Hiroshima J. Med. Sci.
Vol.44, No.4, 129~132, December, 1995
HIJM 44-20

Cisplatin-Based Neoadjuvant Chemotherapy for Invasive Bladder Cancer

Hitoshi KADENA[1], Mikio IGAWA[2], Masanobu SHIGETA[1], Takahisa NAKAMOTO[1] and Tsuguru USUI[1]

1) Department of Urology, Hiroshima University School of Medicine, 1-2-3 Kasumi, Minami-ku, Hiroshima 734, Japan
2) Department of Urology, Shimane Medical University, 89-1 Enya, Izumo 698, Japan

ABSTRACT

Between February 1988 and March 1993, 24 patients with locally advanced bladder cancer (stages $T_{2-4}N_{0-3}M_0$) were included in this study. Combination chemotherapy consisting of methotrexate, vinblastine, epirubicin (doxorubicin) and cisplatin (M-VAC) was given to the patients in a neoadjuvant setting.

The clinical stage was T2N0M0 in eight patients, T3aN0M0 in three, T3bN0M0 in seven, T4N0M0 in five and T4N3M0 in one. After chemotherapy, total cystectomy was performed in 20 patients and partial cystectomy 4. Of 24 patients, one (4%) showed a pathological complete response, and eight (33%) had a pathological partial response, for an overall response rate of 38% (95% confidence limits 20 to 57%). Nine patients who achieved a pathological response to chemotherapy had a significantly higher survival rate than the nonresponders ($p<0.01$). In the relationship between the clinical stage and the response to chemotherapy, clinical T2 and T3a diseases were more likely to respond to chemotherapy than clinical T3b and T4 diseases, with a response rate of 64% and 15%, respectively. While a positive relationship between the pathological response and survival was observed, adequate follow-up is needed to assess the ability of neoadjuvant chemotherapy to improve the prognosis of patients with locally advanced bladder cancer.

Key words: *Invasive bladder cancer, Neoadjuvant chemotherapy, Cisplatin*

The management of muscle invasive bladder cancer continues to be a challenging problem. Despite radical surgery, the majority of patients with invasive transitional cell carcinoma die of metastatic disease within 5 years of diagnosis[2,11]. Cisplatin-based combination chemotherapy is now considered the most effective therapy for advanced or metastatic bladder cancer[5,13], and neoadjuvant chemotherapy for locally advanced bladder cancer has been performed for the purpose of improving the outcome[7,9,12]. Neoadjuvant chemotherapy may have several advantages, such as the possibility of in vivo evaluation of chemosensitivity, conversion of unresectability to resectability, the eradication of micrometastases and organ preservation[15], but the effect of neoadjuvant chemotherapy in treating invasive bladder cancer still remains unclear. We report the results of neoadjuvant chemotherapy consisting of methotrexate, vinblastine, epirubicin (doxorubicin) and cisplatin (M-VAC)[13] in patients with locally advanced bladder cancer.

PATIENTS AND METHODS

Between February 1988 and March 1993, 24 patients with locally advanced bladder cancer (stages $T_{2-4}N_{0-3}M_0$) who had been treated at the Urological Department of Hiroshima University School of Medicine and its affiliated facilities were included in this analysis.

The characteristics of the 24 patients are shown in Table 1. The clinical staging procedures included physical examination, laboratory studies, urine cytology, cystoscopic examination, transurethral biopsy, sonogram, abdominal computerized tomography, chest x-ray and bone scan. Magnetic resonance imaging was not routinely performed.

The M-VAC chemotherapy was administered according to the following schedule: 30mg/m^2 methotrexate on day 1, and 3mg/m^2 vinblastine, 30mg/m^2 doxorubicin and 70mg/m^2 cisplatin on day 2[13]. We used epirubicin instead of doxorubicin for 18 patients to reduce cardiac toxicity.

The clinical response was evaluated according to the criteria of WHO[16]. The pathological response was assessed according to the criteria recommended by the First International Consensus Development Conference on Bladder Cancer[10]. A pathological complete response (pCR)

Table 1. Characteristics of patients

No. of patients		24
Age Range (mean)		39–78 (61.3)
Sex (male: female)		22 : 2
PS#	0	15
	1	8
	2	1
Clinical T stage		
	2	8
	3a	3
	3b	7
	4	6
Histological findings		
	TCC	21
	TCC+SCC	3
Prior treatment		
	TUR	6
	Partial cystectomy	1
	Systemic chemotherapy	1

#Based on the WHO performance score[16].

Table 2. Response to neoadjuvant M-VAC

No.Pts.	Response*			Response rate %
	pCR	pPR	IR	
24	1	8	15	38 (20–57)

* Based on the criteria of the First International Consensus Development Conference on Bladder Cancer[10]. Numbers in parenthesis are 95 % confidence limits

was defined as the complete absence of cancer cells from the bladder and lymph nodes, as well as the absence of any detectable cancer by physical examination and imaging studies. A pathological partial response (pPR) was defined as a downstaging to a stage less than P2. Any response less than pCR and pPR was classified as incomplete (IR).

Overall survival was measured from the date of the initiation of chemotherapy by the method of Kaplan and Meier[6], with the end point being cancer death, and the difference between survival curves was evaluated by the Mantel-Cox test.

RESULTS

Ten patients received only one cycle of neoadjuvant chemotherapy, eleven received 2 cycles, one received 3 cycles and two received 4 cycles, for an average of 1.8 cycles. The median interval from the initial cycle of chemotherapy to surgical treatment was 2.42 months (range 0.97 to 5.07 months). After completion of chemotherapy, 20 patients (83%) received radical cystectomy and 4 patients (17%) underwent partial cystectomy. We observed no excess morbidity in any of the patients who underwent surgery after chemotherapy in this study.

Of these 24 patients, one (4%) achieved pCR and eight (33%) pPR, for an overall response rate of 38% (95% confidence limits 20 to 57%) (Table 2). While the overall response rate of 11 patients with clinical T2 and T3a diseases was 64%, that of 13 patients with clinical T3b and T4 diseases was 15% (Table 3). As to the correlation between the clinical and pathological responses, one clinical complete responder had a pathological complete response, but only five of 13 patients (38%) with a clinical partial response demonstrated pPR (Table 4).

One patient with pCR after partial cystectomy had a recurrence of superficial bladder cancer at 21 months after the start of chemotherapy and is alive without the disease 49 months after transurethral resection of this recurrent tumor. All 8 patients with pPR are alive for a duration of 13 to 63 months (median 39 months) and one of these had lymph nodal metastasis at 45 months after chemotherapy. Of the 15 patients with IR, six patients (40%) are alive for a duration of 24 to 90 months (median 32 months) and one of these had a local recurrence at 32 months. The remaining 9 (60%) patients had metastatic diseases (four in the lymph nodes, two in bone, two in skin and one in the liver) at a median of 14 months (range 2 to 35 months), and died of the disease at a median of 27 months (range 5 to 60 months). There was a significant difference in the survival rates between responders and nonresponders ($p<0.01$) (Fig.).

Table 3. Relationship between T and P categories after neoadjuvant M-VAC

T category	No. Pts.	P category			No. of pts. with P category less than P2/Totals (%)
		P0	Pis/Pa/P1	P2 ≦	
T2–3a	11		7	4	7/11 (64)
T3b–4	13	1	1	11	2/13 (15)
Totals	24	1	8	15	9/24 (38)

Table 4. Relationship between the clinical response and the pathological response

Clinical response	No.Pts.	Pathological response		
		pCR	pPR	IR
Complete	1	1		
Partial	13		5	8
No change	10		3	7
Totals	24	1	8	15

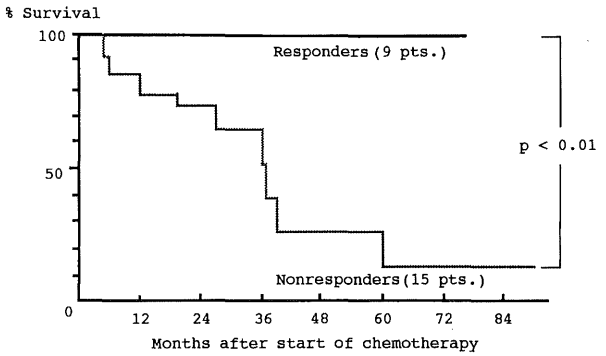

Fig. Survival curves of pathological responders and nonresponders calculated by the method of Kaplan and Meier[6]. The survival rate of responders was significantly higher than that of nonresponders ($p<0.01$).

Hematological toxicity included grade 3 leukopenia in two (8%), grade 2 leukopenia in seven (29%), and grade 2 thrombocytopenia in two (8%). Mucositis occurred in only one patient (4%). Nausea, vomiting and alopecia were universal. There was no significant hepatic or renal toxicity. No drug-related death was observed.

DISCUSSION

There has been little change in the survival rates of patients with muscle-invasive bladder tumors over 40 years, with 50% or fewer surviving 5 years when treated with radical cystectomy and/or radiotherapy[2,11]. These results have led several investigators to try cisplatin-based chemotherapy in neoadjuvant and/or adjuvant settings for locally invasive bladder cancer to improve the survival rate by eradicating any micrometastasis considered present at the initial diagnosis[7,14,15,17]. Splinter et al. reported that pathological responders had a 3 and 5-year survival rate of 85 and 75%, respectively, whereas nonresponders had a 3 and 5-year survival rate of 30 and 20%, respectively[12]. In another report[8], the survival of responders was significantly better than that of nonresponders, with specific death rates of 26 % and 63 %, respectively[8]. Also in our study, we observed a significantly better prognosis in pathological responders than in nonresponders. Although a positive correlation between response and survival was suggested by these results, this relationship does not imply a causal relationship and it may simply be a marker for a more favorable prognosis[4].

In the relationship between clinical stage and response for chemotherapy, Herr et al reported that clinical stage T2 and T3a diseases were most likely to respond to chemotherapy[4]. Similar results were obtained in our study.

Though it is likely that the better prognosis of the responders compared with the nonresponders might be the result of a better prognosis of clinical T2 and T3a tumors than clinical T3b and T4 tumors, Martinez-Pineiro et al reported that the disease-free period and survival time were longer within each T category for patients receiving cisplatin than for those who did not receive cisplatin[8]. This result suggested that the significantly longer survival of responders to chemotherapy is not only the result of comparing patients with less infiltrating and smaller tumors to a more heterogeneous patient population but also to the beneficial effect of chemotherapy. However, Martinez-Pineiro et al. concluded that no significant difference in survival between total cystectomy alone and neoadjuvant chemotherapy with cisplatin combined with total cystectomy was observed in the prospective randomized study[8].

Previously, we reported the low effectiveness of M-VAC in the liver (14%) and bone (25%) metastases of urothelial cancer[5]. Taking this into account, neoadjuvant chemotherapy may not be able to eradicate micrometastasis present in patients with invasive bladder cancer.

Two randomized trials of cisplatin-based combination chemotherapy following surgery versus definitive surgery alone are ongoing[1,3]. These studies will give us a reasonable answer to the true value of neoadjuvant cisplatin-based combination chemotherapy.

(Received August 3, 1995)
(Accepted November 28, 1995)

REFERENCES

1. **Crawford, E.D., Natale, R.B. and Burton, H.** 1990. Southwest oncology group study 8710: Trial of cystectomy alone versus neoadjuvant M-VAC and cystectomy in patients with locally advanced bladder cancer (Inter group Trial 0080), p.111–113. *In* T.A.W. Splinter and H.I. Scher (eds.), Neoadjuvant chemotherapy in invasive bladder cancer. Wiley and Sons, Inc., New York.
2. **Gospodarowicz, M.K., Hawkins, N.V., Rawlings, G.A., Connolly, J.G., Jewett, M.A.S., Thomas, G.M., Herman, J.G., Garrett, P.G., Chua, T., Duncan, W., Buckspan, M., Sugar, L. and Rider, W.D.** 1989. Radical radiotherapy for

muscle invasive transitional cell carcinoma of the bladder: Failure analysis. J. Urol. **142:** 1448–1454.

3. **Hall, R.R. and Parmar, M.K.B.** 1990. Randomized intercontinental trial of locoregional therapy with or without neoadjuvant chemotherapy. Neoadjuvant chemotherapy in invasive bladder cancer. p.105–109. *In* T.A.W. Splinter and H.I. Scher (eds.), Neoadjuvant chemotherapy in invasive bladder cancer. Wiley and Sons, Inc., New York.
4. **Herr, H.W., Whitmore, W.F. Jr., Morse, M.J., Sogoni, P.C., Russo, P. and Fair, W.R.** 1990. Neoadjuvant chemotherapy in invasive bladder cancer: The evolving role of surgery. J. Urol. **144:** 1083–1088.
5. **Igawa, M., Ohkuchi, T., Ueki, T., Ueda, T., Okada, M. and Usui, T.** 1990. Usefulness and limitations of methotrexate, vinblastine, doxorubicin and cisplatin for the treatment of advanced urothelial cancer. J. Urol. **144:** 662–665.
6. **Kaplan, E.L. and Meier, P.** 1958. Nonparametric estimation from incomplete observations. J. Amer. Stat. Ass. **53:** 457–81.
7. **Maffezzini, M., Torelli, T., Villa, E., Corrada, P. and Campo, B.** 1991. Systemic preoperative chemotherapy with cisplatin, methotrexate and vinblastine for locally advanced bladder cancer: Local tumor response and early followup results. J. Urol. **145:** 741–743.
8. **Martinez-Pineiro, J.A., Martin, M.G., Arocena, F., Flores, N., Roncero, C.R., Portillo, J.A., Escudero, A., Cruz, F.J. and Isorna, S.** 1995. Neoadjuvant cisplatin chemotherapy before radical cystectomy in invasive transitional cell carcinoma of the bladder: A prospective randomized phase III study. J. Urol. **153:** 964–973.
9. **Miller, R.S., Freiha, F.S., Reese, J.H., Ozen, H. and Torti, F.M.** 1993. Cisplatin, methotrexate and vinblastine plus surgical restaging for patients with advanced transitional cell carcinoma of the urothelium. J. Urol. **150:** 65–69.
10. **Oosterom, A.T.V., Akaza, H., Hall, R., Hirao, Y., Jones, W.G., Matsumura, Y., Raghaven, D., Tannock, I.F. and Yagoda, A.** 1986. Response criteria phaseII/ phase III invasive bladder cancer, p.301–310. *In* L. Denis, T. Niijima, G. Prout and F. H. Schroeder (eds.), Developments in bladder cancer. Alan R. Liss, Inc.
11. **Smith, J.A. Jr. and Whitmore, W.F. Jr.** 1981. Regional lymph node metastasis from bladder cancer. J. Urol. **126:** 591–593.
12. **Splinter, T.A.W., Scher, H.I., Denis, L., Bukowski, R. and Simon, S.** 1992. The prognostic value of the pathological response to combination chemotherapy before cystectomy in patients with invasive bladder cancer. J. Urol. **147:** 606–608.
13. **Sternberg, C.N., Yagoda, A., Scher, H.I., Watson, R.C., Ahmed, T., Weiselberg, L.R., Geller, N., Hollander, P.S., Herr, H.W., Sogoni, P.C., Morse, M.J. and Whitmore, W.F. Jr.** 1985. Preliminary results of M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) for transitional cell carcinoma of the urothelium. J. Urol. **133:** 403–407.
14. **Stockle, M., Meyenburg, W., Voges, S., Gertenbach, U., Thuroff, J.W., Huber, Ch. and Hohenfellner, R.** 1992. Advanced bladder cancer (stages pT3b, pT4a, pN1 and pN2): Improved survival after radical cystectomy and 3 adjuvant cycles of chemotherapy. Results of a controlled prospective study. J. Urol. **148:** 302–307.
15. **Thrasher, J.B. and Crawford, E.D.** 1993. Current management of invasive and metastatic transitional cell carcinoma of the bladder. J. Urol. **149:** 957–972.
16. WHO Handbook for Reporting Results of Cancer Treatment. Geneva: World Health Organization, 1979.
17. **Zinke, H., Sen, S.E., Hahn, R.G. and Keating, J.P.** 1988. Neoadjuvant chemotherapy for locally advanced transitional cell carcinoma of the bladder: Do local findings suggest a potential for salvage of the bladder? Mayo Clin. Proc. **63:** 16–22.