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Phase III Randomized Trial of Surgery With or Without Intraoperative Photodynamic Therapy and Postoperative Immunochemotherapy for Malignant Pleural Mesothelioma

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Background: Patients with malignant pleural mesothelioma (MPM) usually die of progressive local disease. This report describes the results of a Phase III trial comparing maximum debulking surgery and postoperative cisplatin, interferon α-2b, and tamoxifen (CIT) immunochemotherapy with and without intraoperative photodynamic therapy (PDT) to determine (1) whether such a multimodal approach can be performed with minimum morbidity and mortality in malignant pleural mesothelioma (MPM), and (2) whether first-generation (i.e., 630-nm laser light, Photofrin II) intrapleural PDT impacts on local recurrence or survival.

Methods: From July 1993 to June 1996, 63 patients with localized MPM were randomized to either PDT or no PDT. The tumors of 15 patients could not be debulked to 5 mm. Patients assigned to PDT (n = 25) and no PDT (n = 23) were similar with respect to age, sex, tumor volume, and histology.

Results: The type of resection (11 pleurectomies and 14 pneumonectomies vs. 12 pleurectomies and 11 pneumonectomies), length postoperative stay, and ICU time were comparable (PDT vs. no PDT). There was one operative death (hemorrhage), and each group had two bronchopleural fistulas. Postoperative staging divided patients into the following categories: stage I: PDT, 2, no PDT, 2; stage II: PDT, 2, no PDT, 2; stage III, PDT, 21; no PDT, 17; stage IV, PDT, 0; no PDT, 2. Comparable numbers of CIT cycles were delivered. Median survival for the 15 non-debulked patients was 7.2 months, compared to 14 months for the 48 patients on protocol. There were no differences in median survival (14.4 vs. 14.1 months) or median progression-free time (8.5 vs. 7.7 months), and sites of first recurrence were similar.

Conclusions: Aggressive multimodal therapy can be delivered for patients with higher stage MPM. First-generation PDT does not prolong survival or increase local control for MPM.

Key Words: Mesothelioma—Photodynamic therapy—Immunochemotherapy—Phase III.

The management of pleural neoplasms, specifically malignant pleural mesothelioma (MPM), remains difficult. Surgery alone cannot cure patients with MPM, and chemotherapy response rates range from 10% to 20%, with few complete responses (1). The role of radiation therapy, either as definitive therapy or via intraoperative or postoperative techniques, remains undefined (2). Novel, more aggressive, approaches for managing these malignancies have included intraoperative chemotherapy, surgery combined with postoperative multimodality therapy, intrapleural or systemic immunotherapy, and intraoperative photodynamic therapy (3–10). Photodynamic therapy is appealing in the management of this malignancy because of the tendency of MPM to have local recurrences and to spread along surfaces. Nevertheless, patients with advanced MPM will develop extrathoracic metastatic disease, and will have lymphatic dissemination, which argues for a systemic therapy in addition to local options.

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A series of protocols developed at the National Cancer Institute for patients with malignant MPM included the following: (1) a Phase I trial defining the maximum tolerated dose of intraoperative PDT after maximum cytoreduction (11); (2) a Phase II trial documenting a 19% response rate in unresectable MPM in patients using cisplatinum, interferon, and tamoxifen (CIT) (12); and (3) demonstration that CIT could be delivered safely as adjunctive therapy 5 to 6 weeks after maximum cytoreduction of MPM. These trials were then combined into a Phase III trial that attempted to define the role of first-generation intrapleural PDT in the management of pleural MPM. The specific aims for this trial were (1) to determine whether intrapleural PDT with 630-nm light and Photofrin II had any effect on survival or recurrence patterns in MPM; (2) to confirm the safety of CIT as an adjunctive treatment; (3) to document whether reliable dosimetry could be performed with intrapleural PDT; and (4) to measure the uptake of the sensitizer in the tumor.

PATIENT POPULATION AND METHODS

Between July 1993 and June 1996, 63 patients were registered on the trial. All patients were referred to our institution with a histologic diagnosis of malignant pleural mesothelioma, which was confirmed by our pathologists. The clinical and functional evaluation included complete history and physical examination, routine blood work, and chest radiograph. Computed tomography of the chest, head, and abdomen, and radionuclide bone scan were performed in all cases. Pulmonary function testing, arterial blood gas determination, and selective use of quantitative ventilation-perfusion scanning was performed. FVC, FEV_1, or MVV of less than 50% after optimal respiratory therapy, or a predicted FEV_1 after operation of less than 0.8 L/minute were exclusionary, as was an arterial blood gas revealing a $pCO_2 > 48$ mm Hg or a $Po_2 < 55$ mm Hg on room air. The tumor could be of any size, with direct extension into the chest wall, diaphragm, or pericardium, and patients with presumed tumor in mediastinal lymph nodes were not excluded.

Preoperative and Follow-up Tumor Volume Determinations

The volume of solid tumor (T status) was objectively quantitated using the Voxel Scope II 3-Dimensional Imaging Work Station (Picker International, Highland Heights, OH). The tapes of each patient's computed tomographic examinations were loaded into the memory of the system, and serial images of each study were depicted on the screen. One individual (B.T.) outlined the borders of the solid tumor using a hand-controlled mouse, with discrimination of solid tumor from fluid based on differences in tissue density. The system then calculated the volume in cm^3 of total solid tumor burden or of any desired subset or fraction. The volumetrics were performed before resection, after immunochemotherapy, and on follow-up examinations.

Surgical Cytoreduction of Disease

Patients were considered for the trial if, on review of the computed tomogram of the chest, it was felt that the disease was amenable to a subtotal extirpation such that the maximum thickness after debulking at any intrathoracic site would be 5 mm or less. There could be multiple discontinuous sites of disease or one large plaque-like area of residual disease; in all cases, however, the residual disease was believed to have a thickness of 5 mm or less by gross examination. Pleurectomy decortication, either alone or in combination with anatomic or nonanatomic resection, as well as extrapleural pneumonectomy, was performed. The extrapleural pneumonectomy could be modified to include or not include portions of the pericardium or diaphragm. Postoperative staging was defined by the new International Mesothelioma Interest Group Staging System (13).

Randomization

All patients were required to understand and sign informed consent for entry onto the trial, which was approved by the Institutional Review Board of the National Cancer Institute as well as the Cancer Therapy Evaluation Program. Patients who were registered for randomization were stratified by mesothelioma histology (epithelial, biphasic, or sarcomatoid), age, and sex. The randomization determined whether or not the patient would receive intraoperative photodynamic therapy at the time of maximal cytoreduction. All patients who fulfilled criteria for cytoreduction received postoperative immunochemotherapy.

Intraoperative Photodynamic Therapy

Sensitizer

All patients randomized to intraoperative PDT received 2 mg/kg intravenous dihematoporphyrin ethers (Photofrin II [PII], courtesy of Quadra Logic Technologies, Vancouver, British Columbia, Canada) 24 hours before the planned cytoreduction. All patients receiving photosensitizer were given specific instructions to avoid sun exposure for a minimum of 6 weeks to prevent skin photosensitivity reactions.

Porphyrin Content of Resected Mesothelioma Specimens

Sensitizer uptake in pg PII/mg tissue was approximated by quantitation of fluorescence after extraction of porphyrins from harvested mesothelioma samples at the time of cytoreduction.

Light Source and Dosimetry

Light delivery (630 nm) was achieved with two Coherent pump-dye lasers using Kiton red as the dye or with a specially designed 50-watt (W) laser (Laserionics, Tampa, FL). The Coherent lasers (Model PRT 100, Coherent, Inc., Palo Alto, CA, and Innova 200-25, Model CR 599, Coherent, Inc., Palo Alto, CA) could each deliver 25 W from the argon tube and 5 W at 630 nm from the dye table, and the Laserionics instrument could deliver 9 W to 11 W at 630 nm. The system of light delivery using optical fibers housed in sterile endotracheal tubes has been previously described (11). Briefly, the fiberoptic system is assembled from 600-μm–diameter fused silica optical fiber (Quartz Products Corporation, Plainfield, NJ) and fiber connectors (Radiall Corporation, Stratford, CT) or purchased with specialty terminations to produce spherical or cylindrical light distributions (Laser Therapeutics, Inc., Buellton, CA). These fibers were used directly by attachment to the laser or indirectly by an attachment delivery fiber. The transmission characteristics of fused silica are excellent in this wavelength range. The fibers enable 85% of the laser power to be delivered a distance of 65 meters from the laser site to the operating suite, including coupling losses. Total power delivered into the optical fibers ranged from 4.8 to 10 W.

Light dosimetry was accomplished with a specially designed system to measure light intensity at a number of sites and integrate the values on real time to provide the light dose at each site. The system consisted of an amplifier box, isolation transformers, photodiodes, and a computer. A custom-designed amplifier box contained individual current to voltage converters for 12 photodiodes. Signals were transmitted to a Compaq Model 4 portable computer (Compaq, Houston, TX) with the appropriate software for photodiode calibration, and the location of each photodiode was recorded, as were real time and cumulative dose in J/cm^2. The patented photodiodes (Model VTB 4051, Vactec, St. Louis, MO) were mounted on transparent methylmethacrylate (Lucite) bases, and were placed in seven strategic areas: apex, peri- or epicardial region, anteromedial chest wall, posterolateral chest wall, posterior mediastinal (periesophageal) region, anterior diaphragmatic gutter, and posterior diaphragmatic gutter. The cumulative light dose at each diode site for each patient was 30 J/cm^2.

Immunochemotherapy With CIT

Patients whose tumors were cytoreduced to a thickness of 5 mm were to receive two cycles of immunochemotherapy 4 to 6 weeks after surgery. Tamoxifen, 20 mg orally, two times a day, was given every day for 35 days and interferon-α 2b (5 mU/m^2) was delivered three times a week by subcutaneous injection. Cisplatin (CDDP), 25 mg/m^2, was delivered in 250 ml of normal saline with prehydration and induced diuresis on days 8, 15, 22, and 29 at least 30 minutes after delivery of interferon. Prophylactic antiemetic therapy with ondansetron (0.15 mg/kg) was given ½ hour before and 2 hours after administration of CDDP.

Each patient was monitored prospectively for clinically adverse reactions resulting from the interaction of cisplatin, interferon, and tamoxifen, with history and physical examination. Complete blood count, blood urea nitrogen, creatinine, and serum magnesium levels were obtained on days 0, 8, 15, 22, 29, and 36. Serum electrolytes, as well as hepatic and mineral panels, were performed on days 0, 15, and 29. Toxicities were graded according to the Common Toxicity Criteria for Cancer Clinical Treatment Trials, and dose modifications were specified for dose-limiting myelosuppression, nephrotoxicity, interferon-related fatigue, or elevation of liver enzymes.

Follow-up and Recurrences

Chest and abdominopelvic computed tomograms were performed every 3 months after cessation of therapy for 2 years and every 6 months thereafter, and CT volumetrics obtained. Progression or recurrence of disease was documented histologically if possible.

Statistical Analyses

The full protocol accrual requirement was for 88 patients (44 per arm of the study). Assuming a median survival of 9 months (i.e., 50% alive at 9 months from treatment) for patients with malignant pleural mesothelioma, it was determined that 44 patients per arm would be required to see whether the addition of PDT resulted in an increase to 80% of the patients surviving 9 months with 80% power and 95% confidence. This would correspond to at least a 50% increase in median survival.

The probability of survival was calculated using the Kaplan-Meier method (14), and the significance of the difference between pairs of Kaplan-Meier curves was calculated using the Mantel-Haenszel procedure (15).

TABLE 1. *Preoperative parameters*

	PDT (n = 25)	No PDT (n = 23)
Sex	17M, 8F	16M, 7F
Age, mean years (range)	57 (34–78)	58 (34–73)
Symptoms	25/25	23/23
Intervals (months), mean		
Symptoms to diagnosis	2.4	3.4
Diagnosis to treatment	2.2	2.0
ECOG 1 performance status	25	23

PDT, photodynamic therapy.

TABLE 2. *Preoperative laboratory parameters*

	PDT	No PDT
Pulmonary function (%)		
FEV_1	76	82
FVC	70	79
DLCO	73	80
Tumor volume (cc) (mean ± SE)		
Preoperative	294 ± 63	247 ± 85
Postoperative	28 ± 10	44 ± 21
Platelet count (×1000)	385 ± 33	301 ± 25

RESULTS

From July 1993 to June 1996, 63 patients were registered and randomized on the protocol. The protocol was terminated early because of geographical relocation of the principal investigator (H.I.P.). There were 18 females and 45 males. Of these, 15 patients (3 females and 12 males) were taken off study because (1) their tumors could not be debulked to the prerequisite 5 mm (8 patients: 4 PDT, 4 non-PDT); (2) disease progressed before operative intervention (6 patients); or (3) the patient withdrew before resection (1 patient).

The two groups of patients were similar with regard to preoperative characteristics, including sex, age, symptoms, and interval from diagnosis to treatment (Table 1). All patients were ECOG performance status 1, and the majority had a history of asbestos exposure. Pulmonary function test results for both groups were comparable (Table 2). There were no significant differences between the two groups with regard to preoperative tumor burden, as determined by preoperative quantitative computerized volumetrics (294 + 63 vs. 247 + 85 ml, PDT vs. no PDT, mean + SEM). The residual solid tumor volume as estimated by CT volumetrics before the inception of immunochemotherapy also was comparable (28 + 10 vs. 44 + 21 ml, PDT vs. no PDT, mean + SEM). Platelet counts were significantly higher preoperatively in the PDT group.

The extent of resection needed to accomplish the 5-mm residual disease cytoreduction, as well as the the postoperative histology and stage, was very similar between the two groups (Tables 3 and 4). The photodynamic therapy added 137 minutes to the resection, of which a mean of 64 minutes was "laser on" time. Laser power at 630 nm ranged from 6.2 to 9.2 watts.

TABLE 3. *Operative specifics*

	PDT	No PDT
Operation		
EPP	14	11
Pleurectomy	9	10
Pleurectomy/lobectomy	2	2
OR duration (min) mean (range)	337 (range 175–530)	200 (range 80–390)
Postoperative hospital days	4 (range 6–15)	4 (range 6–22)
Deaths	1	0

There were no differences in the number or severity of complications of surgery or immunochemotherapy between the PDT and no PDT groups. There were 11 postoperative complications in 10 patients, including medically reversible arrhythmia in 4 patients, bronchopleural fistula in 4 patients, cardiac herniation requiring pericardial patching in 1 patient, postoperative bleeding requiring reexploration in 1 patient, and postoperative pancreatitis in 1 patient. There were two bronchopleural fistulas in each group, all occurring more than 30 days after the pleuropneumonectomy. All were treated with open thoracostomy with drainage. One patient's fistula was closed 18 months after the extra-pleural pneumonectomy (EPP), and another patient whose thoracostomy remains open is alive with disease 34 months after his operation. There was one operative death in a PDT patient whose inferior vena cava avulsed after a right-sided pleuropneumonectomy at the termination of anesthesia.

Immunochemotherapy was started at a similar postoperative interval in both arms of the study (1.4 months for the group receiving PDT vs. 1.2 months for the no-PDT group). Most patients received two full cycles (21, PDT, vs. 17, no PDT). Patients who did not receive both cycles of CIT either had disease progression after one cycle or

TABLE 4. *Postoperative histology and stage*

	PDT	No PDT
Histology		
Epithelial	17	16
Biphasic	6	6
Sarcomatoid	2	1
Involved nodes	16	16
N1	8/14	9/15
N2	14/24	15/23
IMIG stage		
I	2	2
II	2	2
III	21	17
IV	0	2

TABLE 5. *Immunochemotherapy toxicity*

	PDT (n = 24)[a]					No PDT (n = 22)[b]				
Toxicity grade	0	1	2	3	4	0	1	2	3	4
WBC	6	5	13			5	10	6	1	
Platelets	14	10				9	13			
Hgb	6	9	9			5	12	5		
Nausea	14	1	5	4		8	4	7	2	1
Vomiting	19		5			17	2	3		
Creatinine	21	2	1			21	1			
Fever		5	19				11	11		
Weight loss	19	3	2			15	6	1		
Hypomagnesemia	7	2	12			5	6	9	2	
Fatigue	4	15	5			1	13	5	1	1

[a] One patient died in the operating room.
[b] One patient progressed before receiving immunochemotherapy.

refused further therapy. Toxicity of the regimen was similar in both arms (Table 5).

It was theorized that, to verify whether the light detection was stable from patient to patient, the amount of time to deliver the prescribed light dose should be directly proportional to (1) the size of the patient's chest (which would be in proportion to the patient's body surface area), and (2) the prescribed dose of light. An inverse relationship, however, should exist between the laser treatment time and the amount of wattage (power) available from the lasers on that given day. When such a proportion was calculated, there was a 95% correlation between these parameters and laser "on" time, revealing consistency of the diode measuring system from patient to patient.

Tissue porphyrin levels were determined from the tumors of 19 no PDT patients and 22 PDT patients. There was a significantly ($P2 = .0001$) higher level of extractable porphyrin from the PDT group (673 +43 pg/mg tissue) compared to the no PDT group (332 + 61 pg/mg).

Survival and Recurrences

The median potential follow-up (time from treatment to analysis date) for the entire group of 63 patients is 23.1 months. The median survival for the 48 PDT and no PDT groups is 14.4. months, and there was no significant difference between the two groups (PDT, 14.1 months vs. no PDT, 14.4 months). The median survival for the 15 patients whose tumors could not be surgically cytoreduced was 7.2 months.

The median recurrence-free survival was 8 months for the entire group (PDT, 8.5 months vs. no PDT, 7.7 months). Once a recurrence was diagnosed, the median time to death was 5.1 months. There were no differences in recurrence patterns between the two groups (Table 6).

TABLE 6. *Sites of first recurrence*

	No. patients (%)		Recurrences (%)	
Site	PDT	No PDT	PDT	No PDT
Local	18 (72)	16 (70)	82	89
Local/systemic	1 (4)	1 (4)	5	6
Systemic	3 (12)	1 (4)	14	6

DISCUSSION

This study is one of the few prospective randomized trials incorporating surgery for the management of malignant pleural mesothelioma. The lack of a uniform management strategy, the small number of cases, and the futility of dealing with this disease as expressed by both surgeons and medical oncologists, has contributed to the inability to conduct innovative and aggressive approaches for MPM. Recently, however, there has been increasing interest in the management of MPM, as well as in the exploration of novel approaches, including gene therapy and immunotherapeutic strategies.

At least five other centers have had an interest in managing pleural mesothelioma with photodynamic therapy (Table 7). In reviewing the data, most of which is presented only in abstract form, it can be appreciated that the studies represent a tremendous amount of labor. Nevertheless, the delivery of PDT is heterogeneous with regard to sensitizer used and dose of light used, and the staging of the patients treated is very unclear. It is far too early to draw conclusions regarding efficacy from these Phase II trials, but they reinforce the efforts of the NCI group to show that delivery of the therapy is feasible and can be performed safely. Moreover, the operative mortality is low in all the studies.

Analysis of the two groups studied in this randomized trial reveals that they are comparable with regard to extent of disease at the time of randomization. This is confirmed by the measurement of T status using CT volumetrics, as well as by the postoperative distribution of IMIG stages, including the number of patients with involved lymph nodes. Moreover, there were no obvious differences in the number of cycles of postoperative adjuvant immunochemotherapy delivered, or in the toxicity from the regimens.

The failure to detect any difference in the two groups with regard to time to recurrence, recurrence patterns, or median survival strongly implies that first-generation intrapleural photodynamic therapy is not beneficial to patients with MPM. Moreover, the anticipated accrual of 44 patients per arm was not reached, for logistic reasons; however, the impact of decreased sample size, considering the identical nature of the survival and recurrence

TABLE 7. *International PDT trials for pleural mesothelioma*

Group	No. patients	Sensitizer/dose	Light dose	Technique	Comments
Roswell Park, Buffalo, NY	23	2 mg/kg PII	20–25 J/cm^2	Preoperative simulation; multiple fibers intraoperative; no online dosimetry	50% complications: 2 deaths; non-uniform debulking
Oreboro, Sweden	1	2 mg/kg PII	20 J/cm^2	Preoperative simulation; thoracoscopic delivery; no online dosimetry	6 h of treatment; no recurrence at 10 mo
Bern, Switzerland	4	0.3 mg/kg mTHPC	10 J/cm^2	2 thoracoscopic; 2 intraoperative; no online dosimetry	1 death; only 3 mo f/u available
Melbourne, Australia	25	5 mg/kg HPD	NA	Pleurectomies only; direct surface illumination; no online dosimetry	Median survival 713 d compared to 250 d in non-matched controls
Oslo, Norway	9	2 mg/kg PII	15–30 J/cm^2	Cooled spherical diffusing fiber intraoperative; no online dosimetry	6 patients recurred locally 4–14 mo postoperatively

PII, Photofrin II; mTHPC, meta-tetrahydroxyphenylchlorin; HPD, hematoporphyrin derivative

curves, was probably minimal. The probability of identifying a significant difference with an additional 40 patients would be very low in view of the similarity of results obtained to date from the 48 evaluable patients. As with any new therapeutic intervention that does not succeed in its first attempt, it would be foolish simply to claim that photodynamic therapy is unsuited for intrapleural cancer control and discard it as a technique of historical interest only. There are obvious aspects of the treatment that can be improved, and, at the very least, this study confirms the ability to (1) perform the cytoreduction safely and (2) deliver safe doses of intrapleural PDT after describing the maximal tolerated dose in Phase I trials. Newer trials can be constructed, based on the evolving interest in the development of longer wavelength sensitizers, as well as the redesigning of light delivery techniques.

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