Cancer Chemother Pharmacol (1987) 20 (Suppl): S 24–S 28

Cancer Chemotherapy and Pharmacology

Adjuvant chemotherapy for invasive bladder cancer

Yasunari Uekado, Toshiaki Shinka, Atsuyuki Hirano, and Tadashi Ohkawa

Department of Urology, Wakayama Medical College, 7-ban-cho 1, Wakayama 640, Japan

Summary. From June 1982 through December 1985, 25 patients who had undergone radical cystectomy with pelvic node dissection for pathologic stage-pT3 or –pT4 and/or N^+ disease received adjuvant chemotherapy involving the injection of cis-platinum alone or in combination with adriamycin and 5-fluorouracil (CAF). Thirteen patients also received preoperative adjuvant chemotherapy involving the infusion of cis-platinum, adriamycin, and mitomycin C into the bilateral internal iliac arteries. Postoperative adjuvant chemotherapy was performed using the following two protocols. Protocol 1 (18 cases) consisted of cis-platinum alone being administered every week for 3 weeks and then every month for 1 year. In protocol 2 (7 cases), cis-platinum, adriamycin, and 5-fluorouracil were administered at 3-week intervals on three occasions and then every month for 1 year. Eighteen patients were still alive with no evidence of disease after an average of 26 months. One patient died as a result of factors unrelated to cancer. Local recurrence and distant metastasis occurred in 6 patients, of whom 3 were still alive for an average of 20.7 months. Three patients died of cancer progression after 9, 19, and 21 months. The survival rate for all 25 patients at 50 months was 77%. Nausea and vomiting occurred in most patients during the administration of cis-platinum. Mild myelosuppression developed in a few patients subjected to protocol 2. Our results indicate that adjuvant chemotherapy consisting of the administration of cis-platinum alone or in combination with other chemotherapeutic agents appears to be effective in patients with invasive bladder cancer.

Introduction

Conventional treatment of bladder cancer invading the muscular layer, which includes radical and simple cystectomy or radiotherapy, has produced 5-year survival rates of less than 40%. In patients with deeply invasive bladder cancer (i.e., at stages pT3b or pT4, or with positive nodes), a uniformly poor prognosis has long been the case. Over the past 10 years, every major advance in the management of solid tumors in humans has been achieved by the development of effective cytotoxic drugs and their aggressive use against known metastatic diseases both in combination and in the adjuvant setting. Recently, cis-platinum has been reported to be one of the most active of these agents in patients with locally invasive and metastatic bladder cancer. Accordingly, in an attempt to improve the poor prognosis in patients with invasive bladder cancer, we have developed a program of treatment based on the application of cis-platinum alone or in combination with other agents before and after treatment by radical cystectomy.

Materials and methods

From June 1982 through December 1985, at Wakayama Medical College 25 patients underwent single-stage radical cystectomy with pelvic lymph-node dissection and urinary diversion with the aim of curing invasive bladder cancer. Details about the patients are given in Table 1. There were 21 males and 4 females, whose ages ranged from 52 to 79 years, the average being 67 years. Of these patients, 21 had transitional cell carcinoma, 2 had squamous cell carcinoma and 2 had undifferentiated carcinoma. Of the 21 patients with transitional cell carcinoma, 19 had grade-3 can-

Table 1. Patient characteristics

Total number of patients	25
Age range (years)	52–79
Average age	67
Males	21
Females	4
Histology:	
Transitional cell carcinoma grade 3	19
grade 2	2
Squamous cell carcinoma	2
Undifferentiated carcinoma	2
Pathological stage:	
pT2	1
pT3a	10
pT3b	9
pT4	5
Prior radiation	0
Prior chemotherapy	0
Prior transurethral resection	4
Cases with upper urinary tract tumor	2
Preoperative intra-arterial infusion	13

Offprint requests to: Y. Uekado

cer, while the other 2 patients had grade-2 cancer. The pathological stage was pT2 with positive nodes in 1 patient, pT3a in 10 patients, pT3b in 9 patients, and pT4 in 5 patients. Node involvement was confirmed histologically in 3 patients. Four patients had previously undergone transurethral resection for the bladder cancer, and 2 patients also had upper urinary tract cancer. Prior radiotherapy or systemic chemotherapy had not been performed in any of the patients.

In addition to a routine physical examination, complete blood counts, screening biochemical tests, and a chest X-ray, the patients were evaluated before operation using the following diagnostic procedures: excretory urography, cystography, endoscopy with biopsy, bimanual examination under anesthesia, computed-tomography (CT) scan of the pelvis and bladder, and other appropriate studies such as transurethral ultrasound or pelvic angiography. Tumor staging was classified according to the criteria of the Japanese Urological Association and the Japanese Pathological Society.

Thirteen patients received preoperative adjuvant chemotherapy by intra-arterial infusion. According to Seldinger's method, we initially performed bilateral internal iliac arteriography. The blood flow was halted by simultaneous occlusion of these arteries by means of inflating the balloon of a double lumen catheter, and anticancer agents were then injected gradually for 30 min. The arterial infusate consisted of 50 mg cis-platinum, 10 mg mitomycin C, 20 mg adriamycin, and 24,000 units of urokinase.

Postoperative adjuvant chemotherapy was performed according to the following 2 protocols (Table 2). Protocol 1, which usually employ only for stage-pT3 cases without node involvement, entails the administration of cis-platinum alone. Cis-platinum was administered intravenously at a dose of 30–50 mg/m^2 beginning 2–3 weeks after the operation. This was given every week for 3 weeks as induction chemotherapy, and then monthly for 1 year. Eighteen patients were treated using protocol 1. Protocol 2, involving the administration of a combination of cis-platinum, adriamycin, and 5-fluorouracil (CAF), was used for patients with deeply invasive bladder cancer, e.g., when pathological specimens revealed pT4 or node involvement. A course of 15–20 mg/m^2 cis-platinum for 3 consecutive days, 30 mg/m^2 adriamycin at day 1, and 300 mg/m^2 5-fluorouracil at day 1 was administered at 3-week intervals on three occasion as induction therapy (beginning 2–3 weeks postoperatively). Maintenance therapy was repeated monthly for 1 year when the patients could tolerate it. Seven patients received CAF combination chemotherapy.

In all 25 patients, mannitol-induced diuresis was instituted in order to reduce the potential nephrotoxicity resulting from the administration of cis-platinum. Survival curves were estimated according to the method of Kaplan and Meier.

Table 2. Protocols for invasive bladder cancer

Protocol 1		
Cis-platinum	30–50 mg/m^2	Every week; 3 courses (induction)
Cis-platinum	30–50 mg/m^2	Every month; 12 courses (maintenance)
Protocol 2		
Cis-platinum	15–20 mg/m^2 days 1–3	Every 3 weeks; 3 courses (induction)
Adriamycin	30 mg/m^2 day 1	
5-Fluorouracil	300 mg/m^2 day 1	
Cis-platinum	30 mg/m^2 day 1	Every month; 12 courses (maintenance)
Adriamycin	30 mg/m^2 day 1	
5-Fluorouracil	300 mg/m^2 day 1	

Protocol 1 was performed for patients with pT3 without node involvement; protocol 2 was used for patients with pT4 or positive nodes

Results

Of our 25 patients with invasive bladder cancer, 18 remained alive with no evidence of disease for an average of 26 months. One patient died as a result of factors unrelated to cancer. Local recurrence and distant dissemination occurred in 6 patients; of these, 3 were alive for an average of 20.7 months. Three patients died of cancer progression at 9, 19, and 21 months. Figure 1 shows the survival curves of our patients.

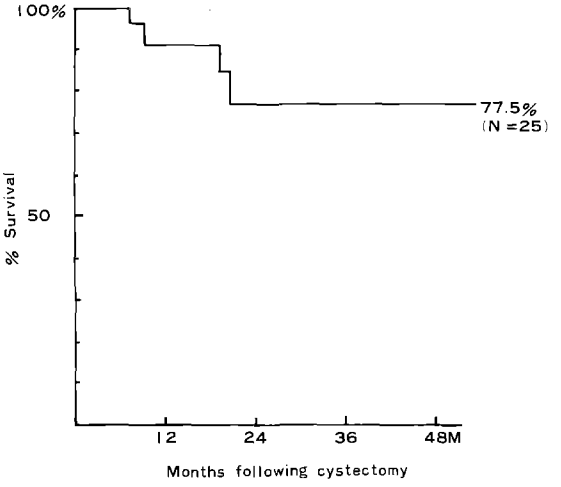

Fig. 1. Survival rate for patients treated with adjuvant chemotherapy

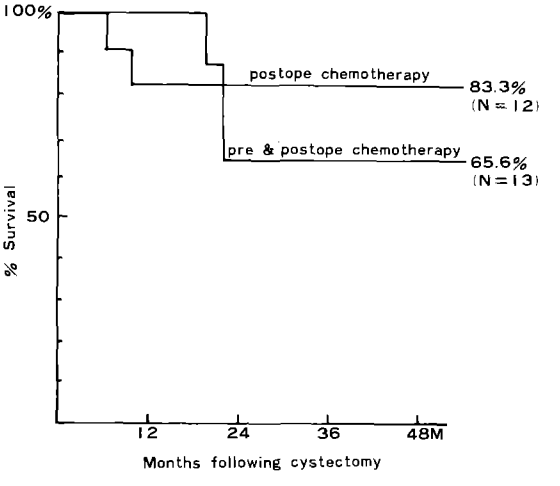

Fig. 2. Comparison of the survival rate for 13 patients who received preoperative and postoperative adjuvant chemotherapy with that for 12 patients who received postoperative chemotherapy alone

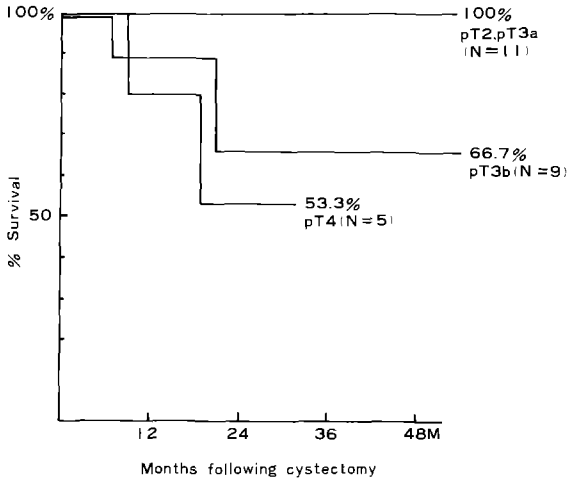

Fig. 3. Survival according to pathological stage

At 50 months, the survival rate of all patients was 77%. The survival rate of the 13 patients who had received adjuvant chemotherapy both pre- and postoperatively was 65.5%, while that of the remaining 12 patients treated with postoperative chemotherapy alone was 83.3% (Fig. 2). There was no statistical difference between the survival rates for the two groups. The correlation between survival and pT stage is shown in Fig. 3. The rates were 100% in pT3a, 66.7% in pT3b, and 53.3% in pT4. All 3 patients with positive nodes are still alive.

Six patients did not benefit from adjuvant chemotherapy (Table 3). In these cases, the interval between operation and recurrence ranged from 7 to 16 months, with an average of 10.7 months. The recurrence site was the pelvic cavity in 2 patients, the lymph nodes in 2 patients, and the lungs in 2 patients. In 1 patient with lung metastasis, CAF combination chemotherapy was continued after 60-Gy irradiation delivered to the metastatic site; he is still alive with stable disease. Another patient with lung metastasis received four courses of CAF and two courses of M-VAC chemotherapy as described by Sternberg et al. [19], but he died of cancer progression. One patient who exhibited lymph-node metastasis 8 months after the operation has since been treated with initial chemotherapy, i.e., the CAF combination. He is still alive in spite of progression of the disease. The remaining 3 patients with recurrence received no further aggressive therapy.

The number of drug courses given to the patients varied from 1 to 15 (Table 4). The most common reason for discontinuing therapy was abnormal liver function, although severe nausea, vomiting, and anorexia were major factors in 4 patients.

The major toxic effects consisted of different degrees of nausea, and vomiting occurred in 88% of patients during the administration of cis-platinum (Table 5). Four patients withdrew from the study because of these complications. Diminution of leukocyte counts to below 3,000 per cubic millimeter was seen in 3 patients receiving CAF combination chemotherapy. Alopecia was observed in 2 patients who had received adriamycin. Mild nephrotoxicity, as shown by an increase in serum creatinine and blood urea nitrogen levels, was observed in only 1 patient, but renal function returned to normal after 2 weeks. Impairment of liver function was seen in 4 patients. Hearing loss was not observed in any of the patients.

Table 3. Recurrence and progression

Case no.	Site	Interval to recurrence (months)	Treatment	Condition
1	Lung	16	Cobalt (60 Gy) CAF	Alive
2	Lung	13	CAF M-VAC	Died
3	Pelvic cavity	10	No treatment	Died
4	Lymph node	8	CAF	Alive
5	Lymph node	7	No treatment	Died
6	Pelvic cavity	7	No treatment	Alive

Table 4. Number of courses of therapy received by patients

Total courses received	Treatment	
	Cis-platinum alone	CAF
15	7	0
13	0	1
12	3	0
11	0	1
9	1	1
8	2	0
7	1	1
6	1	0
4	0	1
3	2	1
2	0	1
1	1	0
Total patients	18	7

Table 5. Toxicity

Toxicity	Treatment	
	Cis-platinum alone	CAF
Nausea	17/18	5/7
Vomiting	16/18	5/7
Alopecia	0/18	2/7
Abnormal liver function	2/18	2/7
Leucopenia ($<3{,}000/mm^3$)	0/18	3/7
Renal impairment (creatinine >2.0 mg/dl)	0/18	1/7
Hearing loss	0/18	0/7

Discussion

Urologists have long been disappointed by the results of surgical treatment of patients with invasive bladder cancer. It has been reported that the 5-year survival rate of patients with invasive bladder cancer treated by cystectomy alone or radiotherapy is less than 40% [5, 6, 8, 14]. Between

1972 and 1981, we observed that patients with stage-pT3 or -pT4 tumors had a 5-year survival rate of less than 30%, and that most of these patients (especially those with pT4 tumors) died of cancer progression within 2 years [20]. The failure of treatment following cystectomy may be due to local recurrence and/or distant dissemination [10]. Undetected, microscopic metastases as well as tumor emboli released during surgical manipulation may result in distant dissemination, while pelvic lymph-node metastases, inadequate resection, or tumor implantation may result in local regional recurrence. Consequently, it is not surprising that disseminated disease may develop when such patients are given local treatment alone. Therefore, it would appear to be logical that surgical resection of a tumor should be combined with aggressive adjuvant chemotherapy in the treatment of invasive bladder cancer with microscopic metastases [3].

The success of adjuvant chemotherapy requires effective chemotherapeutic agents, early initiation of treatment after control of the primary neoplasm, reasonable agent toxicity, and doses sufficient to be effective [3, 7]. Recently, cis-platinum has been shown to have effects on a variety of urinary tract malignancies, especially testicular cancer [2, 9, 17, 18, 22, 23]. In addition, Yagoda has reported a 35% response rate for cis-platinum in patients with bladder cancer [23]. Although this agent is known to cause renal damage, it exhibits a relative lack of myelosuppression, thus making it an attractive agent for combination chemotherapy. For the past few years, at our institution, the application of cis-platinum alone or in combination with adriamycin, mitomycin C, or cyclophosphamide has been found to be effective against disseminated bladder cancer [21]. In June 1982, we initiated the use of adjuvant chemotherapy involving these agents in order to improve the poor prognosis of patients with invasive bladder cancer. In patients with stage-pT3 or -pT4 tumors or node involvement we obtained a 77% survival rate at 50 months: 18 of the 25 patients were still alive with no evidence of the disease. All patients at stage pT3a are still alive, the average postoperative period being 29 months. The survival rate 66.7% for pT3b cases and 53.3% for pT4 cases. All patients with node involvement are still alive, although 1 exhibited recurrence of the disease. Unexpectedly, there was a slight increase in the survival rate of patients treated with postoperative adjuvant chemotherapy alone as compared to those who had undergone adjuvant therapy both before and after cystectomy. These results may be explained by the fact that the latter group included patients with more advanced disease as compared to the former group.

Many investigators have published results obtained by applying adjuvant chemotherapy in the treatment of invasive bladder cancer, using various agents such as cis-platinum, adriamycin, methotrexate, etc. [1, 4, 7, 10–13, 15, 16]. Our present results appear to be more encouraging than any other previously reported results. Although nausea and vomiting were severe for several hours, there were no cases of irreversible deterioration in renal function, and no instances of ototoxicity. Transitory diminution of the leukocyte count to below 3,000 per cubic millimeter occurred in a few patients treated with CAF combination chemotherapy.

In the present study, adjuvant chemotherapy combined with radical cystectomy proved to be effective, and we now intend to investigate whether the high survival rate observed is an indicator of genuine long-term benefits, and to employ further aggressive treatment in patients with invasive bladder cancer.

References

1. Clyne CA, Jenkins JD, Smart CJ, Guthrie J, Buchanan RB (1982) A trial of adjuvant chemotherapy for stage T3 bladder cancer. J Urol 129: 736
2. deKernion JB (1977) The chemotherapy of advanced bladder carcinoma. Cancer Res 37: 2771
3. Einstein AB, Shipley W, Coombs J, Cummings KB, Soloway MS, Hawkins I (1984) Cisplatin as adjunctive treatment for invasive bladder carcinoma; tolerance and toxicities. Urology 23: 110
4. Hall RR, Evans RGB, Pritchett CJ, Price DA (1982) Combination chemotherapy for advanced bladder cancer. Br J Urol 54: 16
5. Heney NM, Proppe K, Prout GR Jr., Griffin PP, Shipley WU (1983) Invasive bladder cancer: tumor configuration, lymphatic invasion and survival. J Urol 130: 895
6. Herr HW (1980) Cis-diamminedichloride platinum II in the treatment of advanced bladder cancer. J Urol 123: 853
7. Herr HW (1985) Preoperative irradiation with and without chemotherapy as adjuct to radical cystectomy. Urology 25: 127
8. Hill DE, Ford KS, Soloway MS (1985) Radical cystectomy and adjuvant chemotherapy. Urology 25: 151
9. Merrin CE (1979) Treatment of genitourinary tumors with cis-dichlorodiammineplatinum (II): experience in 250 patients. Cancer Treat Rep 63: 1579
10. Merrin C, Beckley S (1978) Adjuvant chemotherapy for bladder cancer with doxorubicin hydrochloride and cyclophosphamide: preliminary report. J Urol 119: 62
11. Oliver RTD, England HR, Risdon RA, Blandy JP (1984) Methotrexate in the treatment of metastatic and recurrent primary transitional cell carcinoma. J Urol 131: 483
12. Richards B, Bastable JRG, Freedman L, Glashan RW, Harris G, Newling DWW, Robinson MRG, Smith PH, Yorkshire Urological Cancer Research Group (1983) Adjuvant chemotherapy with doxorubicin (adriamycin) and 5-fluorouracil in T3, NX, MO bladder cancer treated with radiotherapy. Br J Urol 55: 186
13. Schaeffer AJ, Grayhack JT, Merrill JM, Kies S, Bulkley GJ, Shetty RM, Chmiel JS (1984) Adjuvant doxorubicin hydrochloride and radiation in stage D bladder cancer: preliminary report. J Urol 131: 1073
14. Skinner DG, Lieskovsky G (1984) Contemporary cystectomy with pelvic node dissection compared to preoperative radiation therapy plus cystectomy in management of invasive bladder cancer. J Urol 131: 1069
15. Skinner DG, Daniels JR, Lieskovsky G (1984) Current status of adjuvant chemotherapy after radical cystectomy for deeply invasive bladder cancer. Urology 24: 46
16. Socquet Y (1981) Surgery and adjuvant chemotherapy with high dose methotrexate and folinic acid rescue for infiltrating tumors of the bladder. Cancer Treat Rep 65: 187
17. Soloway MS, Einstein A, Corder MP, Bonney W, Prout GR Jr, Coombs J (1983) A comparison of cisplatin and the combination of cisplatin and cyclophosphamide in advanced urothelial cancer. Cancer 52: 767
18. Sternberg JJ, Bracken RB, Handel PB, Johnson DE (1977) Combination chemotherapy (CISCA) for advanced urinary tract carcinoma. JAMA 238: 2282
19. Sternberg CN, Yagoda A, Scher HI, Watson RC, Ahmed T, Weiselberg LR, Geller N, Hollander PS, Herr HW, Sogani PC, Morse MJ, Whitmore WF (1985) Preliminary results of M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) for transitional cell carconoma of the urothelium. J Urol 133: 403

20. Uekado Y, Ogawa T, Hirano A, Funaoka N, Sawada Y, Miyazaki Y, Mori K, Ebisuno S, Shinka T, Nakamura J, Ohkawa T (1983) Clinical evaluation of total cystectomy on patients with bladder cancer. Jpn J Urol 74: 1509
21. Uekado Y, Ogawa T, Yoshida T, Yamamoto S, Hirano A, Watanabe T, Shinka T, Ohkawa T (1985) Chemotheray for advanced bladder cancer: Clinical evaluation of chemotherapy for locally advanced or metastatic bladder cancer and adjuvant chemotherapy for deeply invasive bladder cancer following radical cystectomy. Acta Urol Jpn 31: 1365
22. Williams SD, Donohue JP, Einhorn LH (1979) Advanced bladder cancer: therapy with cis-dichlorodiammineplatinum (II), adriamycin, and 5-fluorouracil. Cancer Treat Rep 63: 1573
23. Yagoda A (1979) Phase II trial with cis-dichlorodiammineplatinum (II) in the treatment of urothelial cancer. Cancer Treat Rep 63: 1565