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Treatment of Primary Peritoneal Mesothelioma by Continuous Hyperthermic Peritoneal Perfusion (CHPP)

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Background: Primary peritoneal mesothelioma is a locally aggressive disease that is difficult to treat or even palliate. Continuous hyperthermic peritoneal perfusion (CHPP) with cisplatin (CDDP) allows uniform, high regional delivery of chemotherapeutics and hyperthermia to the peritoneal surface for the treatment of peritoneal tumors. This article summarizes the results of 18 patients with peritoneal mesothelioma treated with CHPP.

Methods: From June 1993 through April 1998, 18 patients with primary peritoneal mesothelioma (13 male, 5 female; median age, 51 years) underwent surgical exploration and tumor debulking followed by a 90-minute CHPP with CDDP and hyperthermia as part of three consecutive phase I trials conducted at the National Cancer Institute. Seventeen of 18 patients had malignant peritoneal mesothelioma, 13 with associated ascites. One patient had a symptomatic, multiply recurrent, benign, cystic peritoneal mesothelioma. Three patients who had a recurrence after a prolonged progression-free interval (>6 months) after CHPP underwent re-treatment. CHPP parameters included median cisplatin dose of 530 mg (range, 187–816), perfusate volume 6.0 liter (range, 4–9), flow 1.5 liter/min (range, 1–2), intraperitoneal temperature 41°C (range, 38.7–43.2), and central temperature 38.6°C (range, 36.8–39.7).

Results: Median follow-up after CHPP is 19 months (range, 2–56) with no operative or treatment-related mortality. Overall operative morbidity was 24% and included two patients with superficial wound infection and one patient each with atrial fibrillation, pancreatitis, fascial dehiscence, ileus, line sepsis, and clostridium difficile colitis. The major treatment-related toxicity was systemic renal toxicity at doses above what was defined as the maximum tolerated dose of cisplatin. Nine of 10 patients had resolution of their ascites postoperatively. Three patients who developed recurrent ascites (27, 22, and 10 months after initial treatment) were re-treated and had resolution of their ascites with ongoing responses at 24, 6, and 4 months after the second perfusion. The median progression-free survival was 26 months, and the overall 2-year survival was 80%. The median overall survival has not been reached.

Conclusions: CHPP with cisplatin can be performed safely with no mortality and minimal morbidity. In selected patients, successful palliation in the abdomen and long-term survival, compared with historical controls, can be achieved with aggressive surgical debulking and CHPP. Re-treatment after initial response can result in a second long-term response.

Key Words: Primary peritoneal mesothelioma—Continuous hyperthermic peritoneal perfusion (CHPP)—Carcinomatosis—Tumor necrosis factor—Intraperitoneal cisplatin.

Primary peritoneal mesothelioma is a rare tumor, composing 10% to 20% of the roughly 2200 new cases of mesothelioma per year.[1,2] The diffuse, malignant type has been considered a terminal condition with few effective therapeutic or palliative treatment options available. Tumor growth is characterized by peritoneal seeding and ascites formation. Patients commonly present with abdominal pain or cramping, weight loss, and signs of advanced disease in the abdomen, such as ascites or an abdominal mass.[3,4] The disease is usually confined to the peritoneal cavity, and the cause of death is related to progression in the peritoneal cavity. Its locally aggres-

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sive nature results in death from encasement and invasion of bowel and/or intractable ascites. In one large series of autopsies, two-thirds had tumor in the abdomen only, and 78% died as a direct result of complications of intra-abdominal disease.[5] The overall median survival of patients with diffuse malignant peritoneal mesothelioma is 6–10 months.[6,7] Systemic chemotherapy has not made a significant impact on the natural history of peritoneal mesothelioma.[8,9]

Regional therapy approaches have theoretical advantages over systemic chemotherapy and may impact palliation and survival. A pharmacokinetic advantage to intraperitoneal chemotherapy exists as a result of the barrier effect of the peritoneal lining.[10] Concentration gradients of up to 1000-fold can be achieved depending on the characteristics of the drug.[11] A variety of modalities alone and in combination, including cytoreductive surgery, abdominal radiation, and intraperitoneal chemotherapy, have been reported.[12] Whole abdominal radiation in combination with surgical debulking and chemotherapy has been associated with some long-term survival, but its use has not become routine.[13]

Continuous hyperthermic peritoneal perfusion (CHPP) is a regional treatment strategy designed to deliver high concentrations of cytotoxic agents and hyperthermia directly to the peritoneal tumor.[14] Through this technique, high concentrations of chemotherapeutics may be delivered and distributed evenly to the complex peritoneal surface combined with synergistic hyperthermia, while limiting systemic exposure and toxicity. CHPP with agents such as mitomycin C and cisplatin (CDDP) has been used as treatment for and prophylaxis against peritoneal carcinomatosis from high-risk gastric cancer.[15–17] We have developed this technique in three sequential phase I trials that use increasing doses of cisplatin, tumor necrosis factor (TNF), and early postoperative intraperitoneal paclitaxel and 5-FU, and we have found that this therapy is uniquely effective against peritoneal mesothelioma.[18] Early results of the treatment of the initial 10 patients with peritoneal mesothelioma with CHPP have previously been reported.[19] We now report the long-term follow-up and the outcome in 18 patients with peritoneal mesothelioma who underwent 21 treatments of aggressive surgical debulking followed by CHPP with CDDP.

MATERIALS AND METHODS

Patient Eligibility and Enrollment

From June 1993 through April 1998, 18 patients with primary peritoneal mesothelioma were referred to the Surgery Branch of the National Cancer Institute. These patients were treated on one of three Surgery Branch protocols approved by the Institutional Review Board of the National Cancer Institute. Study patients were required to be over 18 years of age with histologically or cytologically proven metastatic carcinoma in the peritoneal cavity. Additional eligibility criteria included (1) Eastern Cooperative Oncology Group (ECOG) performance less than or equal to 2; (2) no comorbid diseases that prevent them from being an operative candidate; (3) a life expectancy greater than or equal to 8 weeks; (4) adequate renal function (serum creatinine <2.0 or 24-hour creatinine clearance $\geq$ 75 ml/min); (5) normal hepatic function (normal bilirubin, PT/PTT, enzymes $<$ 1.5$\times$ normal); (6) adequate hematopoietic parameters (WBC $>$ 3000 and platelet count $>$ 75,000); and (7) no chemotherapy, radiotherapy, or immunotherapy in the past 30 days. None of the peritoneal mesothelioma patients had evidence of extra-abdominal metastases at the time of treatment.

Patients were treated on a protocol of (1) escalating-dose CDDP (100–450 mg/m^2) (Platinol7, Bristol-Myers Squibb, Princeton, NJ) administered via a 90-minute CHPP; (2) escalating-dose TNF (0.1–0.3 mg) delivered by CHPP with a fixed dose of cisplatin (250 mg/m^2); or (3) intravenous paclitaxel (Paclitaxel, 125 mg/m^2) followed by CHPP with cisplatin (250 mg/m^2) followed by early postoperative escalating-dose 5-FU (600–1100 mg/m^2) and paclitaxel (50 mg/m^2) administered as a single intraperitoneal dwell (2–10 days after surgery). A late modification of the third protocol eliminated the intravenous paclitaxel because of unacceptable bone marrow suppression. All patients underwent pretreatment counseling and gave written informed consent according to institutional and federal guidelines.

CHPP Technique

Patients underwent an exploratory laparotomy, extensive lysis of adhesions, tumor debulking, and CHPP as previously described.[20] Every attempt was made to debulk patients down to a maximum tumor diameter of 0.5 cm with some requiring bowel or other organ resections. Two large-bore catheters were then inserted through the abdominal wall; the inflow was placed over the right lobe of the liver while the outflow lay in the pelvis. Temperature probes were placed immediately beneath the peritoneal lining on each side of the abdomen and in the pelvis, and the abdominal fascia was closed. The catheters were connected to a circuit consisting of a roller pump, a heat exchanger, and a reservoir. Chemotherapy containing perfusate was heated and recirculated for 90 minutes through the peritoneal cavity. The perfusion flow rate was maintained at 1.5 liter/min with a perfusate volume that varied from 4 liters to 6 liters

depending on the size of the potential space of the peritoneal cavity (enough to moderately distend the abdomen correlating with intra-abdominal pressures between 5 mm Hg and 15 mm Hg). After stable perfusion parameters were obtained and the peritoneal cavity was warmed to a median temperature of 41°C, CDDP was added to the perfusate at a median dose of 530 mg (range, 187–830). Perfusion was continued for 90 minutes, during which there was constant, manual agitation of the abdomen to minimize streaming and ensure even distribution of the perfusate. Sodium thiosulfate has been shown to bind CDDP in the serum and decrease systemic toxicity from intraperitoneal administration of CDDP.[21] It was given by a loading dose of 7.5 g/m^2 intravenously over 20 minutes before addition of CDDP, followed by a continuous infusion at 2.13 g/m^2/hr for 12 hours as described.[22] Urine output was maximized through aggressive hydration (CVP >12 mm Hg, 30 minutes before CHPP), and diuretics to maintain urine output at greater than 200 ml/hr during the perfusion and 12 hours postoperatively. Urine output was maintained at 100 ml/hr for an additional 12 hours, at which time CDDP is eliminated from the circulation.

The patient's mean core temperature was measured by an esophageal probe and maintained at a median of 38.6°C (range, 36.8–39.7) using a cooling blanket and topical ice packs. At the completion of the perfusion, the fascia was opened, the catheters and temperature probes were removed, the residual perfusate was evacuated, and the peritoneal cavity was irrigated with warm saline.

Pretreatment and Follow-Up Evaluation

Before treatment, each patient underwent a full history, physical examination, routine laboratory studies, and a computed tomographic (CT) scan of the chest, abdomen, and pelvis. Intraoperatively, the extent of disease after debulking was assessed as follows: (1) minimal = fewer than 100 total lesions all smaller than 5 mm, (2) intermediate = more than 100 total lesions all smaller than 5 mm, and (3) bulky = residual tumors larger than 5 mm. Postoperatively, patients underwent routine laboratory screening daily for the first 5 days, then twice weekly until time of discharge. All complications were recorded. Toxicity was assessed using the National Cancer Institute Common Toxicity Criteria. Patients were evaluated at 6 weeks postop for routine laboratory screening and physical examination. They were then seen every 3 months for 1 year, then every 6 months thereafter for blood work, physical examination, and CT scans of the chest, abdomen, and pelvis to assess for ascites or soft tissue masses indicative of tumor recurrence. No second-look operation was performed for assessment of response. Patients were considered to have stable disease until they had radiographic evidence of recurrence.

Statistics

Survival curves are generated using Kaplan-Meier statistics.

RESULTS

Patient Characteristics

Table 1 shows the characteristics of the patients treated on the three phase I CHPP protocols. Thirteen males and five females whose ages ranged from 15 to 75 years (median, 51 years) were treated with CHPP. Seventeen of 18 patients (95%) had malignant mesothelioma, and one patient had a multiply recurrent, symptomatic, benign cystic mesothelioma despite three prior debulking procedures. Twelve patients had undergone a prior laparotomy, and eight patients had a laparoscopy before treatment. Four patients received some form of systemic chemotherapy before enrollment. Ten of 18 patients (56%) had ascites before treatment. There were three patients who underwent treatment, enjoyed a greater than 6-month clinical and radiographic progression-free interval, developed recurrent disease confined to the abdomen (as manifested by recurrent ascites), and underwent a second treatment. All patients received as the core of therapy a hyperthermic perfusion with CDDP at doses ranging from 100–400 mg/m^2. The median total CDDP dose was 530 mg (range, 187–816). Twelve patients were treated on the initial trial with cisplatin alone at doses ranging from 100–400 mg/m^2. Two patients were treated with cisplatin plus TNF delivered via the CHPP circuit. Three patients were treated with intravenous paclitaxel followed by CHPP with cisplatin, followed by postoperative dwell therapy with 5-FU and paclitaxel. One patient was treated with CHPP and post-

TABLE 1. *Patient characteristics*

Number	18
Median age (range)	47 (15–75)
Male:female	13:5
Cisplatin dose (mg/m^2)	
100	1
150	1
250	6
300	4
350	5
400	1
Ascites preop	10
Prior systemic therapy	4
Prior laparotomy	9
Prior laparoscopy	8

operative dwell 5-FU and paclitaxel without the intravenous paclitaxel dose.

Surgery

As shown in Table 2, patients underwent a variety of procedures in an attempt to aggressively debulk their tumors. One patient required a distal pancreatectomy and splenectomy. Two patients had large pelvic masses resected, and two additional patients required major bowel resections to minimize residual disease. A total of five patients had significant disease adherent to the capsule of the spleen that necessitated splenectomy. There were no perioperative deaths. Median time to regular diet was 7 days (range, 3–18). The overall operative morbidity was 24% (see Table 2). Two patients had superficial wound infections, and one patient each had atrial fibrillation, ileus, line sepsis, and clostridium difficile colitis. One patient who underwent laparotomy, omentectomy, and CHPP developed chemical pancreatitis and fascial dehiscence requiring reoperation for closure on postoperative day 8.

Toxicity

Fifteen patients with peritoneal mesothelioma were treated on the dose-escalation CDDP trial administered by CHPP in which the maximum tolerated dose (MTD) for the whole cohort was defined as 300 mg/m^2. Eleven patients in this series (52%) received CDDP at or above the MTD for treatment of their peritoneal mesothelioma. The treatment toxicities are detailed in Table 3. The major treatment toxicity was renal impairment with five patients (all above the now defined MTD of CDDP) who had a grade 3 or 4 rise in creatinine. During the initial dose escalation, no patients suffered grade 4 toxicity at 350 mg/m^2, so the dose was increased to 400 mg/m^2. On initial dose de-escalation, the 350 mg/m^2 was also toxic, so the MTD was defined at 300 mg/m^2. This accounts for five patients treated above the MTD. Only one patient required hemodialysis, and the remainder recovered with supportive care. There were no patients who had grade 4 hematologic toxicity, although three patients experienced grade 3 leukopenia and one patient had grade 3 thrombocytopenia (all of these patients received preoperative

TABLE 2. *Tumor and treatment characteristics*

Pt. No.	Pathology*	IV taxol dose (mg/m^2)	Cisplatin dose (mg/m^2)	5-FU ip dwell dose (mg/m^2)	Taxol ip dwell dose (mg/m^2)	Procedure**	Complications
1	Malig; epith	—	100	—	—	Debulking	Atrial fibrillation
2	Malig; epith; invasive	—	150	—	—	Debulking	None
2***	Malig; epith; invasive	—	300	—	—	Omentectomy, L hemicolectomy, splenectomy	None
3	Malig; epith	—	250	—	—	Omentectomy, distal pancreatectomy, splenectomy	None
4	Malig; epith	—	250	—	—	Omentectomy	None
4***	Malig; epith	271	250	800	50	Debulking	None
5	Malig	—	350	—	—	Omentectomy, debulking	None
6	Malig; epith	—	400	—	—	Omentectomy	None
7	Malig; epith	—	350	—	—	Omentectomy, debulking	None
8	Malig; epith	—	350	—	—	Omentectomy, debulking	Pancreatitis; fascial dehiscence
9	Benign; cystic	—	350	—	—	Omentectomy, debulking	None
10	Malig; epith; invasive	—	350	—	—	Omentectomy, debulking, splenectomy	None
11	Malig; epith-pap; muc; cystic	—	300	—	—	Omentectomy, debulking	None
12	Malig; epith; muc; invasive	—	300	—	—	Debulking	None
12***	Malig; epith; muc; invasive	200	250	1000	50	Revision of ileocolostomy, LAR, ileostomy	Sup wound infection
13	Malig; invasive	—	300	—	—	Omentectomy, resection pelvic mass	Ileus, line sepsis
14	Malig; epith-papillary	—	300	—	—	Omentectomy, debulking	None
15	Malig	216	250	600	—	Omentectomy, debulking	None
16	Malig; epith	195	250	1000	50	Omentectomy, debulking	None
17	Malig; invasive	177	250	1100	—	Omentectomy, diaphragm resection, splenectomy	None
18	Malig; epith-tubulopapillary; lymph node metastasis	—	250	1000	50	Tumor debulking, splenectomy	Sup wound infection; c. diff colitis

* Pathological description: Malig = malignant; Epith = epithelial; muc = mucinous.
** All patients underwent lysis of adhesions and omentectomy (unless it had been resected previously).
*** Second procedure.
Sup = superficial.

TABLE 3. *Toxicity after CHPP (n = 21 treatments)*

			Toxicity Grade				
	Median	Range	0	1	2	3	4
Renal							
Cr_{max}	2.2	1.0–14.9	8	2	6	3	2
Hematologic							
WBC_{min}	4.9	1.1–14.7	17	0	1	3	0
Plt_{min}	139	46–873	9	10	1	1	0
Hepatic							
AST_{max}	73	30–947	1	10	4	4	2
$Tbili_{max}$	1.2	0.2–8.6	10	0	2	7	2

intravenous paclitaxel, which was later discontinued because of this toxicity). Six patients had transient grade 3 or 4 transaminitis, and nine had hyperbilirubinemia, which resolved without symptoms or further sequelae.

Outcome

Table 4 summarizes the outcomes after 21 treatments in eight patients with primary peritoneal mesothelioma using CHPP, along with the final pathological diagnosis, CDDP dose administered and extent of residual disease after surgical debulking. Seventeen patients had malignant lesions with predominantly epithelial subtypes. One patient had a benign, cystic peritoneal mesothelioma that continued to recur despite three previous debulking resections over a 6-year period. This patient underwent surgical debulking and CHPP, and he is now 3 years out with no radiographic evidence of recurrence. Four patients who underwent successful tumor debulking to minimal residual disease and CHPP continue to be free of symptoms with no clinical or radiographic evidence of disease at 29, 31, 34, and 35 months follow-up. Eleven patients were debulked to intermediate residual disease and have either stable or nonimageable disease on follow-up CT scan. Three patients had bulky residual tumor in the abdomen and eventually died of disease. The first was a 46-year-old man with an extensive, poorly differentiated epithelial-type mesothelioma who rapidly progressed after receiving only 100mg/m^2 cisplatin and died 4 months postoperatively. The second was a 34-year-old man with a malignant epithelial-type tumor who had stable disease by CT scan for 5 months, then progressed and died 13 months postoperatively. The third patient was a 38-year-old man with extensive, bulky disease who developed renal toxicity with a maximum creatinine of 14.9 mg/dL requiring hemodialysis and had only a brief 3-month period of stable disease, eventually dying of progressive peritoneal disease at 1 year. Three patients underwent a second CHPP for recurrent peritoneal disease detected radiographically at 27, 22, and 10 months after the initial treatment. These patients have ongoing clinical and radiographic progression-free survival at 24, 6, and 4 months after their second perfusion for an ongoing overall survival of 56, 43, and 23 months after initial treatment.

TABLE 4. *Treatment results after CHPP*

		Ascites		Progression free survival	Overall
Pt. No.	Disease	Preop	Postop	(mos)	survival (mos)
1	Bulky	Yes	Yes	2	4
2	Intermediate	No	No	27	(56+)
2*	Intermediate	Yes	No	24+	56+
3	Bulky	Yes	No	5	13
4	Intermediate	Yes	No	22	(43+)
4*	Intermediate	Yes	No	6+	43+
5	Minimal	No	No	35+	35+
6	Intermediate	Yes	No	18	35+
7	Intermediate	Yes	No	34+	34+
8	Minimal	No	No	34+	34+
9	Minimal	No	No	31+	31+
10	Bulky	Yes	No	3	12
11	Minimal	No	No	29+	29+
12	Intermediate	No	No	10	(23+)
12*	Intermediate	Yes	No	4+	23+
13	Intermediate	Yes	No	14	17+
14	Intermediate	Yes	No	19+	19+
15	Intermediate	Yes	No	12+	12+
16	Intermediate	Yes	No	5+	5+
17	Intermediate	No	No	3+	3+
18	Intermediate	No	No	2+	2+

* Second procedure (see text).

The median potential follow-up time is 19 months (range, 2–56). Figure 1 shows Kaplan-Meier survival curves constructed for progression-free and overall survival for the patients in our series. The median progression-free survival for the 21 CHPP treatments was 26 months. The median overall survival for the 18 patients has not been reached, and the 2-year survival rate is 80%. Nine of 10 patients with ascites had resolution of their ascites after therapy (Table 4). All three patients who were re-treated had their ascites resolve again after the second treatment.

DISCUSSION

The 18 patients with malignant peritoneal mesothelioma who underwent surgical debulking and CHPP with or without postoperative intraperitoneal dwell therapy were enrolled in and treated under three related sequential CHPP phase I protocols. The primary objectives of these trials were to define dose-limiting toxicity and the MTD of CDDP administered via a 90-minute CHPP, initially alone and then with escalating dose of TNF. The most recent trial defined the MTD of 5-FU and paclitaxel administered as a dwell 2–10 days after CHPP with CDDP. No conclusions can be drawn about the relative

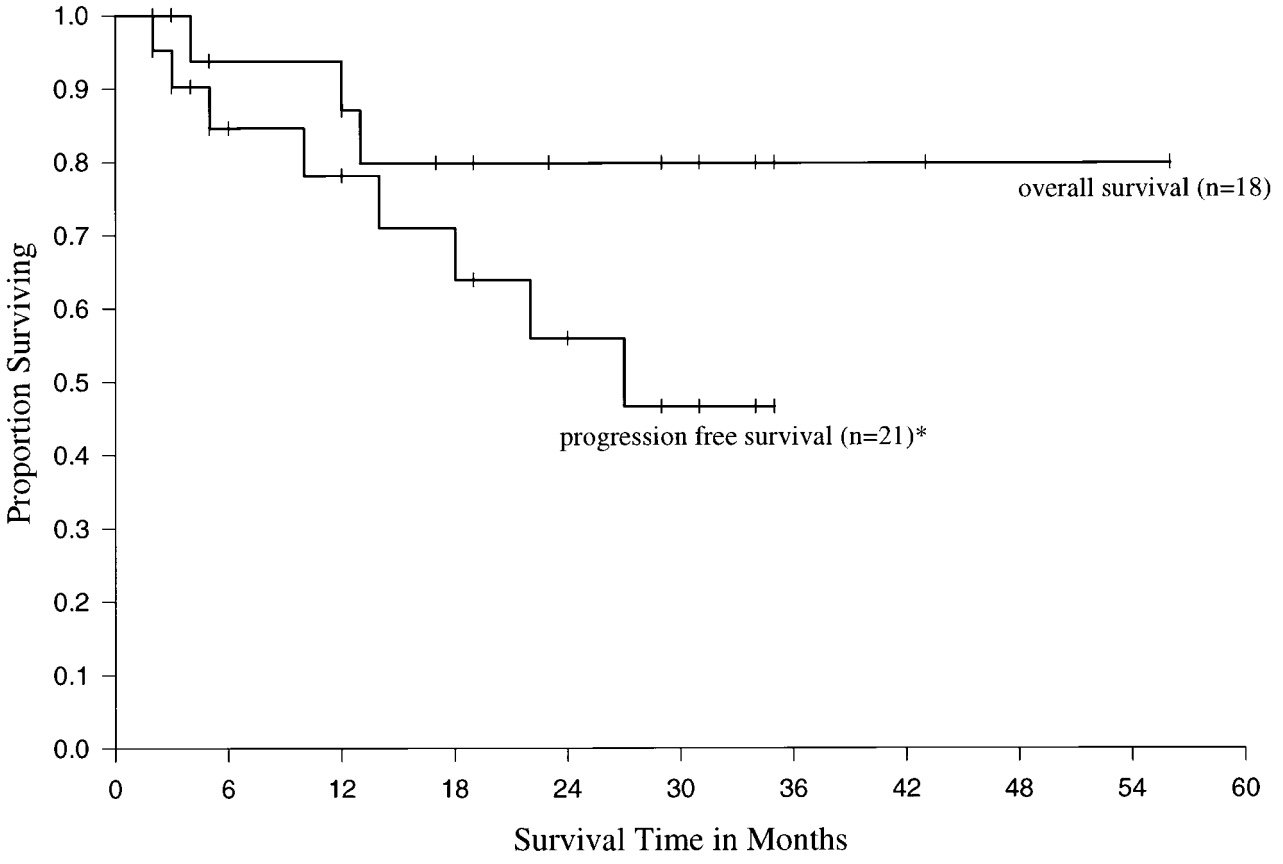

FIG. 1. Kaplan-Meier curve showing progression-free and overall survival for all patients undergoing CHPP for peritoneal mesothelioma. [The progression-free survival analysis includes 3 patients who have been treated twice (total of 21 treatments).]

activity and effectiveness of these agents when compared with one another for the treatment of peritoneal mesothelioma. However, having followed the course of these patients after aggressive surgical debulking combined with CHPP, it seems that this combined modality treatment can be implemented safely with acceptable morbidity and toxicity. Furthermore, across these phase I trials, the peritoneal mesothelioma patients stood out as having palliation and long-term survival after CHPP compared with patients reported in the literature who were treated with surgery or chemotherapy alone.[23,24] We therefore believed that these encouraging initial results deserved special attention.

Because of the rarity of this disease, large studies examining or comparing therapeutic modalities do not exist in the literature. Studies using intraperitoneal chemotherapy alone (cisplatin or cisplatin and mitomycin C) have shown modest clinical responses and improvements in ascites but have failed to demonstrate a survival benefit.[25,26] Markman et al. reported 47% palliation of ascites and a median survival of 9 months in 19 patients who were treated with intraperitoneal cisplatin and mitomycin C.[26] Antman et al. employed multimodality therapy that consisted of surgical debulking, intraperitoneal doxorubicin, and cisplatin, followed by 3000 rad whole abdominal radiation in highly selected patients (those with residual nodules smaller than 1cm in diameter after surgical resection).[12] Whereas similar stage patients who only received either intravenous or intraperitoneal chemotherapy had a median survival of 15 months, those undergoing successful surgical debulking, intraperitoneal chemotherapy, and abdominal radiotherapy were all alive from 9 to 34 months posttreatment. This result suggested that both surgical debulking to minimal residual disease and intraperitoneal therapies are critical for effective treatment of peritoneal mesothelioma.

For this reason, CHPP with cytotoxic chemotherapeutic agents seems to be an attractive regional treatment option for peritoneal mesothelioma. It is a therapy that can be used in conjunction with major surgical procedures and delivers high regional concentrations of chemotherapy with synergistic and tumoricidal hyperther-

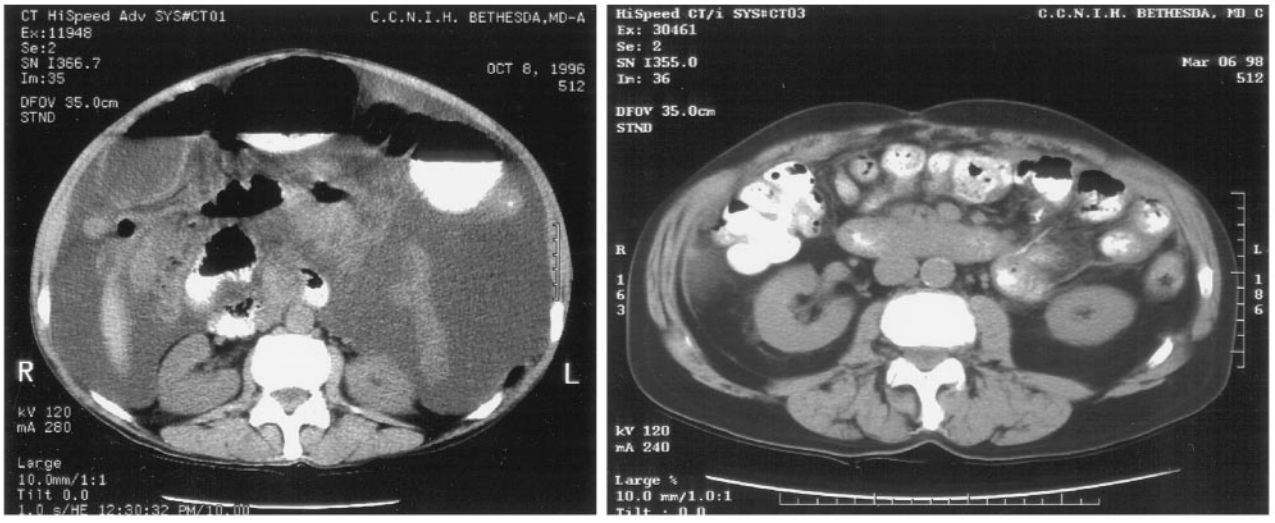

FIG. 2. CT scan demonstrating massive ascites (left panel) in a patient before CHPP. After treatment, using CHPP with cisplatin (300 mg/m^2), the patient shows no evidence of ascites at the 18-month follow-up scan (right panel).

mia to the complex surface of the peritoneal cavity. A variety of investigators have used CHPP to treat or provide prophylaxis against peritoneal carcinomatosis from gastrointestinal malignancies.[15–18,27,29] We have previously reported results of a phase I trial of CHPP with cisplatin and TNF. The MTD of cisplatin alone was 300 mg/m^2, with dose limiting renal toxicity. The MTD for cisplatin + TNF was 250 mg/m^2 CDDP + .1mg TNF. It did not seem that the TNF response at this low dose was significant, yet it added to cisplatin renal toxicity; so we have subsequently dropped TNF from the treatment regimen. We are now in the process of completing a phase I trial that examines the toxicity of early postoperative dwell therapy with escalating-dose 5-FU and paclitaxel after CHPP with cisplatin (250 mg/m^2). This trial is actively accruing patients. Whereas cisplatin is a well-suited drug to use in this setting because of its minimal regional toxicity and advantageous intraperitoneal pharmacokinetic profile,[30] it also has marked synergy with hyperthermia.[31] It has been used in trials against mesothelioma because of its known activity against epithelial malignancies, and investigators have reported responses with systemic CDDP. We feel that it is also worthwhile to take advantage of its synergy with 5-FU and paclitaxel, and that is why we have added early postop intraperitoneal dwell therapy.[32]

An advantage to CHPP over other regional approaches in the treatment of peritoneal mesothelioma is that it does not significantly prolong the hospitalization over what would be expected with surgical debulking. It is a 90-minute treatment while the patient is under anesthesia. It does not require long-term treatment courses as one would expect with radiotherapy and long-term intermittent intraperitoneal-dwell chemotherapy, which have a marked impact on quality of life issues. The therapy was well tolerated by the patient population. There was no operative mortality, and there was an acceptable morbidity rate of 24%, given that a wide range of surgical resections were performed, including a distal pancreatectomy, two major bowel resections, and five splenectomies. The major toxicity was systemic renal impairment at toxic doses of cisplatin. It should be noted that the six most recently treated patients each received a CDDP dose of 250 mg/m^2, and only one patient had transient grade 3 renal toxicity. None of the patients experienced significant regional toxicity, which includes those receiving escalating doses of intraperitoneal 5-FU and paclitaxel.

We have previously reported our early experience of CHPP for the treatment of malignant peritoneal mesothelioma.[19] We showed that CHPP could be performed with minimal morbidity and toxicity, and that at a median follow-up time of 10 months, 8 of 10 patients had no symptoms and no identifiable disease clinically or radiographically. Here we have updated the courses of patients reported previously, as well as the results of the subsequent treatment of eight additional patients with malignant peritoneal mesothelioma. This series of 18

patients (21 evaluable treatments) is one of the largest in the literature and confirms and extends the initial conclusions regarding its efficacy. All patients underwent exploratory laparotomy and attempted surgical debulking to minimal residual disease followed by CHPP. The three patients with bulky residual disease after debulking developed progressive disease despite CHPP and died of disease at 4, 12, and 13 months after treatment. The remaining patients remain alive at a median follow-up time of 19 months. This finding supports the notion that patients with small volume disease are best suited for intraperitoneal therapy.[2,20,33]

The median progression-free survival of 26 months and overall 2-year survival rate of 80% are among the best reported to date for this terminal disease. In addition, 9 of 10 patients (12 of 13 treatments) received palliation of intractable, symptomatic ascites present before treatment (including two patients who eventually died of recurrent peritoneal disease). Re-treatment may be effective because it is unlikely that significant resistance to therapy will develop after a single intensive treatment. The lack of a control group, and reports of long-term spontaneous remissions in peritoneal mesothelioma,[34,35] make conclusions regarding survival advantage over surgical debulking alone impossible. Given these initial encouraging results and the minimal toxicity, we plan to begin a formal phase II trial of CHPP with early postoperative dwell chemotherapy for peritoneal mesothelioma. Ultimately, a phase III trial will be necessary to define survival advantage over surgery alone.

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