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Intraperitoneal Chemotherapy for Malignant Peritoneal Mesothelioma

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4 patients with malignant peritoneal mesothelioma have been treated with intraperitoneal chemotherapy in the Netherlands Cancer Institute in the recent years. 1 patient achieved a complete remission for 36+ months and another patient had a partial remission that lasted for 10 months. Intraperitoneal chemotherapy alone or in combination with other treatment modalities may yield a response rate of 58% with 24% complete remissions in 70 patients reviewed in the literature. Although these data should be considered wtih caution because of the heterogenicity of the patient group treated, cisplatin-based intraperitoneal chemotherapy seems to be the best available treatment for malignant peritoneal mesothelioma at present.
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INTRODUCTION

PRIMARY MALIGNANCIES of the mesothelium, the lining of the pleura, peritoneum, pericardium and tunica vaginalis are rare. Malignant mesothelioma commonly involves the pleura, but in 10–20% of cases the disease is confined to the peritoneal cavity [1, 2]. The observed increased incidence of malignant mesothelioma in the past decades is most likely the result of the widespread exposure to industrial products such as asbestos [1, 3–5]. The reported percentage of asbestos exposure in patients with malignant mesothelioma varies highly depending on the demographic variables of the patient groups studied. Cohort studies in asbestos workers demonstrate a calculated death risk due to mesothelioma of up to 10%, with a latency of 30–40 years after exposure [6].

For malignant peritoneal mesothelioma other risk factors such as abdominal irradiation, exposure to a variety of toxic agents or recurrent peritonitis have occasionally been implied [4, 5]. Usually, malignant peritoneal mesothelioma presents with vague abdominal complaints, abdominal swelling, pain, weight loss and fever of unknown origin [1, 3]. Since conventional radiological examination and computed tomography are non-specific, laparoscopy or laparotomy is often needed to establish the diagnosis. The histological pattern of malignant mesothelioma ranges from the most frequently encountered epithelial type to more sarcomatous forms [1, 3, 5]. Therefore immunohistochemical assays, demonstrating the co-expression of vimentin, keratins and epithelial membrane antigens are often necessary to establish the diagnosis [7].

The prognosis of malignant peritoneal mesothelioma is even worse than that of pleural mesothelioma with a mean reported survival of less than 12 months [4]. The response rates to single agent or combination chemotherapy do not exceed 30% in most reported series [4]. Combination of the various treatment modalities with intracavitary application of radioactive or cytostatic agents may yield significant response rates in patients with malignant peritoneal mesothelioma with long-term survival in some cases [4, 8, 9]. In this paper we present data of 4 patients with malignant peritoneal mesothelioma treated with intraperitoneal chemotherapy in our institute over the recent years, with a review of the literature.

CASE REPORTS

Case 1 (55 years, male). He had previous short-term asbestos exposure, and malignant epithelial mesothelioma was diagnosed at exploratory laparotomy for unexplained right upper abdominal pain and 5 kg weight loss. After cholecystectomy for tumour infiltration in the wall of the gallbladder, diffuse peritoneal involvement remained. Because of rapidly progressive ascites 25 mg/m^2 mitoxantrone was intraperitoneally administered through a Tenckhoff catheter, despite the presence of pleural thickening on the chest X-ray. After three 3-weekly courses that were complicated by transient peritoneal irritation, the treatment was discontinued because of rapid progression. 8 weeks later the patient died, 6 months after the initial diagnosis.

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Case 2 (56 years, male). He presented with abdominal distension with an elevated erythrocyte sedimentation rate (69 mm/h) and a small amount of ascites. Cytology of the ascites was tumour positive. Radiological examination of the alimentary tract revealed no abnormalities. At exploratory laparotomy, omentectomy was performed because of diffuse infiltration of a malignant epithelial papillary mesothelioma, after which diffuse peritoneal involvement remained. Cytology of the peritoneal fluid was still tumour positive after four courses of intraperitoneal cisplatin (60–120 mg/m^2) and three courses of intraperitoneal mitomycin (12 mg/m^2), and treatment with intraperitoneal carboplatin (400 mg/m^2) was started. The third 4-weekly course was complicated by a conservatively treated intra-abdominal hemorrhage. At second-look laparotomy, cytology of the peritoneal washing was tumour negative and only a few histologically confirmed tumourspots (> 50% tumour regression) were noted. We assume that the partial remission was the result of longstanding platinum exposure after both intraperitoneal cisplatin (in a small dose) and intraperitoneal carboplatin. The Tenckhoff catheter was removed as it was embedded in adhesive small bowel loops with pathologically confirmed peritoneal fibrosis. The partial remission lasted for 10 months, when ascites reoccurred. Because of the abdominal adhesions and loculation of the ascites, carboplatin (400 mg/m^2) was administered intravenously. After 6 monthly courses, CT of the abdomen revealed complete disappearance of the ascites, and the patient remained in good clinical condition for 35 months. Despite intravenous administration of 11 courses of 5-fluorouracil (800 mg/m^2) plus leucovorin (80 mg/m^2), and two courses of carboplatin (400 mg/m^2) for intramural gastric infiltration and palpable masses in the abdominal wall, the patient died with signs of intestinal obstruction and tumour-positive ascites, almost 7 years after the initial diagnosis.

Table 1. *Intraperitoneal chemotherapy with cytostatics alone for malignant peritoneal mesothelioma*

Drug(s)	No.	Responses			Ref.
		CR	PR or SR	NR	
MX	1		1		11
CDDP + MMC	10				
CDDP	1	1	5	5	12
CDDP	22	6	5	11	13–17
CDDP + ARAC	1			1	18
CDDP + CYC	1	1			
CDDP + ADM	2		1	1	8
5-FU + LV	2		1	1	19
CYC	1			1	20
ARAC	1			1	21
MX	1			1	Case 1
JM8*	1		1		Case 2
MX	1	1			Case 3
CDDP†	1		1		Case 4
Total	46	9	15	22	

*After failure of intraperitoneal cisplatin and intraperitoneal mitomycin.
†After failure of intraperitoneal plus intravenous LV + 5-FU.
CR = complete remission, PR = partial remission, SR = symptomatic relief, NR = no response, MX = mitoxantrone, CDDP = cisplatin, MMC = mitomycin, ARAC = cytarabine, CYC = cyclophosphamide, ADM = doxorubicin, 5-FU = 5-fluorouracil, JM8 = carboplatin.

Table 2. *Combined intraperitoneal therapy for malignant peritoneal mesothelioma*

Drug(s)	No.	Combined	Responses			Ref.
			CR	PR or SR	NR	
CDDP + ADM	3	RT	1	2		
CDDP + ADM	2	RT + IV		1	1	
ADM	1	RT + IV			1	8
CDDP + ADM	3	RT + S	3			
CDDP + ADM	2	RT + S + IV	2			9, 22
CDDP + ADM	9	RT	1	6	2	23
CDDP	1	IV	1			24
CYC	3	IV or PO			3	20
Total	24		8	9	7	

RT = radiotherapy, S = surgery, IV = intravenous cytostatics, PO = oral cytostatics.

Case 3 (44 years, male). He was admitted because of abdominal pain and 5 kg weight loss. Radiological examination of the gastrointestinal tract was normal, but ultrasound examination revealed ascites. At laparoscopy multiple spots of malignant epithelial papillary mesothelioma were seen with a maximum diameter of 2 mm. After six 3-weekly intraperitoneal courses of 25 mg/m^2 mitoxantrone, second-look laparoscopy revealed blue discoloration of the peritoneum without histologically confirmed malignancy. After one additional course, the treatment was discontinued because of severe but transient peritoneal irritation. During the following months the serum level of CA-125 gradually decreased from 520 U/ml to 20 U/ml (normal below 35 U/ml). The patient remained well until 22 months after the last cytostatic treatment, when abdominal cramps, nausea, vomiting and weight loss occurred with associated rise of the serum CA-125 level to 105 U/ml. CT of the abdomen showed thickened bowel loops and an upper gastrointestinal series revealed dilated small bowel loops due to a localised jejunal stenosis. At laparotomy for progressive intestinal obstruction extensive adhesive fibrosis of the parietal and visceral peritoneum was observed. No localised anatomic stenosis was found, and careful adhesiolysis was performed. Multiple biopsies showed extensive fibrosis without signs of malignant mesothelioma. The patient experienced an excellent symptomatic relief of the abdominal complaints with a normalisation of the serum CA-125 level and is still in complete remission, 36+ months after the initial intraperitoneal treatment.

Case 4 (53 years, male). He presented with unexplained lower abdominal complaints, low grade fever and 10 kg weight loss. At exploratory laparotomy for a thickened mesenterium demonstrated on CT of the abdomen, a small amount of tumour positive ascites was found with diffuse involvement of omentum and peritoneum of a malignant epithelial mesothelioma. After 8-weekly courses of 5-fluorouracil (400 mg/m^2 intravenously plus intraperitoneally) and leucovorin (80 mg/m^2 intravenously plus intraperitoneally) second-look laparoscopy showed no changes. Four 3-weekly courses of intraperitoneal cisplatin (120–200 mg/m^2) resulted in a markedly improved clinical condition with a 5 kg weight gain. A (non-measurable) tumour regression was noted on CT of the abdomen and two additional intraperitoneal cisplatin courses were administered.

DISCUSSION

These 4 cases clearly demonstrate the non-specific signs and symptoms of malignant peritoneal mesothelioma. Because the patients had non-bulky disease with only peritoneal involvement they were considered good candidates for intraperitoneal chemotherapy. 1 patient (case 3) is still in a pathologically confirmed complete remission for 36+ months after seven intraperitoneal courses of mitoxantrone, and another patient (case 2) had a documented, by laparotomy, partial remission for 10 months after four intraperitoneal courses of carboplatin. A 3rd patient (case 4) experienced an excellent symptomatic relief with documented tumour regression after 4 intraperitoneal courses of cisplatin.

For pharmacological reasons it is attractive to administer drugs such as 5-fluorouracil, cytarabine, cisplatin, doxorubicin and mitoxantrone intraperitoneally, especially in patients with minimal peritoneal involvement [10]. Because of the low peritoneal adsorption of these agents, intraperitoneal administration of relatively high doses result in high and longstanding cytotoxic concentrations in the peritoneal fluid without significant systemic toxicity.

In malignant peritoneal mesothelioma, intraperitoneal administration of various cytostatic agents alone (Table 1) or combined with other treatment modalities (Table 2) may yield a response rate of 58% (41/70) with 24% (17/70) reported complete remissions of sometimes long duration [8, 9, 11–24]. Only 4 of the complete remissions have been pathologically confirmed (Refs 15, 23, 24 and case 3 in this study). These figures favourably contrast with the poor results of intracavitary cytostatic treatment of malignant pleural mesothelioma [17]. The reported response rates, however, should be interpreted with caution because in most reports the remission criteria and the stage of disease were ill defined. Furthermore, the data presented in Table 2 are collected from phase I, phase II and retrospective studies or isolated case reports. In addition, the dosage of the agents and the number of courses are highly variable or even not clearly stated. Nevertheless, the data suggest that intraperitoneal chemotherapy alone or in combination with other treatment modalities is more effective than systemic treatment [4, 25–30]. In view of a response rate of 63% (37/59 patients), therapeutic regimens based on intraperitoneal cisplatin seem to be the best treatment for malignant peritoneal mesothelioma to date.

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