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Intraperitoneal cisplatin and etoposide in peritoneal mesothelioma: favorable outcome with a multimodality approach

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Abstract. Ten patients with histologically documented peritoneal mesothelioma were treated with intraperitoneal cisplatin 200 mg/m^2, sodium thiosulfate rescue and etoposide 65–290 mg/m^2 every 4 weeks for a maximum of six cycles. All had epithelial or mixed epithelial-fibrous histology. Toxicity was tolerable, with 50% sustaining grade 3 or 4 granulocytopenia. There was one episode of neutropenic fever. Grade 2 peripheral neuropathy occurred in one patient, grade 1 in five patients. Complete remission occurred in one of five patients with measurable disease. Median survival for patients whose tumors were surgically debulked to <2 cm residua prior to treatment was 22 months, while it was 5 months for those with measurable, surgically inaccessible disease (P = 0.0731 by Cox regression proportional hazard model). These data suggest that patients who present with resectable disease may benefit from an aggressive adjuvant approach. This possibility warrants prospective testing in a randomized clinical trial.

Introduction

Peritoneal mesothelioma is a rare malignancy, with some 400 new cases each year in the USA. It is linked to remote asbestos exposure and characterized by intraperitoneal spread, with late invasion of abdominal organs and eventual pleural extension [1, 13]. Median survival without treatment is usually less than 6–8 months, with the majority of sufferers dead within a year; most die as a result of malignant inanition and intestinal obstruction [13, 19].

No standard approach to treatment exists. As early as 1955, therapy with intraperitoneal ^{198}Au resulted in symptomatic improvement and prolonged progression-free survival [17]. Legha and Muggia summarized nine other cases of patients with peritoneal mesothelioma treated with colloidal ^{196}Au, two of whom were progression-free at 3.5 and 5 years [11]. In 1972, Rogoff et al. reported on three patients who survived 9 years or more after treatment with intraperitoneal ^{32}P and total abdominal irradiation [16]. To date, no standard chemotherapeutic manipulation for peritoneal mesothelioma has been identified, although intraperitoneal (IP) treatment with platinum-based regimens [2, 10] has produced prolonged progression-free survival, particularly in patients who have undergone surgical debulking of their tumors prior to treatment. Intraperitoneal treatment is a reasonable tactic, given this tumor's propensity for extending along peritoneal surfaces and the potential reduction in systemic toxicity using an IP approach [2, 7].

We have recently evaluated the pharmacokinetics and toxicity of etoposide by IP administration. The relative pharmacologic advantage (ratio of peritoneal to plasma area under concentration-time curve) for IP administration was 2.8 and was independent of dose; based on the high plasma protein binding of etoposide (94%) and its minimal protein binding in fluid instilled intraperitoneally, a theoretical pharmacologic advantage of 47 was postulated [14]. In combination with cisplatin (200 mg/m^2), etoposide is well tolerated, with a maximum tolerated dose (MTD) of $\leq$170 mg/m^2 and pharmacologic advantage of 3.6$\pm$2.0 [9], which is presumed to be several-fold greater in the presence of high protein binding in the circulation.

We report the results of IP therapy with cisplatin and etoposide administered monthly to patients with peritoneal mesothelioma, who were treated as part of a larger phase I study which included patients with a variety of intra-abdominal malignancies.

Materials and methods

Patient population. The patients reported here had a histologically documented diagnosis of abdominal mesothelioma; Eastern Cooperative Oncology Group (ECOG) performance status 0, 1, 2; creatinine clearance >50 ml/min or serum creatinine $\leq$1.5 mg/dl; adequate hematologic in-

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Table 1. Patient characteristics

No. of patients	10
No. of courses	
Two	2
Three	1
Four	2
Five	2
Six	3
Age (years)	
Median	61
Range	24–70
Performance status	
0	2
1	8
Sex	
Male	5
Female	5
Prior therapy	
None	4
Surgical debulking/MRD	4
Surgical debulking/MRD and IP cisplatin	1
Surgical resection with gross residia >2 cm	1

MRD, Minimal residual disease; IP, intraperitoneal

Table 2. Maximum toxicity experienced in any course (dose levels pooled ($n = 10$)

Toxicity	Grade				
	0	*1*	*2*	*3*	*4*
Gastrointestinal	3	1	6	0	0
Myelosuppression					
Leukopenia	4	2	1	3	0
Granulocytopenia	3	2	0	3	2
Thrombocytopenia	9	1	0	0	0
Neurotoxicity	4	5	1	0	0
Hearing loss	2	7	0	1	0

dices (WBC $\geq 3000/mm^3$, platelets $\geq 100\,000/mm^3$); adequate hepatic function (bilirubin, SGOT, and alkaline phosphatase <2 times upper limit of normal); >3 weeks elapsed interval from prior chemotherapy and/or radiotherapy; absence of active infection; and capacity to give informed consent in accordance with institutional and federal guidelines.

Treatment plan. Prior to treatment, an abdominal infusion port or semi-permanent indwelling Tenckhoff catheter was inserted in all patients. Before treatment, the abdominal cavity was drained, while patients were prehydrated with 3 l normal saline (NS) with 20–40 mEq KCl/l. One hour prior to cisplatin administration, sodium thiosulfate 3.3 gm/m^2 was given intravenously in 500 ml sterile water over 1 h, followed by 6.6 gm/m^2 intravenously in 500 ml sterile water over 2 hours. Thirty minutes before starting cisplatin, 12.5 g mannitol and 20 mg furosemide were given intravenously.

Cisplatin at a dose of 200 mg/m^2 and etoposide at escalating doses were admixed in 2 l 0.9% normal saline for IP instillation and administered over 2 h. The peritoneal cavity was not drained after chemotherapy instillation. Hydration was continued after treatment for 16–24 h. Appropriate antiemetics, including dexamethasone, lorazepam, diphenhydramine and metoclopramide, were administered just prior to cisplatin; the latter three agents were repeated two to three times every 3–4 hours after cisplatin.

Treatment was repeated at 4-week intervals for a maximum of six cycles. CT scans of the abdomen and pelvis and audiograms were obtained with each treatment, and peritoneal fluid when available, was examined pathologically for evidence of persistent mesothelioma. Standard ECOG response criteria were used [12]. Patients were removed from the study if progressive disease or unacceptable toxicity intervened. At the conclusion of treatment, all patients underwent periodical physical examination and CT scans of the abdomen and pelvis. They were also followed up for long-term adverse effects. Disease-free survival and overall survival were measured from the initiation of treatment.

Results

Patient characteristics

From 13 October 1987 to 21 August 1990, ten patients with pathologically documented diffuse peritoneal mesothelioma were enrolled in the study. None had evidence of hematogenous metastases, and only one had clinical pleural extension. Eight had epithelial histology and two had mixed epithelial-fibrous histology. Five had measurable disease on CT scan and were evaluable for objective response, while the other five patients had undergone laparotomy prior to study enrollment with debulking of peritoneal tumor, to <2 cm residual deposits, and did not have measurable disease (Table 1). All were evaluable for progression-free survival and overall survival. Ages ranged from 24 to 70 years (median 63.5 years). Except for one patient who had received one dose of IP cisplatin, none had received prior chemotherapy or radiation.

Patients received etoposide at various dose levels (Table 4) as part of a larger phase I study. Eight of ten received the MTD (170 mg/m^2) or more. Two to six cycles were administered to each patient (median five, total 43 cycles).

Table 3. Cycle-specific nadirs: all patients

Cycle	*n*	WBC nadir $\times 10^3/mm^3$ median (range)	ANC nadir median (range)	Platelet nadir $\times 10^3/mm^3$ median (range)
1	10	4.2 (1.1–6.3)	1856 (308–4524)	299 (79–653)
2	10	3.9 (1.9–6.2)	2184 (608–2892)	238 (136–418)
3	8	4.4 (2.4–8.8)	2094 (936–5104)	202 (145–330)
4	7	3.2 (2.2–6.8)	1422 (1070–3264)	176 (100–232)
5	5	2.9 (1.9–8.3)	1140 (874–5395)	217 (100–391)
6	3	3.7 (3.5–3.9)	1880 (1872–1908)	190 (177–207)

Table 4. Neurologic toxicity

Grade[a]	Neurosensory	Auditory
0	None	None
1	Mild paresthesias; loss of deep tendon reflexes	Asymptomatic hearing loss documented by audiometry only
2	Mild or moderate objective sensory loss; moderate paresthesias	Tinnitus
3	Severe objective sensory loss or paresthesias that inhibit normal function	Hearing loss interfering with function but correctable with hearing aid
4		Uncorrectable deafness

[a] Eastern Cooperative Oncology Group classification

Toxicity

The side effects observed in this study are summarized in Table 2. Myelosuppression was the principal toxicity; grade 4 granulocytopenia occurred, at or above the MTD of etoposide, in two patients; grade 3 granulocytopenia occurred in three patients. There was one episode of neutropenic fever in an elderly man who received 290 mg/m^2 during the first cycle. Thrombocytopenia was minimal or non-existent. Myelosuppression was not cumulative (Table 3). Treatment was given on schedule or, at most, with a 7- to 10-day delay. The etoposide dose was reduced in two patients by 50% during six cycles because of neutropenia. There were no other dose reductions due to myelosuppression.

Renal toxicity was non-existent. Gastrointestinal toxicity was mild, grade 1 or 2 at all dose levels. There were no episodes of grade 3 or 4 neurotoxicity. Grade 2 peripheral neuropathy occurred in one patient and grade 1 neuropathy in five patients (Table 4). Grade 1 asymptomatic hearing loss, documented by audiometry alone, occurred in seven patients, with cisplatin dose halved in two patients as a result. Grade 3 hearing loss, defined as auditory toxicity interfering with normal function, occurred in one patient, necessitating cessation of treatment. Peripheral neuropathy obligated removal of a second patient from the study after five cycles. A third patient refused a sixth cycle after receiving five cycles without significant toxicity. Four were removed from the study before receiving all six cycles because of death or disease progression. Three received a full six cycles, and then were observed off treatment.

Response and survival

Of five patients with measurable tumor, complete remission occurred in one patient, stable disease was noted in another, and disease progression occurred in two (Table 5). One patient died of a pulmonary embolus 6 weeks after protocol entry and was inevaluable for response although his initially malignant peritoneal cytology subsequently turned negative. The patient with complete response experienced resolution of abdominal pain, fevers, and hypoglycemia, with complete resolution of a diffuse peritoneal mass on CT scan by the fourth cycle. This patient remained in continuous clinical complete remission off treatment for 6 months after completion of protocol therapy before recurrence of the mesothelioma locally in the peritoneum. Subsequent treatment with intravenous (IV) carboplatin alone, carboplatin and etoposide, and weekly 5-fluorouracil infusion proved ineffective. The median event-free sur-

Table 5. Response and survival

Patient no.	Sex	Age (years)	Histology	Laparotomy/ residual tumor	Dose (mg/m^2) VP-16/DDP	Performance status	No. of cycles	Response	Survival (months)	
									Event-free	Overall
1	F	67	E	(+) NGR	65/200	0	4	NMD	40+	40+
2	F	24	E	(+) MRD	65/200	0	5	NMD	47+	47+
3	M	67	E	(+) BRD	290/200	1	6	CR	11	26
4	M	70	EF	(–)	170/200	1	2	PD	2	2
5	M	66	E	(–)	170/200	1	4	SD[a]	4	7
6	F	56	EF	(+) NGR	170/200	1	6	NMD	10	22
7	M	61	E	(–)	170/200	1	2	NE	1.5	1.5
8	F	44	E	(+) MRD	170/200	1	5	NMD[a]	7.5	9
9	F	38	E	(+) MRD	170/200	1	6	NMD	9	20
10	M	67	E	(–)	170/200	1	3	PD	2	5

E, Epithelial; F, fibrous; NGR, no gross residua following resection; MRD, minimal residual disease, $\leq$2 cm; BRD, bulky residual disease, >2 cm following resection; NMD, no measurable disease by physical exam or CT scan; CR, complete remission; SD, stable disease; PD, progressive disease; NE, not evaluable for response

[a] Decrease or resolution of ascites

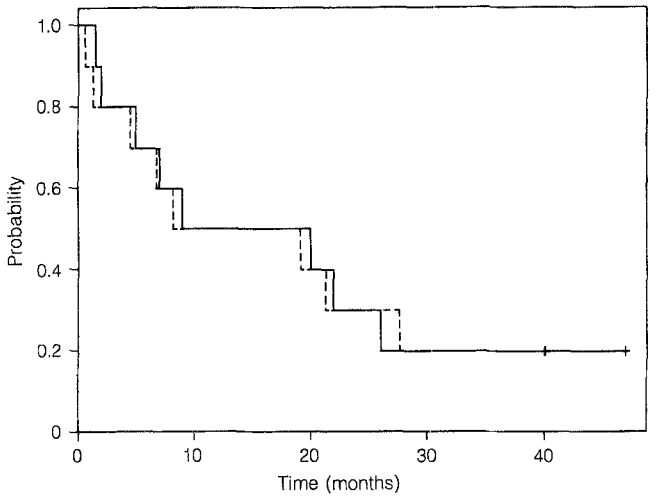

Fig. 1. Plot of observed (———) and expected (– – –) survival. The median survival for all patients with peritoneal mesothelioma was 14.5 months. Two patients, both free of clinical progression, were alive at 40 and 47 months

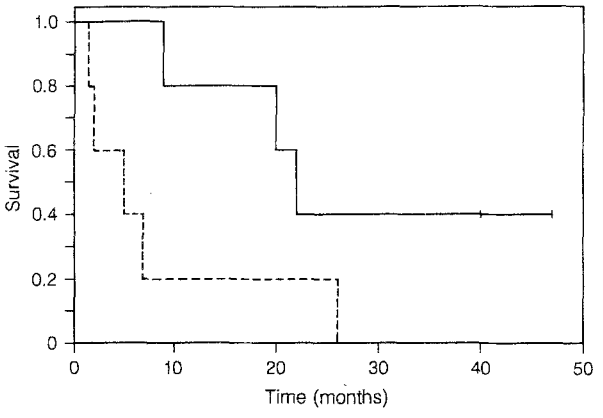

Fig. 2. Effects of surgical debulking on survival. The data set was too small to discern a significant difference in survival at $p \leq 0.05$ between patients who had undergone surgical debulking of their tumors (——) and those who had not (– – –)

vival (freedom from progression or time to death due to intercurrent illness) was 2 months for this group, with median survival of 5 months.

Five patients, all female, lacked measurable disease. Each had undergone laparotomy and surgical resection of grossly visible disease and their tumors were felt to be maximally debulked with <2 cm residual implants prior to IP therapy. At the time treatment was initiated, one had minimal ascites on CT scan and malignant peritoneal cytology, both of which resolved prior to the third cycle of IP therapy. Four others had negative CT scans prior to and during the course of treatment; peritoneal fluid for cytology either could not be aspirated through the abdominal infusion port or was not obtained in these four women. Median freedom from progression for this group was 9 months, with median survival of 22 months; at the time of writing two were still alive and free of disease at 40 and 47 months.

The data set was too small to allow multivariate analysis. By the Cox regression proportional hazard model, the difference in median survival between "debulked" and non-"debulked" patients was significantly only at the 10% level ($P = 0.0731$); the power was inadequate to detect a significant statistical difference at the 5% level. The median survival for the entire group ($n = 10$) was 14.5 months; the observed and expected survival plots are shown in Figs. 1 and 2.

Discussion

Peritoneal mesothelioma is a rare disease for which no "standard" therapy has yet been identified. The studies of Antman et al. [2] and Howell et al. [7] and the results of our study strongly suggest the potential benefit of combined modality treatment for peritoneal mesothelioma, particularly surgical debulking followed by IP cytoreductive modalities. All three studies used cisplatin-based regimens. Howell et al. demonstrated that cisplatin could be administered intraperitoneally without local toxicity, that this route was pharmacokinetically advantageous, with 15-fold greater exposure for the peritoneal cavity than with IV administration (defined as the ratio of peritoneal to serum blood concentration × time integrals) and that the concurrent infusion of sodium thiosulfate could further augment the therapeutic index by protecting against systemic toxicity. Howell et al. showed that in combination with IV thiosulfate, the dose of IP cisplatin could be escalated to 270 mg/m^2 body surface area without inducing untoward renal toxicity, myelosuppression or local symptoms. In deference to the addition of etoposide, and in recognition of the dose used by others [20], we empirically chose a fixed IP cisplatin dose of 200 mg/m^2 in conjunction with sodium thiosulfate.

In their phase I trial, Howell et al. reported a patient with peritoneal mesothelioma who responded to IV cisplatin and sodium thiosulfate rescue with resolution of ascites and an abdominal wall mass lasting 4 months until he was lost to follow-up [7]. In a subsequent phase II study, Howell's group reported on 19 patients with peritoneal mesothelioma who received IP cisplatin at a dose of 90–100 mg/m^2 weekly for 3 weeks, followed by a 3-week rest; 10 of 17 evaluable patients responded, including five with CR. Median survival was 12 months, with a range of 1–46 months [8]. Antman et al. showed that patients whose tumors were inoperable prior to IP therapy with cisplatin and doxorubicin did not respond to treatment and had a median survival of 17 months, while those whose tumors were surgically debulked prior to treatment were found to have a partial response by pathologic criteria at second-look laparotomy [2]. Four of six in the latter group, including three who subsequently received whole abdominal irradiation, were alive and well 3 years or more after initial diagnosis. In our study, four of five patients whose tumors were surgically debulked survived 18 months or

more, and two were alive and free from progression at 40 and 47 months respectively.

If the results of our study are pooled with the findings of Antman et al., patients who receive IP therapy after surgical debulking have a median survival in excess of 3 years, while those with bulky measurable disease invariably die within 3 years. The same survival pattern has been observed in ovarian cancer, with a clear dichotomy between patients with surgically debulked minimal residual disease and those with inoperable or bulky residual disease [4].

The role of aggressive treatment in determining the outcome of patients with favorable prognostic factors cannot be determined from these results. However, in our trial an administered cisplatin dose intensity of 200 mg/m^2/4 weeks in conjunction with IV sodium thiosulfate exhibited tolerable toxicity. Although there is no evidence that this dose is therapeutically superior to lower doses of IP cisplatin without thiosulfate, it is clear experimentally that sodium thiosulfate can provide protection against certain toxic effects of intracavitary cisplatin [6, 7]. This aggressive chemotherapy regimen, therefore, is appropriate for further investigation as an adjunct to surgery. Based on the survival data, a phase III collaborative multigroup trial comparing surgical debulking plus adjuvant postoperative IP therapy with surgical debulking alone should be conducted, although the definition of optimal surgical debulking in peritoneal mesothelioma remains unclear and the limited number of patients with this diagnosis may preclude such a randomized study.

Finally, the improved survival of women, compared with men, in our study is curious. It may be serendipitous, reflecting the more aggressive surgical approach that happened to be used for the women, most of whom were thought initially to have ovarian carcinoma, although outside pathologic review in four of five cases subsequently confirmed mesothelioma and excluded ovarian or primary peritoneal adenocarcinoma. Alternatively, it may be due to an intrinsic biologic difference that histology or surgical status alone cannot define. Cytogenetic studies of peritoneal mesothelioma, as yet in their infancy, may reveal alterations that could potentially predict outcome and provide new insight regarding proper treatment [3, 5, 15, 18].

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