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TREATMENT OF PRIMARY OR METASTATIC PLEURAL EFFUSION WITH INTRACAVITARY CYTOSINE ARABINOSIDE AND CISPLATIN

A phase II study

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Thirty-three patients with microscopically verified primary or metastatic malignant pleural effusion were studied: 7 had malignant mesothelioma and 26 metastatic pleural disease. The treatment was based on biochemical and clinical studies which show a synergy between cytosine-arabinoside (Ara-C) and cisplatin. These drugs were instilled in the pleural cavity at the dose of 100 mg for Ara-C and 100 mg/m^2 for cisplatin. The cavity was drained after 4 h. If it was possible, the treatment was repeated weekly for 3 times and, after a 6-week rest, it could be started again with the same schedule. The overall response rate (complete plus partial remissions) was 74%. Toxicity was mild or moderate. We conclude that the combination of Ara-C and cisplatin is well tolerated and produces a high response rate in the treatment of malignant pleural effusions.

In experimental systems, cytosine-arabinoside (Ara-C), a cell-cycle phase-specific agent, has exhibited synergistic cytotoxicity with cisplatin, one of the most active drugs in the treatment of a broad spectrum of solid tumors (1). In a phase I clinical evaluation of Ara-C and cisplatin, Schilsky et al. (2) observed a 42% response rate after systemic administration in patients with non-small cell lung cancer. Markman et al. (3–5) achieved a high response rate in patients with malignant pleural effusions using a combination of Ara-C and cisplatin administered intrapleurally. When instilled into the pleural cavity, these drugs produce peak intracavitary levels that are many times greater than the plasma levels (6, 7) and, perhaps, there is the opportunity to take advantage of long-term exposure of tumor cells to these drugs with minor systemic toxicity. We have investigated the value of this kind of therapy in the treatment of malignant pleural effusions.

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Material and Methods

Thirty-three patients (14 men and 19 women) aged 37–78 (mean 61) were enrolled in this study: 7 had malignant mesothelioma and 26 metastatic pleural disease. All patients gave informed consent. All had histologically and/or cytologically confirmed malignant pleural effusion. Patients details are shown in Table 1.

Systemic chemotherapy was not administered during at least 4 weeks before and 4 weeks after the intrapleural therapy. Entry requirements also included performance status 0–2 according to Eastern Cooperative Oncology Group (ECOG), serum creatinine <15 mg/l, white blood cell count (WBC) $>4 \cdot 10^9$/l and platelet count $>120 \cdot 10^9$/l. Prior to beginning the intrapleural chemotherapy, evaluation included complete history, physical examination, chest x-ray, ECG, complete blood count and, serum biochemical screening profile. Serum WBC and platelet

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Table 1

Characteristics of the patients

Patient No.	Age (years)	Sex	Tumor type	Other tumor sites
1	44	F	Mesothel	-
2	59	M	Mesothel	-
3	53	M	Mesothel	-
4	68	M	Mesothel	-
5	37	M	Mesothel	-
6	57	M	Mesothel	-
7	78	M	Mesothel	-
8	50	F	Breast ca	Bone
9	42	F	Breast ca	Skin/bone/lung
10	50	F	Breast ca	Skin
11	62	F	Breast ca	-
12	60	F	Breast ca	Bone/skin
13	61	F	Breast ca	Bone
14	73	F	Breast ca	Bone
15	42	F	Breast ca	Lymph nodes
16	70	F	Breast ca	-
17	50	F	Breast ca	Skin
18	49	F	Breast ca	-
19	70	F	Breast ca	Lung
20	69	F	Breast ca	Bone/skin
21	63	F	Breast ca	Liver
22	66	F	Breast ca	-
23	63	M	SCLC	Lung
24	70	M	NSCLC	Lung
25	57	M	NSCLC	Lung
26	55	M	NSCLC	Lung
27	69	M	NSCLC	Lung
28	70	M	NSCLC	Lung
29	72	M	NSCLC	Lung
30	66	F	Ovarian ca	Abdomen
31	65	F	Ca unknown primary	-
32	58	M	Ca unknown primary	-
33	76	F	Ca unknown primary	-

Abbreviations: SCLC: small cell lung cancer, NSCLC: non-small cell lung cancer

counts, serum creatinine and electrolytes were determined weekly before each intracavitary administration. The cavity was drained as completely as possible by a thoracentesis. The chemotherapy regimen consisted of cisplatin 100 mg/m^2 and Ara-C 100 mg instilled in the pleural cavity diluted in 0.4 l of 0.9% sodium chloride over 20 min immediately after fluid withdrawal. Concurrent with the instillation of Ara-C and cisplatin, all patients began a 3-h hydration with 2 l of 0.9% sodium chloride including electrolyte supply. Diuresis was established by rapid i.v. injection of 20 mg of furosemide. The patients were asked to change position every 20–30 min in order to obtain uniform dispersion of the drugs.

The first patients received metoclopramide 1–2 mg/kg i.v. and methylprednisolone 3–4 mg/kg i.v. against nausea and vomiting. More recently the patients were treated with ondansetron 8–16 mg i.v. followed by 8 mg orally twice daily for 2 days. The cavity was drained again 4 h later with a new thoracentesis. If possible, the intrapleural administration was repeated weekly for three weeks. After a 6-week rest, therapy could be started again with the same weekly schedule. At the time of second and third administration, treatment was delayed one week if pretreatment WBC fell below $3 \cdot 10^9$/l and/or platelets were less than $100 \cdot 10^9$/l and serum creatinine was >15 mg/l.

A single intracavitary administration was considered sufficient for response. Response criteria were employed as follows: complete response (CR) = disappearance of all measurable disease for >4 weeks with clinical and radiographic evaluation (posteroanterior and lateral chest films, CT scan for patients with mesothelioma); partial response (PR) = a reduction by $>50\%$ of all measurable disease lasting >4 weeks; stable disease or progressive disease was evaluated as no response (NR). Duration of response was determined from the start of therapy.

Results

Between March 1988 and October 1992, 33 patients were enrolled in this study. Thirty-two were evaluable for response and toxicity. Reason for non-evaluability was sudden death of a 78-year-old man one week after the second administration of drugs. The patients received a total of 92 courses (range 1–8, mean <3). Only one patient (No. 1 in Table 1) received more than 6 intracavitary administrations: 6 as primary therapy and 2 at relapse 15 months later. Eighteen patients (55%) received less than 3 intrapleural instillations.

Toxicity. The overall toxicity was acceptable. Hematologic toxicity was generally modest. Median WBC count nadir was 2.1 (range 0.9–3.6) $\cdot 10^9$/l and median platelet count nadir was 180 (range 110–360) $\cdot 10^9$/l. Treatment delay of one week to allow myelotoxicity recovery was necessary in 11 (12%) of the courses. Fever or sepsis did not occur. One patient showed transient increase of serum creatinine to a maximum of 19 mg/l and 3 developed a mild peripheral sensory polyneuropathy. Although patients treated with metoclopramide experienced moderate nausea and vomiting, only 2 out of 12 treated with ondansetron showed mild nausea. There was no pneumothorax. A 78-year-old man died suddenly 8 days after second instillation. ECG before the start of therapy was normal. No autopsy was performed.

Response. Local responses, defined as CR, PR and NR, are summarized in Table 2. Twelve patients (37%) achieved local CR, and 12 (37%) local PR. The overall response rate was 74%. The 7 patients with mesothelioma (6 evaluable) obtained 3 CR and had disappearance of the disease as judged by CT scan and pleural biopsy. Patient No. 1 relapsed 15 months from start of therapy. She was treated with a new pleural instillation using the

Table 2

Response of intrapleural treatment

Patient No.	Prior therapy	Cources of Ara-C/CDDP	Following therapy	Response	Response duration (months)
1	A	6	–	CR	15
2	–	6	–	CR	23
3	–	3	–	PR	9
4	E	4	–	NR	–
5	A + Rx	6	–	CR	16
6	β-IFN	3	–	NR	–
7	β-IFN	2	–	Nonevaluable	
8	–	1	Tam	CR	55+
9	–	2	FEC	CR	20
10	FAC	3	Tam	PR	2
11	Tam	1	Mpa	CR	14
12	Tam	3	CMF	PR	7
13	CMF + E	3	Mpa	PR	6
14	CMF	2	Agl	CR	16+
15	CMF	2	FEC	PR	2
16	Tam	2	–	PR	2
17	CMF	3	FEC	NR	–
18	CMF	5	Tam	PR	18+
19	Tam	1	–	PR	2
20	Tam	2	Map	CR	12+
21	FEC	3	FN	NR	–
22	CMF	3	Tam	PR	7
23	CEV-Vp + Rx	2	Vp	CR	6
24	–	2	–	NR	–
25	–	4	Ca Vp	PR	6
26	–	2	Ca Vp	NR	–
27	–	3	–	PR	7+
28	–	3	–	PR	7+
29	–	2	Ca Vp	NR	–
30	–	2	PEC	CR	31
31	–	1	–	CR	12+
32	–	2	–	CR	9+
33	–	3	–	NR	–

β-IFN = β-interferon, Tam = tamoxifen, Mpa = medroxyprogesterone acetate, Agl = aminoglutethimide, C = cyclophosphamide, M = methotrexate, F = 5-fluorouracil, A = doxorubicin, E = epirubicin, N = mitoxantrone, V = vincristine, Vp = etoposide, P = cisplatin, Ca = carboplatin, Rx = radiotherapy, CR = Complete remission, PR = Partial remission, NR = No response

same drugs and achieved a new clinically complete remission. She underwent pleurectomy and decortication and intrapleural administration of cisplatin and Ara-C at the completion of thoracotomy. She relapsed 50 months from start of the first therapy with peritoneal involvement and died one month later. Patient No. 2 died with liver metastases 23 months after loco-regional therapy; Autopsy showed no loco-regional relapse. Patient No. 5 is still alive 32 months after the diagnosis. Among 15 patients with advanced breast cancer, 5 had previously required adjuvant chemotherapy and 5 adjuvant endocrine therapy. In the former patients, the interval between end of adjuvant treatment and relapse was more than 6 months; in the latter patients the relapse occurred during the treatment with tamoxifen. Four patients had pleural effusions as the single manifestation of tumor relapse; 3 were resistant after systemic therapy for advanced disease. Six achieved complete and 8 partial pleural remission. Up to date 4 patients are alive without signs of pleural disease at 55, 18, 16 and 12 months after first treatment. Among 5 patients with non-small cell lung cancer, 3 achieved PR. The two patients with small-cell lung cancer and ovarian cancer achieved complete pleural remission lasting till their death.

Discussion

The present study showed that Ara-C and cisplatin can be safely administered intrapleurally and that this treatment modality gives a high rate in malignant pleural effusions and only minor systemic toxicity. Our findings are in good agreement with a recent report by Rusch et al. (8) who used a single intrapleural injection of cisplatin

(100 mg/m^2) and Ara-C (1 200 mg/m^2) and observed a response rate at 3 weeks of 49%. The somewhat higher response rate in our study might be explained by different treatment schedules, different response criteria and a different spectrum of primary malignancies; the study by Rusch et al. contained a majority of patients with non-small cell lung cancer whereas our series contained a large proportion of patients with breast cancer and mesothelioma.

With regard to the known relation between dose and response (9) the favorable response was probably related to the much higher local concentrations of the drugs that are obtained after intrapleural instillations compared to systemic administration. Another factor might be a more long-term exposure of the tumor cells to the cytotoxic agents (10, 11). Some agents used for intrapleural treatment of malignant effusions seem to act mainly by their sclerosing effect; however, cisplatin probably exerts a direct cytotoxic effect after intrapleural injection (12–15).

Intracavitary instillations of radioactive or chemotherapeutic agents in malignant mesothelioma has previously achieved very limited success (16). The positive effects in 6 of our 7 patients with mesothelioma (one patient was not evaluable) are therefore very promising. It is possible that Ara-C and cisplatin should be given at an early stage in patients with mesothelioma and more limited disease.

In conclusion, intrapleural weekly injections of cisplatin and Ara-C seem to be an effective and well-tolerated treatment of patients with malignant pleural effusions. Further studies of this interesting treatment modality are highly warranted.

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