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Efficacy of cisplatin-based intraperitoneal chemotherapy as treatment of malignant peritoneal mesothelioma

Maurie Markman and David Kelsen

The Breast/Gynecology Oncology Service and the Gastrointestinal Oncology Service, Division of Solid Tumor Oncology, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, New York, USA

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Summary. In an effort to examine the potential clinical utility of intraperitoneal (i.p.) therapy in the management of patients with malignant peritoneal mesothelioma, 19 individuals with this disease were treated with a cisplatin-based i.p. treatment regimen. All but 1 patient also received i.p. mitomycin. The treatment was generally well tolerated, although a maximum of only four or five courses of cisplatin (100 mg/m^2 every 28 days) and mitomycin (5–10 mg/treatment given 7 days after each i.p. cisplatin administration) could be administered, the treatment principally being stopped because of disease progression or catheter failure. Of 15 patients with malignant ascites, 7 (47%) experienced control of fluid reaccumulation ranging from 2 months to 73+ months (median 8 months). While the median survival for the 19 patients was only 9 months, 4 (21%) patients survived for more than 3 years from the initiation of therapy, and 2 patients are currently alive and clinically disease-free more than 5 years from the start of the i.p. treatment program. We conclude that a subset of patients with peritoneal mesothelioma, principally those with small-volume residual disease following surgical tumor debulking, can benefit from a cisplatin-based i.p. treatment strategy with control of ascites and prolonged disease-free survival.

Key words: Peritoneal mesothelioma – Intraperitoneal chemotherapy – Cisplatin – Mitomycin

Introduction

Peritoneal mesothelioma is an uncommon malignancy that has been considered to have an almost universally unfavorable clinical outcome (Antman et al. 1983). There are no firmly established effective therapeutic options for individuals with this cancer. Because of its anatomical location, investigators at a number of centers have begun to explore the use of intraperitoneal chemotherapy in the management of this disease. Several reports have suggested that patients with peritoneal mesothelioma can achieve objective antitumor responses and experience prolonged survival following treatment with this therapeutic strategy (Antman et al. 1985; Kirmani et al. 1988; Lederman et al. 1987; Markman et al. 1986; Markman and Kelsen 1989; Pfeifle et al. 1985).

Over the past 7 years we have treated patients with peritoneal mesothelioma at our institution on an experimental intraperitoneal program employing cisplatin and mitomycin (Markman and Kelsen 1989), two drugs with documented modest single-agent activity in malignant mesothelioma when administered systemically (Bajorin et al. 1987; Mintzer et al. 1985). In our initial report of the results of this trial, objective antitumor responses (principally control of malignant ascites) were observed, with several patients experiencing prolonged survival (>2 years) following intraperitoneal chemotherapy initiation (Markman and Kelsen 1989).

In the current paper we report the results of intraperitoneal therapy for an expanded patient population and provide an additional 3-year follow-up for the patients included in our initial publication describing this therapeutic regimen.

Materials and methods

Protocol entry criteria. Patients entered into this trial had to have a histologically confirmed diagnosis of malignant peritoneal mesothelioma. Patients with evidence of pleural involvement with tumor were eligibile for protocol entry if the major clinical manifestations of their disease involved the peritoneal cavity. While the protocol was initially limited to patients with measurable disease, the trial was subsequently modified to allow patients without measurable disease to be trated with this regimen. Patients without measurable disease were followed for survival.

Laboratory requirements for protocol entry included: white blood cell count $\geq 3000/mm^3$, platelet count $\geq 100\,000/mm^3$, serum creatinine ≤ 1.5 mg/100 mg, creatinine clearance >60 ml/min, and serum bilirubin <2.0 mg/100 mg. Patients were required to have a

Offprint requests to: M. Markman, Department of Medicine, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021, USA

Karnofsky performance status of at least 60, clinically normal hearing, and a life expectancy of at least 6 weeks. Finally, patients were required to sign an informed consent statement indicating they were aware of the investigational nature of the treatment program.

Drug dosages and treatment schedule. The cisplatin was delivered by the intraperitoneal route at a dose of 100 mg/m^2 in 2 l normal saline. Treatment with cisplatin was repeated on a 21- to 28-day schedule, depending on recovery from the toxicities of the previous treatment cycle. One week after each cisplatin instillation, mitomycin was administered intraperitoneally in 2 l normal saline. The initial dose of mitomycin was 5 mg for all patients. If there was no significant abdominal pain noted (i.e., no requirement for narcotic analgesia and pain lasting less than 72 h) following the first course of intraperitoneal mitomycin, subsequent courses were administered at a dose of 10 mg in the 2-l treatment volume. The treatment protocol allowed for a maximum of eight treatment courses (16 total intraperitoneal chemotherapy instillations).

Protocol modifications for toxicity included 50% reduction in cisplatin and mitomycin dose for a white blood cell count of 2500–3000/mm^3 or platelet count of 80000–100000/mm^3 on the day of 1.6–2.0 mg/100 mg on the day of therapy. If the white blood cell count was below 2500/mm^3, the platelet count below 80000/mm^3, or serum creatinine above 2.0 mg/100 mg on the day of treatment, therapy was withheld until the laboratory parameters returned within the range where treatment was permitted.

For the cisplatin courses only, patients were hydrated with dextrose 5½ NS plus 20 mequiv KCl/l at 175 ml/h. This infusion was begun the night prior to cisplatin administration. In addition, mannitol (12.5 g) was delivered by intravenous push at the time of cisplatin instillation. This bolus of mannitol was followed by an intravenous infusion of the agent (20% solution at 50 ml/h, 10 g/h for 6 h).

The toxicity of this treatment protocol was evaluated utilizing the World Health Organization (WHO) toxicity scale.

Peritoneal cavity access. All patients entered into this trial had a surgically implanted semi-permanent intraperitoneal catheter (Tenckhoff type) through which the intraperitoneal treatments were administered. In most patients this catheter was attached to a subcutaneous portal delivery system (Port-a-Cath, Pharmacia Nu-Tech, Piscataway, N.J., USA).

Response criteria. Where measurable disease was present standard response criteria were employed (Miller et al. 1981). Complete response was defined as the disappearance of all clinical evidence of active malignancy, including any cancer-related symptoms, for a minimum of 4 weeks. Partial response was defined as at least a 50% decrease in the sum of the products of the two greatest perpendicular diameters of the index lesions(s) lasting at least 4 weeks.

In patients with malignant ascites as the only clinical manifestation of active cancer, a clinical response was defined as a major reduction in the amount of ascites, determined either by physical assessment or computed tomography scan findings. The improvement had to persist for a minimum of 4 weeks for the patient to be considered to have achieved a clinical response.

The duration of response and survival on this protocol were determined from the date of initiation of the intraperitoneal program.

Results

Patient characteristics

A total of 19 patients have been entered into this trial examining intraperitoneal cisplatin and mitomycin in the treatment of malignant peritoneal mesothelioma since it opened in August 1985 (Table 1). One additional patient was diagnosed as having peritoneal mesothelioma just prior to the initiation of this protocol and was treated with intraperitoneal cisplatin (100 mg/m^2) only on a 21- to 28-day cycle. The clinical information generated from this patient's treatment was included in our previous analysis and will be included in this report because of the very limited information available in the oncology literature concerning the therapeutic effectiveness of this or any other treatment strategy in peritoneal mesothelioma.

As noted in our previous report, 1 of the 19 patients entered into this trial was subsequently found at a repeat laparotomy to have ovarian cancer. This patient has not been included in the analysis of efficacy but will be included in the evaluation of toxicity of the treatment program.

Table 1. Patient characteristics

Patients treated with intraperitoneal therapy ($n=20$)	
Sex	Male 13; female 7
Age (years)	Median 54; range 22–75
KPS[a]	Median 70; range 50–90
Patients with peritoneal mesothelioma ($n=19$)	
Number receiving prior chemotherapy	3 (16%)
Number with ascites	15 (79%)

[a] KPS, Karnofsky performance status

Table 2. Reasons for discontinuation of therapy

Reason	Number of patients
Progression of disease	8
Catheter failure	6
Patient preference	2
Systemic cisplatin toxicity	2
Bacterial peritonitis	1
Abdominal pain	1

Toxicity

A total of 127 treatment instillations (66 with cisplatin, 61 with mitomycin) were administered to the 20 patients undergoing therapy with this investigational strategy. The median number of courses per patient was four (range of one to seven). One patient had therapy initiated at a cisplatin dose of 50 mg/m^2, secondary to concern for his medical condition. No patient required dose modifications for bone marrow suppression, gastrointestinal dysfunction, renal or neurological toxicity. All patients eligible to receive a second dose of mitomycin had the dose successfully raised to 10 mg. Of the 20 patients, 2 (10%) experienced an episode of bacterial peritonitis. In 1 of the 2 patients the catheter was changed and therapy was able to be resumed. In the second case the catheter was removed and intraperitoneal treatment stopped.

The reasons for discontinuation of therapy in the 20 patients are outlined in Table 2. It should be noted that only 1 patient was able to receive more than five courses

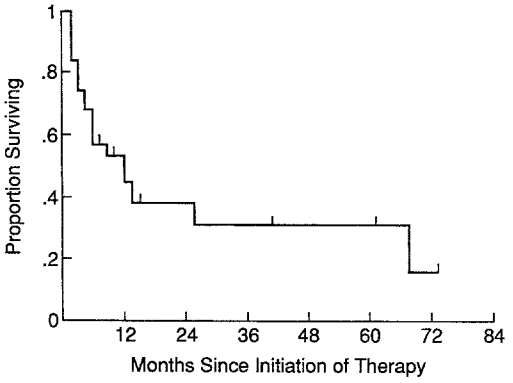

Fig. 1. Survival of 19 patients with peritoneal mesothelioma treated with intraperitoneal cisplatin-based therapy

of therapy even though the protocol allowed for up to eight courses in responding patients. As Table 2 demonstrates, there were several reasons why therapy could not be continued beyond four or five courses. The most common explanations for treatment discontinuation were disease progression and catheter failure, principally due to mitomycin-induced adhesion formation.

Responses

No patient demonstrated evidence of shrinkage of a palpable intra-abdominal mass. All patients who ultimately progressed did so initially in the abdominal cavity.

Of the 15 patients with peritoneal mesothelioma and clinically evident ascites at the initiation of the intraperitoneal chemotherapy program, 7 (47%) demonstrated evidence of a clinical response. Of the 2 patients with ascites who had previously received chemotherapy before the intraperitoneal program, neither responded to this regional treatment regimen. The duration of control of ascites in the 7 responding patients ranged from 2 months to 73+ months (median 8 months).

Survival

The actuarial median survival of the 19 patients with malignant peritoneal mesothelioma treated on this trial was 9 months (Fig. 1). The median follow-up from the initiation of therapy for the 6 patients currently alive is 25+ months (range 7+ to 73+ months). Four patients (21%) survived for more than 3 years from the start of therapy, with 2 patients presently clinically free of disease more than 5 years following institution of this treatment program.

Discussion

In this trial we have demonstrated that a subset (approximately 20%) of patients with malignant peritoneal mesothelioma can achieve long-term disease-free survival following treatment with a cisplatin-based intraperitoneal chemotherapy program. Despite the long-term follow-up of patients treated on this clinical study, it remains uncertain if any of the patients treated with this regimen are actually "cured" of their disease. Even longer evaluation of the surviving patient population (>8–10 years) will be required to address this important point, definitively.

As two of the longest survivors in our study were female, it can appropriately be questioned whether these patients actually had ovarian cancer rather than malignant mesothelioma. This is a particularly relevant point as cisplatin is a very active drug in ovarian cancer (60% –80% objective response rate) (Ozols and Young 1987). While the differentiation of these two conditions can be difficult, as demonstrated by the fact that one of our "responding" patients had an initial diagnosis of mesothelioma changed to ovarian cancer when a larger tissue sample was available at the time of an exploratory surgery, review of the long-term survivors confirms the diagnosis of mesothelioma.

Objective responses of bulky intra-abdominal mesothelioma were not observed in this trial. This observation is in complete agreement with experimental data demonstrating that the actual depth of penetration of cytotoxic agents (including cisplatin) directly into tumor or normal tissue is quite limited, perhaps of the order of 0.1 mm to 1–2 mm from the surface (Los et al. 1989; Ozols et al. 1979). In patients with ovarian cancer, where there is considerably more experience with cisplatin-based intraperitoneal therapy, objective antitumor responses are rarely observed in patients with any mass lesion above 0.5–1 cm in maximal diameter (Markman et al. 1991).

Thus, it would be anticipated, and the results of this trial confirm, that any major benefit to be obtained from the intraperitoneal administration of cytototoxic agents in patients with malignant peritoneal mesothelioma will be principally limited to those individuals with small-volume residual disease when treatment is initiated. These data provide support for the suggestion that there may be a role for aggressive tumor debulking in patients with malignant peritoneal mesothelioma being considered for an intraperitoneal chemotherapy program, as most patients with this disease will have significant tumor bulk at initial diagnosis. Patients with bulky residual disease and ascites as their major clinical problem may benefit symptomatically through the use of the intraperitoneal route of drug delivery, but the responses will generally be of short duration and the overall impact of the treatment approach on survival will likely be quite limited.

As malignant peritoneal mesothelioma is an uncommon condition, it is not realistic to ask or require that a randomized controlled clinical trial be conducted to compare a cisplatin-based intraperitoneal chemotherapy regimen to alternative treatment options in the disease. Even at Memorial Hospital, an institution with an established record of seeing large numbers of cancer patients with uncommon tumor types, we only entered 19 patients with malignant peritoneal mesothelioma into this trial in more than 6 years.

Thus, in the absence of a controlled clinical trial defining the true benefits of the regional administration of cytotoxic chemotherapy in malignant peritoneal mesothe-

lioma, we are left with the following conclusions. First, objective anti-neoplastic responses, principally control of malignant ascites accumulation, can be observed following intraperitoneal chemotherapy with a cisplatin-based treatment program. Second, while these responses may result in significant palliation of symptoms, they are generally of short duration (<8–10 months), particularly in individuals with bulky residual disease. Third, in patients with bulky residual disease there will be little or no impact of intraperitoneal therapy on overall suvival. Thus, in patients with malignant peritoneal mesothelioma, strong consideration should be given to tumor debulking, if technically feasible, prior to the institution of an intraperitoneal chemotherapy regimen. Finally, a subset of patients with peritoneal mesothelioma can be anticipated to experience long-term disease-free survival (>5 years) following treatment with a cisplatin-based intraperitoneal chemotherapy regimen. Unfortunately, an optimal treatment program for this disease remains to be defined.

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