples) or 0.6 mL (50-mg samples) capacity. The fluorescence of the solubilized sample was measured by a spectrofluorometer (FluoroMax-3, Jobin Yvon, Inc., Edison, NJ) with λ_{ex} of 405 nm and λ_{em} of 627 nm. Porfimer sodium concentration in the tissue was calculated based on the increase in fluorescence resulting from the addition of a known amount of porfimer sodium to each sample after its initial reading. Triplicates of each sample were run.

Photofrin concentrations were determined in the tumors of 48 patients with 26 patients having multiple tumor tissues sampled from various sites. Within each stratum, we described these concentrations by pooling all of the measurements and determining the median and range (minimum and maximum concentration). For each patient with multiple measurements, we determined an overall mean Photofrin concentration, a SD, and a coefficient of variation percent for each patient [CV% = (SD / mean) × 100]. We summarized the coefficient of variations within each strata using the median and the range. Stratum-specific means of tumor Photofrin concentration were calculated using individual measurements for patients with exactly one measurement and from within-patient means for patients with multiple samples. For consistency with analyses to be reported later, the mean for each patient was calculated by first averaging across each site with multiple measurements and then forming an overall mean. Statistical analyses were done using the software package SPSS (SPSS, Inc., Chicago, IL) or R 2.0 (http://www.r-project.org).

Summary statistics for tumor to normal ratios of Photofrin in large bowel without mucosa and small bowel without mucosa were determined using only those patients with samples from tumor as well as normal bowel tissues. We first averaged Photofrin concentrations across all tumor samples and across all samples of either small or large bowel within a patient. We then formed a ratio for each patient and summarized the results using medians and ranges.

Statistical considerations. This study was designed to evaluate toxicity and efficacy of photodynamic therapy for i.p. malignancies. Patients were enrolled into one of three disease strata: ovarian cancer, gastrointestinal cancers, and sarcoma. Toxicities were graded using Common Toxicity Criteria, version 1.0. Response was coded as either complete response (no evidence of abdominal disease) or treatment failure (new or recurrent abdominal disease) based on laparoscopy and/or radiographic findings at 6 months after surgery. The secondary objectives were to estimate failure-free and overall survival within each disease stratum and to characterize tissue Photofrin concentrations. Failure-free survival was measured from study entry (date of Photofrin injection) to first documented progression, death due to any cause, or last patient contact. For patients who were found ineligible to receive photodynamic therapy at the time of surgery, failure-free survival was measured from date of Photofrin injection to date of surgery, which was 2 days. Overall survival was measured from study entry to death due to any cause or last patient contact in all patients.

Within each stratum, we used a two-stage design under the premise that a true complete response rate of ≥20% would indicate an active treatment, whereas a true complete response rate of 5% would indicate an inactive treatment. In the first stage, enrollment continued until 14 patients received Photofrin injection and photodynamic light therapy. If at least one complete response was observed, then enrollment continued in the second stage until an additional 21 patients had received Photofrin injection and photodynamic light therapy. After the second stage, if at least four complete responses were seen, then the treatment would be declared active. At the end of the trial, the probabilities of either accepting an inactive treatment or rejecting an active treatment were each <10%. The accrual goal was 105 patients (35 per strata) treated with Photofrin injection and photodynamic light therapy. Accrual of sarcoma patients was terminated in January 2002 due to slowed enrollment after imatinib mesylate was approved for gastrointestinal stromal tumors. In consultation with the coinvestigators and the study biostatisticians in March 2004, it was determined after a review of the response data and the accrual rates that accrual to the ovarian cancer and gastrointestinal cohorts would be terminated.

Failure-time analyses were based on follow-up data available as of January 2005. The primary analyses of patient characteristics, toxicity, complete response rate failure-free survival, and overall survival were based on the intent-to-treat population (i.e., all patients who received Photofrin injection, regardless of whether photodynamic light therapy was administered). Patients who did not receive photodynamic light therapy were excluded from the decision to terminate the study early in the two-stage design but were included in the primary analyses. A subset analysis was also done based on patients who received both drug and light. Median failure-free and overall survival were estimated using the Kaplan and Meier method with 95% confidence intervals for medians based on Greenwood's formula (9, 10). Statistical analyses were done using the software package SPSS (SPSS) or R 2.0 (http://www.r-project.org).

Results

Patient characteristics. As shown in Fig. 1, 100 patients were enrolled into three strata (33 ovarian cancer, 37 gastrointestinal cancer, and 30 sarcoma patients) and received Photofrin injection 24 hours before surgery: all 100 patients comprise the intent-to-treat population. Twenty-nine patients were not eligible for intraoperative light delivery due to tumor not resectable to <5 mm (26 patients), localized disease only (two patients), or malignancy could not be confirmed by pathology (one patient). Seventy-one patients received intraoperative light therapy (23 ovarian, 22 gastrointestinal, and 26 sarcoma cancer patients). Patients with gastrointestinal cancers and ovarian cancer were more likely to have disease that could not be resected to the thickness required for light therapy.

As presented in Table 1, approximately half of the gastrointestinal cancer and sarcoma patients were male. The average age at enrollment was ~50 years. The vast majority of patients were Eastern Cooperative Oncology Group performance status 0 or 1. All ovarian cancer patients had undergone surgery and chemotherapy before photodynamic therapy. All sarcoma patients had undergone surgery, and some had received chemotherapy (10 of 30) and radiotherapy (4 of 30). The majority of gastrointestinal cancer patients (32 of 37) had undergone surgery, and most had also received chemotherapy (29 of 37). Only two gastrointestinal patients had previously undergone radiotherapy, whereas four patients had received no preoperative therapies.

Table 1. Characteristics of patients

	Ovarian (number enrolled = 33)	Gastrointestinal (number enrolled = 37)	Sarcoma (number enrolled = 30)
Gender, *n* (%)			
Male	0 (0.0)	20 (54.1)	17 (56.7)
Female	33 (100.0)	17 (45.9)	13 (43.3)
ECOG performance status (%)			
0	8 (24.2)	6 (16.2)	4 (13.3)
1	24 (72.7)	30 (81.1)	26 (86.7)
2	1 (3.0)	1 (2.7)	0 (0.0)
Prephotodynamic therapies (%)			
None	0 (0.0)	4 (10.8)	0 (0.0)
Surgery	33 (100.0)	32 (86.5)	30 (100.0)
Chemotherapy	33 (100.0)	29 (78.4)	10 (33.3)
Radiotherapy	0 (0.0)	2 (5.4)	4 (13.3)
Age (y)*	48.3 ± 10.4	50.8 ± 11.4	49.4 ± 9.8
WBC ($\times 10^3/\mu L$)*	5.8 ± 2.1	7.9 ± 2.7	7.2 ± 2.0
Platelets ($\times 10^3/\mu L$)*	221.9 ± 82.2	333.9 ± 135.6	264.0 ± 82.1
Creatinine (mg/dL)*	0.88 ± 0.16	0.87 ± 0.25	0.89 ± 0.16
Bilirubin (mg/dL)*	0.51 ± 0.22	0.58 ± 0.22	0.59 ± 0.27
Liver function test (AST/ALT), (%)			
Normal	29 (87.9)	32 (86.5)	29 (96.7)
2.5 × ULN	3 (9.1)	4 (10.8)	0 (0.0)
2.5-5.0 × ULN	1 (3.0)	1 (2.7)	1 (3.3)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ULN, upper limit of normal.
*mean ± SD.

Table 2. Treatment outcome

	Ovarian	Gastrointestinal	Sarcoma
Intent-to-treat analysis			
Number enrolled	33	37	30
Number progressed (%)	33 (100.0)	37 (100.0)	30 (100.0)
Number dead (%)	28 (84.8)	33 (89.21)	20 (66.7)
Median failure-free survival (95% CI), mo	2.1 (0.5-3.7)	1.8 (0.0-4.0)	3.7 (3.1-4.4)
Median overall survival (95% CI), mo	20.1 (13.9-26.4)	11.1 (4.9-17.2)	21.9 (10.9-33.0)
Photodynamic therapy subset analysis			
Number received photodynamic therapy	23	22	26
Number progressed (%)	23 (100.0)	22 (100.0)	26 (100.0)
Number dead (%)	20 (87.0)	19 (86.4)	17 (65.4)
Median failure-free survival (95% CI), mo	3.0 (2.5-3.5)	3.3 (2.1-4.6)	4.0 (1.9-6.1)
Median overall survival (95% CI), mo	22.0 (14.1-30.0)	13.2 (4.9-21.5)	21.9 (3.6-40.3)

Abbreviation: CI, confidence interval.

Treatment outcome. The median potential follow-up for all 100 patients was 51 months. For the 19 patients alive, the median potential follow-up was 46 months. As presented in Table 2, all 100 patients had progressed by the time of statistical analysis. Treatment response was assessed on a continuous basis. At least one response was observed in the first 14 patients enrolled in each cohort. At 6 months after photodynamic therapy, a total of 3 of 33 (9.1%) ovarian, 2 of 37 (5.4%) gastrointestinal, and 4 of 30 (13.3%) sarcoma cancer patients had achieved a complete response, as assessed by minilaparotomy or laparoscopy.

Figure 2A to C displays treatment outcome for the intent-to-treat population. The median failure-free survival and overall survival by strata were ovarian, 2.1 months [95% confidence interval (95% CI), 0.5-3.7 months] and 20.1 months (95% CI, 13.9-26.4 months); gastrointestinal cancers, 1.8 months (95% CI, 0.0-4.0 months) and 11.1 months (95% CI, 4.9-17.2 months); sarcoma, 3.7 months (95% CI, 3.1-4.4 months) and 21.9 months (95% CI, 10.9-33.0 months). Figure 2D to F shows treatment outcome for the photodynamic therapy–treated subset of patients. The median failure-free survival and overall survival by strata were ovarian, 3.0 months (95% CI, 2.5-3.5 months) and 22.0 months (95% CI, 14.1-30.0 months); gastrointestinal cancers, 3.3 months (95% CI, 2.1-4.6 months) and 13.2 months (95% CI, 4.9-21.5 months); sarcoma, 4.0 months (95% CI, 1.9-6.1 months) and 21.9 months (95% CI, 3.6-40.3 months).

Toxicity. Toxicities related to photodynamic therapy in all patients treated are shown in Table 3. The most common toxicity observed postoperatively was a capillary leak syndrome. This manifested itself as tachycardia and hypotension and necessitated massive fluid resuscitation. Typically, patients had a net positive fluid balance of 20 liters in the first 24 hours. The patients required fluid resuscitation for the first 4 to 5 days postoperatively. Additional details regarding this toxicity have previously been reported (7). One patient died in the immediate postoperative period from an inferior wall myocardial infarction. A second patient developed intra-abdominal bleeding, which required a reoperation. This patient died in the postoperative period from sepsis. Prolonged intubation and an adult respiratory distress syndrome–like picture were observed in four patients and were precipitated by infection or a pulmonary embolism. Bowel fistulae or an anastomotic leak were seen postoperatively in four patients Wound dehiscence or delayed wound healing was observed in two patients. Wound infection was observed in two patients. Postoperative ileus was common in patients treated on this protocol. A prolonged ileus or small bowel obstruction was seen in three patients. Metabolic complications, including liver function test abnormalities, hypocalcemia, and hypomagnesemia, were commonly seen but were reversible. Mild photosensitivity (grades 1 and 2) was observed in 20 patients.

Photosensitizer concentration in tumor samples. Uptake of the photosensitizer Photofrin was measured in a total of 143 tumor samples from 48 patients (Fig. 3). In general, a high degree of intrapatient and interpatient heterogeneity in Photofrin levels was observed. Forty-eight patients contributed multiple tumor samples. In 30 tumor samples from 10 ovarian cancer patients, the median tumor Photofrin concentration was 3.37 ng/mL (range, 1.40-6.33 ng/mL; Fig. 3A). Substantial intrapatient variability was noted especially in patient 7 (six samples, CV% = 56%) and patient 10 (five samples, CV% = 45%). The Photofrin concentrations were lower in 31 tumor samples from 15 sarcoma patients compared with the ovarian cancer cohort (median, 2.10 ng/mL; range, 0.49-7.83 ng/mL; Fig. 3B). Samples from patient 12 also displayed high intrapatient variability (five samples, CV% = 44%). In 82 tumor samples from 23 gastrointestinal cancer patients, the median tumor Photofrin concentration was 2.88 ng/mL (range, 0.13-6.23 ng/mL; Fig. 3C). Modest intrapatient variability was observed for most patients, with the exception of patient 21, who exhibited a single high concentration in a total of seven samples (CV% = 117%).

Also of note is patient 18, the single patient with small bowel disease, whose tumor samples displayed high tumor Photofrin concentrations (median, 5.21 ng/mL) yet low intrapatient variability (five samples from peritoneum, CV% = 13%). Interestingly, patient 22 with gastric cancer, exhibited low variability (CV% = 22%) despite that fact that 10 tumor samples were drawn from stomach, upper quadrant of

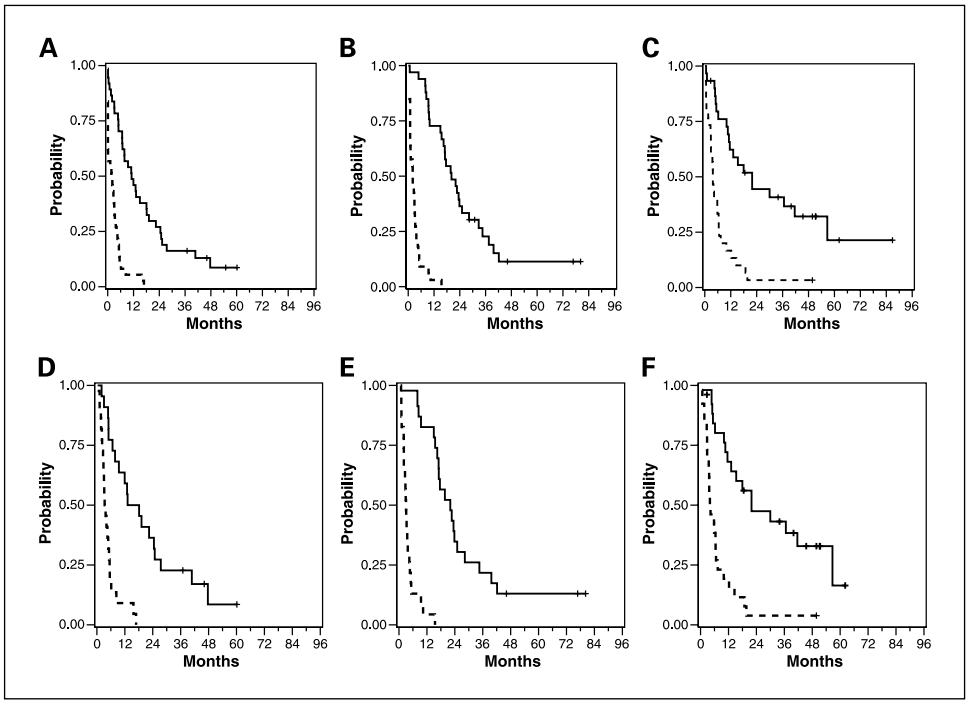

Fig. 2. Treatment outcome in the intent-to-treat and photodynamic therapy – treated subset population by disease stratum. Kaplan-Meier estimates of overall and failure-free survival probabilities by strata: (*A*) gastrointestinal cancer patients, (*B*) ovarian cancer patients, and (*C*) sarcoma patients. The solid line represents overall survival, and the dashed line represents failure-free survival. Tic marks indicate censored cases. *D,* photodynamic therapy – treated gastrointestinal cancer patients. *E,* photodynamic therapy – treated ovarian cancer patients. *F,* photodynamic therapy – treated sarcoma patients. The solid line represents overall survival, and the dashed line represents failure-free survival. Tic marks indicate censored cases.

peritoneum, and other locations. In general, tumors of patients with pseudomyxoma peritoneii (patients 11, 20, and 23) displayed lower tumor Photofrin concentrations, with the exception of one sample from patient 23, which had a concentration of 3.64 ng/mL. Tumor-to-normal (*T*/*N*) tissue ratios of Photofrin uptake were calculated for the large bowel and small bowel with and without mucosa (i.e., a toxicity-limiting normal tissue). Without mucosa, the median *T*/*N* for small bowel (four patients) was 2.1 (range, 1.3-3.6), and the median *T*/*N* for large bowel (three patients) was 2.1 (range, 0.8-4.5). The median *T*/*N* ratio was 1.1 for large bowel samples with mucosa and 2.1 for samples without mucosa.

Discussion

Treatments for patients with peritoneal carcinomatosis are limited and include systemic chemotherapy, whole abdominal radiotherapy, and debulking surgery in combination with hyperthermic peritoneal perfusion with chemotherapy. No curative treatment exists, in general, for this group of patients.

Photodynamic therapy is a cancer treatment that employs the use of a photosensitizing agent and laser light of a specific wavelength to activate the photosensitizer in the presence of oxygen. The effective depth of cellular damage of photodynamic therapy in tissue is dependent upon several factors, including photosensitizer concentration, wavelength of laser light, amount of tissue oxygen, and the optical properties of the underlying tissues. In general, photodynamic therapy is a superficial treatment with an effective depth of cellular damage for Photofrin-mediated photodynamic therapy of 2 to 5 mm (1, 2). The superficial nature of Photofrin-mediated photodynamic therapy makes this treatment a potentially ideal therapy for surface malignancies, such as cancers, which have spread to the serosal surfaces of the peritoneum and pleura. The limited penetration of photodynamic therapy tissue effect would theoretically limit the potential for damaging underlying critical organs. We have recently reported our experience with treating non–small cell lung cancer, which has spread to the pleural surface (11). That study showed that excellent local control could be achieved with acceptable toxicity using Photofrin-mediated photodynamic therapy. Furthermore, we showed that the median survival of these patients exceeded what would normally be expected in patients with pleural carcinomatosis. This study provides some evidence that photodynamic therapy might be effective as a treatment for patients with malignancies that have spread to serosal surfaces.

Patients with malignancies that spread to the peritoneum (including patients with ovarian cancer, sarcoma, and gastrointestinal cancers) have few to no curative treatment options. These patients present with abdominal pain, altered bowel function, ascites, and recurrent small bowel obstruction. Chemotherapy is often administered to these patients, especially those with ovarian cancer and gastrointestinal malignancies. The subset of sarcoma patients with gastrointestinal stromal tumors is usually treated with imatinib mesylate (12, 13). Whole abdominal radiotherapy is not a curative treatment option for patients with peritoneal carcinomatosis and sarcomatosis because the underlying abdominal organs limit the ability to deliver a curative dose of radiation. Radical surgical approaches have been attempted in these patients but are unlikely to sterilize the peritoneum.

The phase I trial of Photofrin-mediated photodynamic therapy completed at the National Cancer Institute (4, 5) showed that this procedure could be done with acceptable toxicities. Encouraging preliminary responses, especially in ovarian cancer patients, provided the rationale for performing this phase II study. Our results show that Photofrin-mediated photodynamic therapy is feasible after surgical debulking but does not lead to control of peritoneal carcinomatosis or sarcomatosis after surgical debulking. Some of our patients

had clinical benefit from i.p. photodynamic therapy that did not qualify as a complete response. Reduction in the number of peritoneal nodules and the elimination of the need for abdominal paracentesis were observed in selected individuals but could not be scored as a complete response. It should be kept in mind that the criteria used for efficacy in this study were rigorous and required the complete absence of clinical, radiographic, and, in some cases, pathologic disease within the abdomen. This is a standard of efficacy that is higher than is typically used in studies of chemotherapy in this patient population. Notwithstanding the strict criteria used, complete responses to Photofrin-mediated photodynamic therapy were uncommon, and failure-free survival was short in all disease cohorts. The toxicity caused by surgical debulking and Photofrin-mediated photodynamic therapy was substantial, including a capillary leak syndrome (7, 14) observed in many patients in the immediate postoperative period. It is likely that this systemic toxicity of i.p. photodynamic therapy is a result of tissue damage to the serosal surfaces of the peritoneum similar to that observed in burn victims. The presence of this toxicity and the absence of a significant therapeutic response suggest that i.p. photodynamic therapy has a narrow therapeutic ratio.

One of the reported theoretical advantages of photodynamic therapy as a cancer treatment is that systemically administered

Table 3. Toxicities related to photodynamic therapy

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
↑ Transaminases	31	11	9		
↑ Alkaline phosphatase	11	2			
Hyperbilirubinemia		5	4	1	
Hypocalcemia	22	8			
Hypomagnesemia	10	1			
Thrombocytopenia	32	6			
Neutropenia		1			
↑ Creatinine	1	1			
Hydronephrosis	2	6	1		
Volume depletion			1		
Volume overload	3	9	2		
Edema	17	26	4		
Bowel edema			1		
Pleural effusion	23	13	2		
Pulmonary edema vs ARDS				1	
ARDS/prolonged intubation			3		
Respiratory distress			2	1	
Tachycardia	3	3			
Bradycardia				1	
Cardiac ischemia					1
Hypotension	1	1	2	1	
Anastamotic leak			1		
Vaginal/peritoneal fistula		1			
Wound abscess			1		
Wound infection	1				
Wound dehiscence		1			
Rectal stump dehiscence			1		
Delayed wound healing		1			
Enterocutaneous fistula			2		
Ileus		1			
Partial small bowel obstruction		1			
Pancreatitis/ileus		1			
Diarrhea	5	5	2	1	
Abdominal pain	1	1			
Gatrointestinal bleed			1		
Nausea and vomiting		2			
Sunburn	15	5			
Acidosis			1	1	
Weight loss	1	1			
Neurodepression	1	1			
Fatigue	2				

Abbreviation: ARDS, adult respiratory distress syndrome.

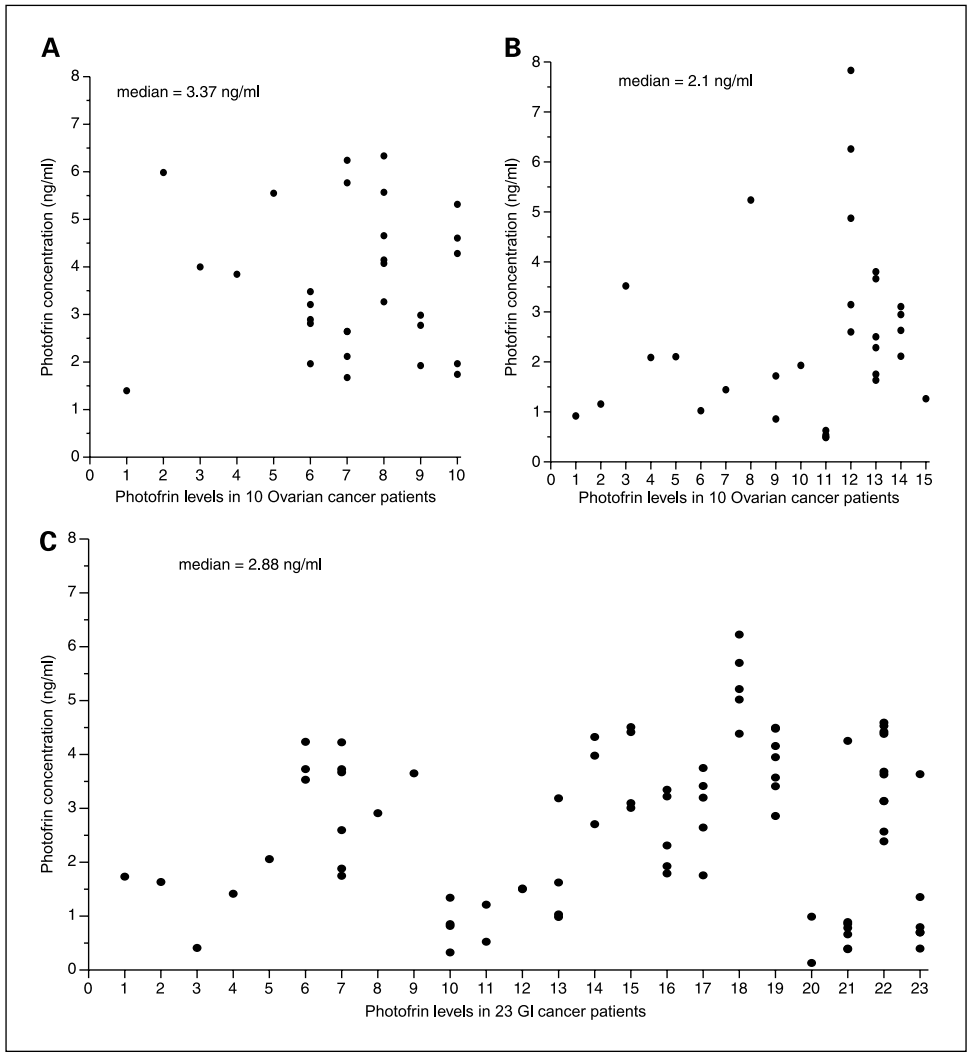

Fig. 3. Photofrin concentrations in tumor samples of individual patients. Photofrin concentrations for individual patients within each strata: (*A*) 10 ovarian cancer patients, (*B*) 15 sarcoma patients, and (*C*) 23 gastrointestinal cancer patients.

photosensitizers in animal models have greater retention in cancers compared with selected normal tissues (2, 3, 15). These studies, however, compared the uptake of photosensitizers in tumor to that in normal tissues, such as muscle or skin, which are not particularly relevant to normal tissues at risk for toxicity from i.p. photodynamic therapy. If confirmed in human clinical trials, the selectivity of photosensitizers in tumor compared with relevant normal tissues would provide an enhanced therapeutic ratio for photodynamic therapy. The need for tumor selectivity of photosensitizer retention is particularly important when considering treatment of large surface areas, such as the peritoneum, where a large number of sensitive normal tissues are at risk for toxicity and where activation of a photosensitizer in large surface areas has been associated with systemic inflammatory response syndrome or capillary leak syndrome (16). The photosensitizer uptake measurements in patients on this trial show that absolute tissue levels in human tumors are similar to those described for tumors in murine models (17, 18). However, tumor-to-normal tissue (*T*/*N*) ratios for relevant normal tissues, such as the large bowel, were very modest, with median values ranging between 1.1 and 2.1, depending on whether tissue contained mucosa (data not shown). Furthermore, substantial heterogeneity was found among patients, as could be expected from the variability among absolute tumor levels of drug within disease strata. Such heterogeneity would be expected to limit the photodynamic therapy dose that could be achieved before reaching clinical toxicity and likely contributes to the disappointing clinical findings described above. In a separate clinical trial, Photofrin measurements in several patients with non–small cell lung cancer with pleural spread (11) also identified modest drug selectivity between tumor and relevant normal tissues (normal pleura and lung). *T*/*N* ratios within specific tissue types were consistent among the first three patients evaluated on this study, but it is too early to assess the degree of intrapatient and interpatient heterogeneity in tissue Photofrin uptake on this trial in non–small cell lung cancer. A more expansive report with detailed statistical analysis of tumor and normal tissue levels of Photofrin uptake in the patients of the i.p. photodynamic therapy trial is currently being prepared. Overall, these data highlight the importance of assessing tumor to normal tissue ratios in human tumors and relevant normal tissues as part of the clinical evaluation of photodynamic therapy.

The photosensitizer measurements described in this study and in our previous reports (19) collectively shed some light on

the delivery of drugs to tumor nodules on the peritoneal surface and are potentially relevant to the delivery of chemotherapy drugs to peritoneal tumors. We have previously shown that Photofrin is present in tumor nodules as small as 1 mm in size (17, 19). In addition, a preliminary evaluation of photosensitizer uptake and oxygen levels in these patients also suggested substantial interpatient and intrapatient heterogeneity in Photofrin and oxygen levels in tumor (19). The photodynamic process is dependent upon the presence of adequate photosensitizer and oxygen (2). Either of these factors may limit the efficacy of the treatment. An additional factor of importance is that a major mechanism of action for Photofrin-mediated photodynamic therapy is a vascular effect, which may not be optimal in a clinical setting where small volume disease is treated after debulking surgery.

The peritoneum is a complex cavity with a surface area similar to the external body surface area (4). There are regions of the peritoneal cavity that are difficult to access for light delivery, such as the diaphragmatic surfaces and deep within the pelvis. We have also previously shown that there is heterogeneity in the optical properties in peritoneal light delivery and light dose absorbed in various regions within a patient as well as in the same region among different patients (6, 20). These data suggest, therefore, that individualization of light doses based upon measured optical properties and measurement of both scattered and incident light will be necessary to adequately control light dose deposition in tissues.

In summary, we have shown that i.p. Photofrin-mediated photodynamic therapy is feasible but does not lead to significant objective responses or tumor control. Heterogeneity in photosensitizer uptake and tumor oxygenation, lack of significant tumor specificity for photosensitizer uptake, and the heterogeneity in tissue optical properties may account for the lack of efficacy observed. Photofrin-mediated i.p. photodynamic therapy delivered as a single treatment is unlikely to lead to a sustained complete response in patients with i.p. malignancies who have gross disease. This situation is similar to the early development of radiation therapy where it was discovered that single, large doses of ionizing radiation were not as effective as fractionated treatment. The use of methods to enhance the efficacy of photodynamic therapy against tumor compared with normal tissues, improved techniques for light delivery, and fractionated photodynamic therapy are reasonable approaches to consider in future studies of i.p. photodynamic therapy.

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