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Results of adjuvant chemotherapy for invasive uroepithelial cancer*

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Summary. Between June 1982 and July 1990, 55 patients (41 with bladder cancers and 14 with renal pelvic or ureteral cancers) who had undergone radical extirpative surgery and/or node dissection for pathological stage pT2-4 and/or nodal disease received adjuvant chemotherapy consisting of cisplatin alone or in combination with other agents. In all, 26 of the bladder-cancer patients also received preoperative chemotherapy consisting of arterial infusion of cisplatin, mitomycin C, and Adriamycin. Adjuvant chemotherapy was performed according to the following protocol. Between June 1982 and July 1987, 30–50 mg/m^2 cisplatin either alone or in combination with Adriamycin and 5-fluorouracil (CAF) was given to 35 patients in an induction and maintenance setting for 1 year. After July 1987, short-course cisplatin (70 mg/m^2) or cisplatin, etoposide, and Adriamycin combination chemotherapy (CVA) was given to 20 patients. Of the 55 patients, 38 are alive and show no evidence of disease, three are alive with disease, 13 have died of their disease, and 1 has died of an unrelated cause. The 5-year survival of all patients was 65.1%. The survival of the 20 patients who were treated after July 1987 was better than that of the 35 patients who were treated before June 1987. Local recurrence and/or distant dissemination occurred in 16 patients, 13 of whom died of cancer progression. Nausea and vomiting and anorexia occurred in most patients during the administration of cisplatin. Mild to moderate myelosuppression developed in patients who received CAF or CVA combination chemotherapy. Although adjuvant chemotherapy combined with radical surgery seemed to be effective in cases with a pathological stage of pT3a or less, more intensive pre- or postoperative chemotherapy is needed to improve the poor prognosis of patients with deeply invasive uroepithelial cancer.

Introduction

The conventional approaches to the treatment of invasive uroepithelial cancer, including radical surgery and/or radiotherapy, have achieved 5-year survival values of <40% [2, 4, 7, 9]. Approximately 50% of these patients survive for 5 years, even if their disease is clinically confined to the original organs. If nodal disease is present, the 5-year survival amounts to ≤10%, with the majority of these patients developing metastatic disease within 1 year of radical surgery [4, 10]. In recent years, advances have been made in the use of chemotherapeutic regimens for metastatic transitional-cell carcinoma. Cisplatin is generally considered to be the most effective single agent, and it is currently the cornerstone of most combination regimens [1, 14].

We have developed a program based on the administration of cisplatin alone or in combination with other agents in adjuvant settings [13]. In 1982, we initiated a study in which patients with pathological stage pT2-4 and/or nodal disease who showed no evidence of disseminated disease were given adjuvant chemotherapy following radical surgery. We summarize the results we obtained in 55 patients with locally advanced uroepithelial cancer who underwent radical extirpative surgery and adjuvant treatment with cisplatin alone or in combination with other agents.

Patients and methods

Patients. The study included 55 patients, consisting of 44 men and 11 women between 46 and 82 years of age (Table 1). Of these patients, 41 had bladder cancer and 14 had renal pelvic and/or ureteral cancer. Of the 41 subjects with bladder cancer, 38 underwent radical cystectomy and pelvic node dissection, and the other 3 underwent segmental resection. All 14 patients with renal pelvic and ureteral cancer underwent total nephroureterectomy; 2 of these subjects had concomitant bladder cancer, which was treated by cystectomy in 1 case and by fulguration in the other. None of the patients had received prior radiotherapy or systemic chemotherapy. Preoperative intraarterial infusion therapy was performed in 26 of the patients with bladder cancer.

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Table 1. Patients' characteristics

Characteristic		Primary site	
		Bladder	Renal pelvis and/or ureter
Number of patients		41	14
Sex (M/F)		34/7	10/4
Age (years)		52–82	46–80
Histological findings:			
	TCC	29	13
	Non-TCC	12	1
Pathological stage:			
	pT2	9	0
	pT3	25	12
	pT4	7	2
Nodal involvement:			
	+	7	5
	–	34	9
Small-vessel invasion:			
	+	25	11
	–	9	0
	Unclear	7	3

Table 2. Protocols used in the present study

Tumor stage	Protocol	
	IA (1982–1987)	IB (1987–1990)
pT2-3a pN(–)	CDDP, 30–50 mg/m^2, once every week 3 courses + Monthly maintenance	CDDP, 70 mg/m^2, once every 2 weeks 3 courses Without maintenance
	IIA	IIB
pT3b-4 or pN(+)	CDDP, 20 mg/m^2; (days 1–3); ADR, 30 mg/m^2 (day 1); 5-FU, 300 mg/m^2 (day 1); once every 3 weeks 3 courses + Monthly maintenance	CDDP, 50 mg/m^2 (day 1); VP-16, 50 mg/m^2 (days 1–5); ADR, 30 mg/m^2 (day 1); once every 4 weeks 4 courses Without maintenance

CDDP, Cisplatin; ADR, Adriamycin; 5-FU, 5-fluorouracil; VP-16, etoposide

The tumors manifested as transitional-cell carcinoma (TCC; grade 3, 38; grade 2, 4) in 42 patients and as non-TCC [squamous-cell (SCC), undifferentiated (UC), or mixed-type carcinoma] in 13 subjects. The bladder tumors were staged as pT2 in 9 cases, as pT3a in 15 cases, as pT3b in 10 cases, and as pT4 in 7 cases, whereas the upper-urinary-tract tumors were staged as pT3 in 12 cases and as pT4 in 2 cases. Nodal involvement was histologically confirmed in 7 of the 41 patients with bladder cancer and in 5 of the 14 subjects with upper-urinary-tract cancer. Small-vessel invasion was confirmed in 25 of the 41 patients with bladder cancer and in 11 of the 14 patients with upper-urinary-tract cancer.

Protocols. Patients were treated according to the protocols shown in Table 2. Between 1982 and June 1987, protocol I-A, consisting of intravenous cisplatin alone, was given to patients with tumors of stage pT2 or pT3a who showed no evidence of nodal disease, beginning at 2–3 weeks after surgery. It was given once every week for 3 weeks as induction chemotherapy and then once monthly for 1 year as maintenance treatment. A total of 22 patients were treated according to this protocol. Protocol II-A, consisting of a combination of cisplatin, Adriamycin, and 5-fluorouracil (CAF), was used only in patients with stage pT3b, stage pT4, or nodal disease. It was given at 3-week intervals for three courses as induction therapy and then once monthly for 1 year. In all, 13 patients were treated according to this protocol.

As of July 1987, the protocol was modified in view of the results achieved in the 5 years up to that time. In protocol I-B, which we used instead of protocol I-A only in patients with stage pT2 or pT3a tumors who showed no evidence of nodal disease, the cisplatin dose was increased to 70 mg/m^2 and maintenance therapy was abandoned. In protocol II-B, which was used instead of protocol II-A in patients with deeply invasive cancer, a combination of cisplatin, etoposide, and Adriamycin (CVA) was given. In all of the patients, mannitol-induced diuresis was instituted to reduce the potential nephrotoxicity of cisplatin administration.

Table 3. Results of adjuvant chemotherapy

	Primary disease	
	Bladder	Renal pelvis and/or ureter
NED	30	8
Alive with disease	0	3
Died of disease	10	3
Died of unrelated cause	1	0
Totals	41	14

NED, No evidence of disease

Results

Clinical effects

Because the number of patients in each group was small and the follow-up period of patients treated after July 1987 was short, all treated patients were analyzed together. Of the 55 patients, 38 (30 with bladder cancer and 8 with renal pelvic and/or ureteral cancer) are alive and show no evidence of disease (Table 3), and 3 with renal pelvic and/or ureteral cancer are alive with disease. In all, 13 patients (10 with bladder cancer and 3 with renal pelvic and/or ureteral cancer) died of progressive disease, and 1 subject with bladder cancer died of an unrelated cause.

The overall 5-year survival of the 55 patients was 65.1% (Fig. 1). The survival of the bladder-cancer patients was 66%, and that of the upper-urinary-tract cancer patients was 60%; this difference did not reach statistical significance. The 5-year survival values determined according to pathological stage for the 41 bladder-cancer patients were 77.7% for pT2, 83.3% for pT3a, 45.0% for pT3b, and 57.1% for pT4; the corresponding values obtained for the 14 renal pelvic and/or ureteral cancer patients were 75% for pT3 and 0 for pT4. The 5-year survival determined according to histological type was 70.3% in the TCC group and 53.3% in the non-TCC group; this difference also failed to reach statistical significance. The 5-year survival of patients showing no nodal involvement was better than that of subjects with nodal disease, but the

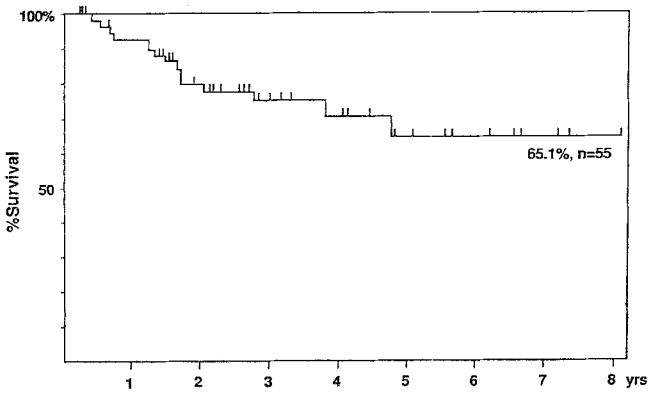

Fig. 1. Survival of all patients

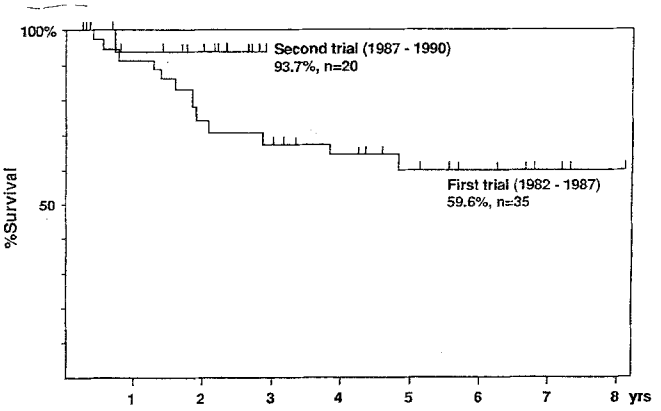

Fig. 2. Survival according to treatment period

Table 4. Details of patients with local recurrence and/or metastasis

Site	Primary disease	
	Bladder ($n = 10$)	Renal pelvis and/or ureter ($n = 6$)
Pelvic cavity	5	2
Lymph node	2	4
Lung	5	2
Bone	5	3
Bladder	1	1

Table 5. Toxicity encountered in the present study

Side effect	Number of patients (%)
Nausea/vomiting	49 (89%)
Leukopenia	26 (47%)
Alopecia	20 (36%)
Anemia	18 (32%)
Liver dysfunction	11 (20%)
Thrombocytopenia	8 (15%)
Renal impairment	1 (2%)
Mucositis	1 (2%)

difference was not significant. The 5-year survival of patients displaying no small-vessel invasion was 76.2%, whereas that of subjects exhibiting small-vessel invasion was 55.4%.

Figure 2 compares the actuarial survival of the 35 patients who received long-term, low-dose cisplatin or CAF chemotherapy with that of the 20 patients who received short-course, high-dose cisplatin or CVA chemotherapy. Although the number of patients in the latter group was small and the follow-up period was short, the survival of that group was better than that of the former group (93.7% vs 59.6%).

Local recurrence and/or distant dissemination occurred in 16 patients (10 with bladder cancer and 6 with renal pelvic or ureteral cancer). Various sites were involved, most often the pelvic cavity, lung, and bone (Table 4).

Most of the patients who received protocol I-A (cisplatin alone) or protocol II-A (CAF) did not complete the scheduled 12 months of therapy; the average number of courses received was 8.6. In contrast, all 20 patients in the short-course cisplatin or CVA chemotherapy group who were treated after July 1987 completed the planned schedule.

Toxicity

The most common complications encountered were gastrointestinal symptoms, including nausea, vomiting, and anorexia due to the administration of cisplatin (Table 5). About 90% of all patients suffered from these complications. Four patients with severe gastrointestinal symptoms refused further chemotherapy. Mild to moderate hematological side effects were seen in 28 patients. Anemia was observed in 18 patients; leukopenia (WBC, <3000/mm^3), in 26 subjects; and thrombocytopenia (platelet count, <100,000/mm^3) in 8 patients. One patient who underwent CVA chemotherapy suffered from severe mucositis. Moderate to severe alopecia was observed in 20 subjects who received the CAF or CVA regimen. An increase in serum levels of creatinine was noted in one patient after the administration of cisplatin, but the values returned to normal within 2 weeks.

Discussion

When radical extirpative surgery (cystectomy or nephroureterectomy) is the sole therapeutic modality for muscle-invasive uroepithelial cancer, >50% of the patients do not survive for 5 years, with the majority dying of cancer progression [2, 4, 7, 9]. Radiation therapy alone results in 5-year survival values ranging from 20% to 40% [3, 5, 10], whereas preoperative radiation therapy combined with radical cystectomy does not produce any significant improvement in the 5-year survival of these patients [3, 10]. It is thus evident that further improvement in the survival of patients with locally invasive uroepithelial cancer will require effective systemic therapy.

During the last decade, numerous single chemotherapeutic agents have been tested for their efficacy in the treatment of uroepithelial cancer [1, 14]. To date, cisplatin and methotrexate have been identified as the most effective single agents, and recent studies have evaluated the effi-

cacy of cisplatin-based combination chemotherapy [1, 8, 14].

In 1982, we started the present study in an attempt to improve the poor prognosis of patients with invasive uroepithelial cancer, who were given chemotherapy consisting of cisplatin alone or in combination with Adriamycin and 5-fluorouracil. This trial, performed during the period between June 1982 and June 1987, did not alter the survival of patients with deeply invasive cancer (stage pT3b-4 and/or nodal involvement). Most patients could not complete the planned schedule; the long-term schedule and the drug-related toxic effects seemed to compromise their compliance. At the start of this study, the patients' compliance approached 100%, yet as the intensity of treatment and the use of cisplatin increased, the number of patients completing the protocol diminished.

Einstein et al. [1] and Herr [3] have suggested that the success of adjuvant chemotherapy requires effective chemotherapeutic agents, early initiation of treatment after control of the primary tumors, a tolerable level of toxicity, and doses sufficient to be effective. After 1987, we changed the regimen and initiated the use of a short-course adjuvant chemotherapy schedule. Our recent preliminary results show that three courses of cisplatin for stage pT2-3a tumors and CVA chemotherapy for deeply invasive cancer are likely to be completed and relatively effective, with the patient's compliance being good.

Of various combination chemotherapy regimens, the M-VAC regimen (methotrexate, vinblastine, doxorubicin, and cisplatin), which was first reported in 1985 by Sternberg et al. [11], is probably the most effective. Following its use in metastatic uroepithelial cancer, complete and partial responses were achieved by 72% of 121 evaluable patients with TCC [12]. More recently, M-VAC has been used in neoadjuvant settings, producing favorable initial results [6]. The intent of neoadjuvant chemotherapy is to downstage the tumor, eliminate micrometastases, improve the completeness of disease resection, and improve the prospect for long-term survival. Miller et al. [6] have obtained CR and PR rates of 22% and 44%, respectively, in nine patients undergoing neoadjuvant M-VAC chemotherapy and radical cystoprostatectomy. They and other investigators have suggested the importance of pathological restaging of patients who have received neoadjuvant chemotherapy [6, 12]. The short-term results have shown neoadjuvant chemotherapy to be effective, but the long-term survival has not yet been reported. In the future, a randomized, prospective study will be needed to evaluate the efficacy of this approach. Systemic therapy consisting of neoadjuvant and/or adjuvant chemotherapy may play an important role in the management of invasive uroepithelial cancer.

In conclusion, adjuvant chemotherapy combined with radical surgery for invasive uroepithelial cancer seems to be effective in some of these patients. However, to improve the poor prognosis, more intensive systemic chemotherapy such as the M-VAC regimen is needed in a neoadjuvant and/or adjuvant setting.

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