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CLINICAL TRIAL REPORT

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High-dose 5-fluorouracil and leucovorin as second-line chemotherapy in patients with platinum-resistant epithelial ovarian cancer

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Abstract A total of 14 patients with platinum-resistant advanced epithelial ovarian cancer were treated with a continuous infusion of high-dose 5-fluorouracil (5-FU, 1200 mg/m^2 per day) for 2 consecutive days weekly for 4 weeks and, thereafter, every 2 weeks in combination with a push injection of folinic acid (20 mg/m^2) given just before 5-FU and after 24 h. No objective response was documented, and only five patients showed stable disease. The median survival was 6.5 months. There was minimal toxicity. This schedule of 5-FU in combination with folinic acid is not effective as second-line chemotherapy in advanced ovarian cancer.

Key words Ovarian cancer · Chemotherapy · 5-Fluorouracil · Folinic acid

Introduction

Standard treatment of ovarian cancer of FIGO stage III or IV consists of surgery followed by platinum-containing chemotherapy. This treatment results in a 70–80% overall response rate and a 20% rate of 10-year survival. This means that most patients will suffer a relapse of their disease [3, 11]. Patients who have responded to initial therapy or have shown no progression for at least 6 months should be offered platinum-containing chemotherapy again. On the other hand, if there is no regression on initial therapy or progression of the malignancy within 6 months, second-line chemotherapy should be considered [3, 11].

The results of second-line chemotherapy with, for example, ifosfamide, taxol, or hexamethylmelamine are poor due to the low response rates of 10–30% [11]. 5-Fluorouracil (5-FU) is effective in ovarian cancer [1]. 5-FU inhibits DNA synthesis by interaction with the enzyme thymidylate synthetase. Leucovorin (folinic acid) stabilizes this complex [8], thereby enhancing the effect of 5-FU, as has been shown in colorectal cancer [9]. Platinum resistance is thought to be caused by a mechanism other than the mode of action of 5-FU and leucovorin [4]. Recently, Louvet et al. [7] reported the results obtained using 5-FU and leucovorin in the treatment of patients with cisplatin-resistant ovarian cancer. They found a response rate of 19% and a median survival of 9 months. Toxicity was minimal [7]. Herein we report the results of treatment with high-dose 5-FU in combination with leucovorin in similar patients with platinum-resistant ovarian cancer.

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Patients and methods

In the period ranging from March 1990 until May 1993, 14 patients (mean age, 59.5 years; range, 45–73 years) participated in this study after giving their informed consent. They had epithelial ovarian cancer of FIGO stage III or IV, and the tumor either was progressive despite previous platinum-containing chemotherapy or relapsed within 6 months after completion of the last platinum-containing regimen. Treatment consisted of a continuous infusion of 5-FU (1200 mg/m^2 per day over 2 days) given weekly for 4 weeks and, thereafter, every 2 weeks. Leucovorin (20-mg/m^2 push dose) was given intravenously just before the 5-FU infusion and after 24 h. Evaluation was scheduled after six courses unless there was major toxicity or clear progression

Table 1 Patients' characteristics and results (*CR* complete remission, *PR* partial remission, *NC* no change, *PD* progressive disease

Patient number	Age (years)	Stage (FIGO)	Previous chemo[a] (response)	Interval[b] (months)	PS[c]	Courses (*n*)	Response[d]	CA-125[e]	Time to PD (months)	Survival (months)
1	66	IIIB	PC-7(PR)	12	1	11	NC[f]	↓[f]	4	6
2	73	IV	PC-6(NC)	7	1	11	PD	↑	2	8
3	48	IV	PC-6(PR) CC-3(PR) CAP-1(NE)	15	1	5	ePD	NE	3	5
4	70	IIIC	CC-3(PD)	11	2	4	ePD	↔	1	3
5	64	IIIB	PC-6(CR)	12	0	6	PD	↔	2	20
6	60	IIIC	PC-7(PD)	9	1	5	ePD	↑	2	5
7	61	IIIC	CC-6(PR)	10	1	8	NC	↔	3	5
8	55	IIIC	PC-6(PR)	11	0	7	PD	↑	2	7
9	55	IIIC	CEP-9(PR) CI-6(PR)	42	1	15	NC	↔	8	23
10	59	IIIC	CHAC-9(CR) CC-6(CR) PC-6(PR) CEP-2(PD)	77	1	12	NC	NE	6	16
11	58	IV	PC-9(CR) CC-6(PD)	31	2	4	ePD	↑	1	3
12	45	IV	PC-7(CR) CC-2(CR)	16	0	7	PD	↑	2	18
13	68	IIIC	PC-1 CC-5(PR) CC-2(PD)	9	1	4	ePD	↑	1	2
14	51	IIIC	PC-5(PD) HORM(PD) TAX-2(NC) MEL-1(PD)	18	1	12	NC	↔	5	10

[a] Chemotherapy – numbers represent the number of courses received: PC, cisplatin/cyclophosphamide; CC, carboplatin/cyclophosphamide; CHAC, cyclophosphamide/hexamethylmelamine/Adriamycin/carboplatin; CI, carboplatin/ifosfamide; CAP, cyclophosphamide/Adriamycin/cisplatin; CEP, cyclophosphamide/etoposide/cisplatin; HORM, hormonal treatment; MEL, melphalan; TAX, taxotere

[b] Interval from diagnosis until the start of second-line chemotherapy

[c] Performance status according to the Eastern Cooperative Oncology Group at the start of protocol treatment

[d] ePD, Early progressive disease; progression within 6 courses independently of time. Response based on CT scan and/or CA-125 levels measured after 6 (or fewer) courses

[e] CA-125 levels measured after 6 courses or earlier if fewer courses were given: ↑, >25% increase; ↓, >50% decrease; ↔, between 50% decrease and 25% increase; NE, not evaluable or measured

[f] In patient 1, CA-125 levels decreased by more than 50% but increased shortly afterwards; this is considered no change

during the chemotherapy. Response was measured by computerized tomography (CT) and/or by CA-125 levels.

Results

The patients' characteristics and results are summarized in Table 1. In all, 4 patients showed progression during the first-line platinum-containing chemotherapy, 2 were progressive following platinum-containing regimens, and 6 had a recurrence within 6 months. Altogether, 2 patients were not eligible; 1 received more modes of (chemo)therapy (patient 14), and the other was free of disease for more than 6 months (patient 12). These patients were also evaluated.

An average of 8 courses of 5-FU and leucovorin were given (range, 4–15 courses); 5 patients received fewer than 6 courses because of early progression (4 cases) and worsening of the clinical condition (1 case). CA-125 levels decreased by >50% only very briefly in 1 patient and remained stable in 5 patients. CT scanning showed no change in 3 patients and progression in 7. In all, 1 patient was evaluated by X-ray of the chest (progression), 1 was evaluated by ultrasound (stable disease), and 2 patients were not evaluated with roentgenological investigations (no measurable disease).

Overall, stable disease was reported in 5 cases and progression, in 9. The median time to progression was 2 months (mean 3 months), and the median survival was 6.5 months (mean, 9.4 months). Altogether, 4 patients survived for more than 1 year; 3 of them received addi-

tional chemotherapy, radiotherapy, and/or hormonal therapy. Finally, all patients developed progressive disease and died.

Side effects were acceptable, involving nausea or vomiting in 9 patients [3 cases being severe (WHO grade 3)] and diarrhea in 6 (2 cases being severe). Neurological side effects (in 2 patients), stomatitis (3 cases), alopecia (1 case), and hand-foot syndrome (2 cases) were reported incidentally. There was no major hematological toxicity.

Discussion

Second-line treatment in platinum-resistant ovarian cancer is troublesome. Agents that are not cross-resistant are sought, but only low response rates and short periods of median survival have been reported. Such agents include taxol (response, 24–30%; median duration of response, 4 months), ifosfamide (response, 12%) and, maybe, hexamethylmelamine (response anecdotal) [11].

The mode of action of 5-FU is thought to be different from that of platinum-containing compounds [4]. This makes the combination of 5-FU and leucovorin an interesting option for patients with platinum-resistant ovarian cancer. In our study, no objective response was documented; 5 patients had stable disease and 9 showed progression.

This outcome, i. e., no response and a median survival of 6.5 months, is worse than the results reported by Louvet et al. [7]. In 16 evaluable patients they obtained 1 complete response and 2 partial responses. The median survival was 9 months. These investigators gave a lower dose of 5-FU (1000 mg/m^2 per day given for 2 days every 2 weeks), albeit partly as a push injection (400 mg/m^2). In our study we infused 5-FU continuously (1200 mg/m^2 per day for 2 days) weekly for 4 weeks and, thereafter, every 2 weeks. The dose of leucovorin used by Louvet et al. [7] was 10-fold that given by us.

In colorectal cancer, numerous schedules for 5-FU and leucovorin have been evaluated, but the best regimen is not known. A combination of 5-FU and leucovorin provides better results than does 5-FU alone [6, 9]. One study suggests that a combination regimen involving continuous infusion of 5-FU is superior to bolus treatment with 5-FU [10], but another investigation shows no difference [2]. A nonrandomized study in which 5-FU was given as a bolus and by continuous infusion in combination with leucovorin to 37 patients revealed a higher response rate and a longer median survival than those reported for former regimens [5]. Therefore, the push injection of 5-FU in combination with continuous infusion might explain the observed difference in outcome between our study and that of Louvet et al. [7]. The dose of leucovorin is probably of less importance since high and low doses are equally effective in colorectal cancer [9]. Another difference might be that the patients in the present study had been more heavily pretreated. We conclude this regimen given at the dose and dose schedule used in our study is not effective as second-line treatment in platinum-resistant ovarian cancer.

References

1. Bagley CM, Young RC, Canellos GP, De Vita VT (1972) Treatment of ovarian carcinoma: possibilities for progress. N Engl J Med 287: 856
2. Budd GT, Fleming TR, Bukowski RM, McCracken JD, Rivkin SE, O'Bryan RM, Balcerzak SP, Macdonald JS (1987) 5-Fluorouracil and folinic acid in the treatment of metastatic colorectal cancer: a randomized comparison. A Southwest Oncology Group study. J Clin Oncol 5: 272
3. Cannistra SA (1993) Cancer of the ovary. N Engl J Med 329: 1550
4. Canon J-L, Humblet Y, Symann M (1990) Resistance to cisplatin: how to deal with the problem? Eur J Cancer 26: 1
5. De Gramont A, Krulik M, Cady J, Lagadec B, Maisani J-E, Loiseau J-P, Grange J-D, Gonzalez-Canali G, Demuynck B, Louvet C, Seroka J, Dray C, Debray J (1988) High-dose folinic acid and 5-fluorouracil bolus and continuous infusion in advanced colorectal cancer. Eur J Cancer Clin Oncol 24: 1499
6. Erlichman C, Fine S, Wong A, Elhakim T (1988) A randomized trial of 5-fluorouracil and folinic acid in patients with metastatic colorectal carcinoma. J Clin Oncol 6: 469
7. Louvet C, Gramont A de, Demuynck B, Varette C, Beerblock K, Bennamoun M, Krulik M (1992) Bi-weekly 2-day schedule of high-dose folinic acid, 5-fluorouracil bolus and infusion in pretreated advanced epithelial ovarian cancer: a phase II study. Ann Oncol 3: 657
8. Pinedo HM, Peters GJ (1988) Fluorouracil: biochemistry and pharmacology. J Clin Oncol 6: 1653
9. Poon MA, O'Connell MJ, Moertel CG, Wieand HS, Cullinan SA, Everson LK, Krook JE, Mailliard JA, Laurie JA, Tschetter LK, Wiesenfeld M (1989) Biochemical modulation of fluorouracil: evidence of significant improvement of survival and quality of life in patients with advanced colorectal carcinoma. J Clin Oncol 7: 1407
10. Seifert P, Baker LH, Reed ML, Vaitkevicius VK (1975) Comparison of continuously infused 5-fluorouracil with bolus injection in treatment of patients with colorectal adenocarcinoma. Cancer 36: 123
11. Thigpen JT, Vance RB, Khansur T (1993) Second-line chemotherapy for recurrent carcinoma of the ovary. Cancer 71: 1559