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SESSION II

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Intra-arterial chemotherapy using a reservoir for endocrine-refractory prostate cancer

Abstract For local control in patients with endocrine-refractory prostate cancer, an intra-arterial chemotherapy regimen comprising methotrexate (MTX), Adriamycin (ADM), and cisplatin (CDDP) was evaluated. A total of 19 patients having a mean age of 66.4 ± 8.8 years and a mean performance status (PS) of 1.3 ± 1.0 were enrolled. Of these patients, 3 had proved to be resistant to initial endocrine therapy and the remaining 16 had relapsed from disease stabilization after endocrine therapy. The catheter tip was placed in the internal iliac artery in 16 cases, in the common iliac artery in 2 cases, and in the aorta in 1 case after occlusion of the contralateral feeding artery. The intra-arterial chemotherapy was performed mainly using MTX (30 mg/m^2), ADM (30 mg/m^2), and CDDP (50 mg/m^2) as one course and was repeated for a mean of 2.9 ± 2.3 courses. Then, in an outpatient clinic, 5-fluorouracil (5-FU), ADM, or MTX was given intra-arterially as maintenance chemotherapy until re-relapse. As based on the criteria for evaluation of nonsurgical therapy in prostate cancer proposed by the Japanese Urological Association, the prostatic lesion showed a partial response (PR) in 9 cases and no change (NC) in 10 cases. As judged from the response of prostate-specific antigen (PSA), a complete response (CR) was obtained in 6 cases, a PR, in 3 cases; and NC and progressive disease (PD), in 2 cases each. Therefore, the overall response rate was 63%. Improvement in the symptoms was observed in 83% of patients. The duration of the response was 15.1 ± 10.5 months for the PR cases and 7.4 ± 5.7 months for the NC cases. Furthermore, the mean survival time observed in the PR group was 38.9 months, which was better than that seen in the NC (16.4 months) and PD (10.5 months) groups. These results suggest that intra-arterial chemotherapy may become an option for the treatment of locally advanced and endocrine-refractory prostate cancers. Using a reservoir, this chemotherapy can be easily given in an outpatient clinic.

Key words Prostate cancer · Endocrine refractory tumor · Intra-arterial chemotherapy · Reservoir

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Introduction

The prognosis remains poor for patients with prostate cancer that has proved to be resistant to initial therapy or has relapsed from disease stabilization [4, 5]. Although the main cause of death is progression of metastasis, about 10% of the mortality is thought to be due to local progression. Therefore, local control in these patients remains important. In this paper, we evaluated our experience with intra-arterial chemotherapy for endocrine-refractory or -resistant prostate cancer. Using a reservoir, the chemotherapy is expected to be continued in an outpatient clinic.

Materials and methods

A total of 19 patients having a mean age of 66.4 years were enrolled in this study. All cases underwent castration, and 18 patients also received antiandrogen therapy, chemotherapy, or radiation therapy. Of these patients, 3 had proved to be resistant and the remaining 16 had relapsed from disease stabilization. The mean overall duration of the response had been 34.5 months. At the start of intra-arterial chemotherapy, the mean performance status (PS) was 1.32 and the mean serum prostate-

Table 1 Patients' characteristics (*WEL* Well differentiated, *MOD* moderately differentiated, *POR* poorly differentiated, *DESD* diethylstilbestrol diphosphate, *CMA* chlormadinone acetate, *EST* estramustine phosphate, *PR* partial response, *NC* no change, *PD* progressive disease)

Number of cases	19
Age (years)	66.4 ± 8.76 (range 49–81)
Clinical stage (C:D2)	2:17
Pathological grade (WEL:MOD:POR)	2:5:12
Initial therapy:	
Castration	19
+ DESD ± chemotherapy	11
+ CMA	2
+ EST ± chemotherapy ± radiation	5
Treatment response:	
Responders: nonresponders	16:3
PR:NC:PD	11:6:2
Duration of response (months)	34.5 ±40.0 (range, 0–124)
PS at relapse	1.32± 1.00 (range, 0–3)
PSA at relapse (ng/ml)	39.3 ±52.0 (range, 0.8–177)

Table 2 Intra-arterial chemotherapy using a reservoir for prostate cancer (*VP-16* Etoposide)

Number of cases	19
Location of catheter tip:	
Aorta	1
Common iliac artery	2
Internal iliac artery (IIA)	16 (84%)
Occlusion of contralateral IIA	19
Position of reservoir:	
Abdominal wall	4
Thigh	15 (79%)
Induction chemotherapy:	
ADM+CDDP+MTX	17 (89%)
+CDDP+VP-16	1
+VP-16	1
Number of courses	2.9 ± 2.3 (range, 1–9)
Maintenance chemotherapy:	
None	5
5-FU	3
+MTX	4
+MTX+ADM	2
MTX+ADM	2
ADM+CDDP+VP-16	1
+CDDP+CPM	1
CDDP+VP-16	1

specific antigen (PSA) level was 39.3 ng/ml. A total of 16 patients who responded to the initial endocrine therapy were free of progression for 3–124 months. The mean period of stable disease was 38.7 months (Table 1).

The intra-arterial chemotherapy was performed mainly using 30 mg/m^2 methotrexate (MTX), 30 mg/m^2 Adriamycin (ADM), and 50 mg/m^2 cisplatin (CDDP) as one course. This induction chemotherapy was repeated for a mean of 2.9 ± 2.3 courses at 3-week intervals. Then, 14 patients were continued on this chemotherapy in an outpatient clinic using ADM, MTX, 5-fluorouracil (5-FU), or their combination. The chemotherapy was started in March of 1987, and the observation period was at least 8 months.

Since the objective of this study was local control, the clinical effects were evaluated in relation to the primary lesion and the serum PSA value. Using these parameters, the survival time of the patients, duration of response, and catheter's technical survival (i.e., the duration of patency of the catheter for the intra-arterial chemotherapy) were compared.

Results

Table 2 presents a summary of the data on the intra-arterial chemotherapy used in this study. All patients underwent occlusion of the contralateral internal iliac artery, and then the catheter tip was inserted mainly into the internal iliac artery beyond the superior gluteal artery in 84% of cases. Reservoirs were positioned in the subcutaneous space of the abdominal wall in 4 cases and in that of the thigh in 15 cases.

As based on the criteria for evaluation of nonsurgical therapy in prostatic cancer proposed by the Japanese Urological Association [6], 9 cases of partial response (PR) and 10 cases of no change (NC) were obtained for the primary lesion. Evaluation of the effect on the PSA level showed 6 cases of complete response (CR), 3 cases of PR, 2 cases of NC, and 2 cases of progressive disease (PD). Therefore, the overall response was 12 cases of PR, 5 cases of NC, and 2 cases of PD. The overall response rate was estimated to be 63%. During the observation period, no progression of metastatic lesions was found in any patient as evaluated by imaging diagnostic methods. The mean duration of response was more than 15.1 months for the PR cases and 7.4 months for the NC cases. Furthermore, voiding symptoms were improved in 83% of the patients (Table 3). The clinical effects and doses of each drug are compared in Table 4. Due to decreased renal or heart

Table 3 Clinical effect of intra-arterial chemotherapy

Clinical response	Evaluable lesion		Overall response[a]	Duration of response (months)	Voiding symptoms
	Primary	PSA			
CR	0	6 (46%)	0		
PR	9 (47%)	3 (23%)	12 (63%)	15.1 ± 10.4 (range, 0–31+)	
NC	10 (53%)	2 (15%)	5 (26%)	7.4 ± 5.7 (range, 0–13)	
PD	0	2 (15%)	2 (11%)		
Improved					15 (83%)
Unchanged					3 (17)

[a] The response criteria were those of the Japanese Urological Association [6]

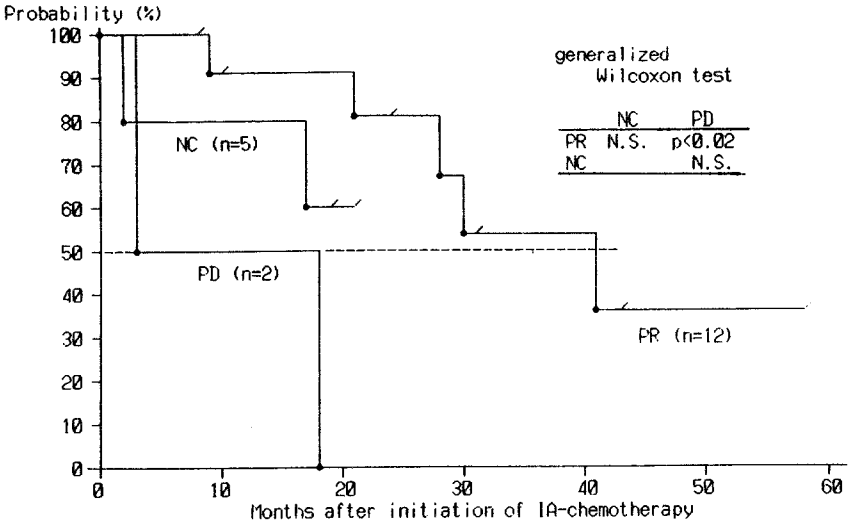

Fig. 1 Survival rate according to clinical response

Table 4 Clinical effect and dose of chemotherapeutic agents

Drug	Number of cases	Dose/course (mg/body)		
		PR	NC	PD
ADM	19	33.4 ± 9.0	36.0 ± 15.2	21.7 ± 2.3
CDDP	18	59.6 ± 23.0	75.0 ± 28.9	54.2
MTX	17	50.7 ± 9.5	50.0 ± 0.0	50
VP-16	2	150	50	

function, the doses of ADM and CDDP had to be reduced relative to the initially planned doses. However, there was no correlation between the doses given and the clinical effect.

Table 5 summarizes the complications and adverse effects of the intra-arterial chemotherapy used in this study. During the chemotherapy, the catheters were obstructed and reconstructed in three cases. Except for one case of gluteal ulcer, no major complication was observed. Adverse effects were observed in 84% of the cases, but they were less severe than grade 2 according to WHO criteria. There was no death due to the chemotherapy.

Figure 1 plots the survival rate as a function of the clinical response. The mean survival time was 38.9 months in the PR group, 16.4 months in the NC group, and 10.5 months in the PD group. A statistically significant difference ($P < 0.02$) was observed between the PR and PD groups. Figure 2 presents the survival rate, the duration of response, and the catheters' technical survival. The mean duration of the intra-arterial chemotherapy was 16.3 months,

Fig. 2 Survival rate and duration of response

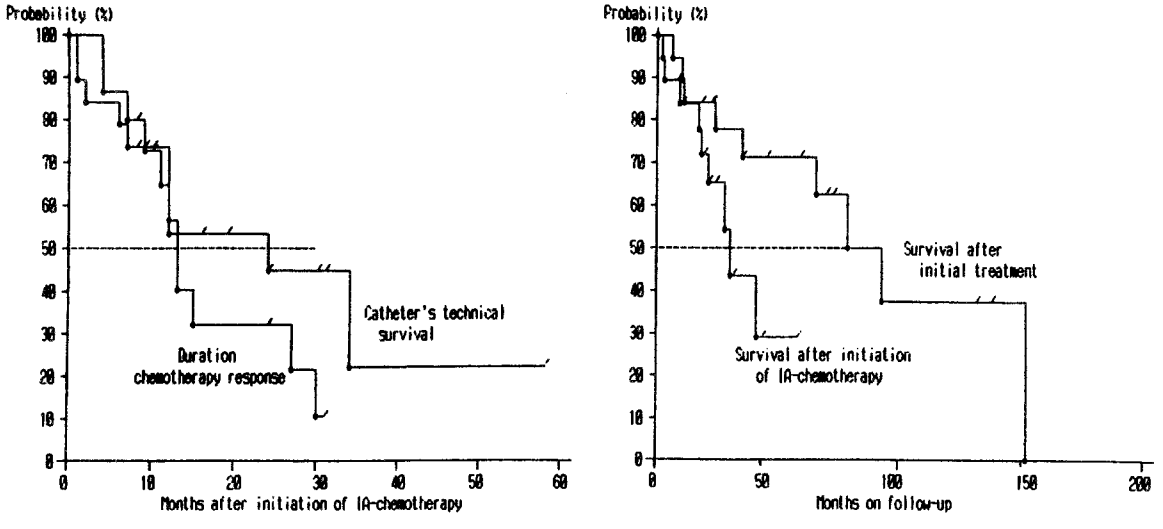

Table 5 Complications and adverse effects of intra-arterial chemotherapy

Complication	Cases (%)	Adverse effect	Cases (%)
Number of cases	7 (37)	Number of cases	16 (84)
Cathether obstruction	3 (16)	Anorexia	15 (79)
Wound infection	2 (11)	Nausea/vomiting	15 (79)
Intimal injury	1 (5)	Skin pigmentation	6 (32)
Gluteal ulcer	1 (5)	Stomatitis	7 (37)
Lymphocele	1 (5)	Alopecia	6 (32)
		Leukopenia (2,000/mm^3)	7 (37)
		Thrombocytopenia (< 10^5/mm^3)	6 (32)

and the mean duration of catheter patency was 26.0 months. Patients survived for a mean of 89.4 months after the initial treatment and 33.4 months after the intra-arterial chemotherapy.

Discussion

Patients with endocrine-resistant prostate cancer have a poor prognosis, and about 50% of them die within 1 year [9]. Although many secondary hormonal and chemotherapeutic regimens have been employed, none has provided satisfactory long-term results [1, 3, 7, 8, 10]. As Rangel et al. [8] have reported, patients with metastatic prostatic carcinoma are not ideal candidates for chemotherapy because they are usually elderly and generally have a poor performance status. Therefore, the most important point in the treatment of metastatic prostate cancer patients is considered to be prevention of disease progression [2, 4].

Rangel et al.'s experience with weekly ADM administration in hormone-refractory stage D2 prostate cancer showed almost no significant improvement in progression-free survival (mean, 15 weeks) or overall survival (mean, 47 weeks) [8]. They emphasized the limited value of administration of a single agent. In the Japanese literature, Yoshimoto et al. [10] reported in 1985 that they achieved a PR rate of 50%, a mean duration of response of 6.3 months, and a mean survival of 22 months in the PR group for 30 patients with endocrine-refractory prostate cancer treated with vincristine, ifosfamide, and peplomycin (VIP regimen). As compared with their data, our results show an almost equivalent PR rate (47%) and a slightly longer duration of response (10.1 months) and survival time (38.9 months) in the PR group. The efficacy was obtained because the anticancer agents directly reached the tumor tissues via the intra-arterial route. Furthermore, adverse effects and toxicity were not severe enough to require discontinuation of the chemotherapy.

Although the efficacy is not yet fully satisfactory, intra-arterial chemotherapy with MTX, ADM, and CDDP seems to have potential as an option for the treatment of locally advanced prostate cancer. Moreover, using a reservoir, this chemotherapy can be easily given in an outpatient clinic.

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