

NEOADJUVANT CHEMOTHERAPY AND BLADDER PRESERVATION FOR INVASIVE BLADDER CANCER

Mikio IGAWA^a, Shinji URAKAMI^a, Hiroki SHIRAKAWA^a, Hiroaki SHIINA^a, Tomoyuki ISHIBE^a, Hitoshi KADENA^b and Tsuguru USUI^b

Department of Urology^a, Shimane Medical University, Izumo 693, Japan and Department of Urology^b, Hiroshima University School of Medicine, Hiroshima 734, Japan

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A total of 16 patients with muscle invasive bladder cancer, clinical stage T2N0M0 (6), T3aN0M0 (7) or T3bN0M0 (3), underwent 1 to 4 cycles of neoadjuvant cisplatin-based chemotherapy followed by either partial cystectomy or transurethral resection. The overall response rate to the chemotherapy was 56% (95% confidence limits 32 to 79%). For the stages T2 and T3a cancer patients the overall response rate was 69%, while all 3 patients with T3b cancer showed incomplete response. Ten (63%) of 16 patients relapsed. Recurrence of superficial bladder cancer was observed in 5 patients with T2G2-3 or T3aG2 tumors, whereas invasive bladder cancer or metastases developed in 5 patients with T3a-3bG3 tumors. Eleven (69%) patients are alive with a functional bladder at a median followup of 48 months+. While bladder preservation may be permitted in selected patients with T2-3a disease, it is inconclusive whether neoadjuvant chemotherapy improves the survival of patients with invasive bladder cancer.

Effective systemic chemotherapy is the only current modality which offers the potential for improving long-term disease-free survival for patients successfully controlled locally for muscle invasive transitional cell carcinoma (1). In most cystectomized patients who die of bladder cancer, distant metastases are found at the time of death, even in the absence of local recurrence (2). An unknown proportion of these distant lesions is probably present as unrecognized micrometastases at the time of cystectomy (3). The rationale behind the use of chemotherapy in the neoadjuvant setting is the treatment of microscopic metastases, the presumed cause of systemic failure (4). While the ultimate endpoint for neoadjuvant chemotherapy is survival, bladder preservation may be permitted in selected patients. We have reviewed the data of neoadjuvant chemotherapy and bladder preservation in 16 patients with invasive bladder cancer.

MATERIALS AND METHODS

From 1988 to 1993, 16 patients with invasive bladder cancer were treated with cisplatin-based chemotherapy in the neoadjuvant setting and bladder preserving surgery. The median age was 65 years (range, 43 to

76) and all were male. Performance status based on WHO (5) was 0 in 12 patients, 1 in 3 and 2 in 1. Prior therapy included transurethral resection in 5 patients and irradiation in 2. Histology was transitional cell carcinoma in all patients and the grading of the tumor based on the criteria of the International Union Against Cancer (6) was 2 in 8 patients and 3 in 8 patients. Pre-chemotherapy staging consisted of cystoscopy, intravenous urography, computerized tomography (CT), transurethral ultrasonography, chest x-ray and bone scan. Clinical stage was T2N0M0 in 6 patients, T3aN0M0 in 7 and T3bN0M0 in 3.

The treatment regimen consisted of 1 to 4 cycles of cisplatin-based neoadjuvant combination chemotherapy followed by partial cystectomy or transurethral resection. Combination chemotherapies included methotrexate, vinblastine, doxorubicin and cisplatin (M-VAC) in 8 patients, methotrexate, etoposide and cisplatin (MEC) in 3, and methotrexate, vinblastine, epirubicin and cisplatin (M-VEC) in 5. M-VAC and M-VEC were administered according to the protocols of Sternberg (7) and Ruther (8), respectively. MEC consisted of 30mg/m² methotrexate on day 1, 80mg/m² etoposide on days 1, 2 and 3, and 70mg/m² cisplatin intravenously on day 2 (9). Response was assessed using the criteria of the First International Consensus Development Conference (10). A complete response was defined as disappearance of all tumors proven clinically (cCR) or pathologically (pCR). Patients were classified as clinical partial response (cPR) if they attained more than 50% decrease in size of measurable lesions by clinical staging. All other categories of response were classified as incomplete (IR). The duration of response and survival was measured from the initiation of therapy until relapse or death, respectively.

RESULTS

Six patients received one cycle of neoadjuvant chemotherapy, 6 received 2 cycles, 3 received 3 cycles and 1 received 4 cycles, for an average of 1.9 cycles. The median interval from the initial cycle of chemotherapy to the operation was 2.1 months. Partial cystectomy was done in 4 patients and transurethral resection in 12. The overall response rate was 56% (95% confidence limits 32 to 79%). pCR was attained in 1 patient and cCR in 1, respectively. Seven patients attained a cPR, whereas 7 patients showed IR. Response was evaluated in terms of initial stage

Correspondence to : Mikio Igawa, M.D., Department of Urology, Shimane Medical University, Izumo 693, Japan

Table 1. Response after neoadjuvant chemotherapy compared with clinical stage

Clinical stage before chemotherapy	No.	Response after chemotherapy			
		pCR	cCR	cPR	IR
T2	5			3	2
T3a	8	1	1	4	2
T3b	3				3

Table 2. Relationship between relapse, tumor stage and grade

Tumor stage	Grade	Relapse		
		Superficial Ca.	Invasive Ca.	Metastasis
T2	2	1		
	3	2		
T3a	2	2		
	3		1	1
T3b	3		2	1

(Table 1). In 3 of 5 (60%) of T2 patients, cPR was seen, and a major response (pCR, cCR or cPR) was observed in 6 of 8 (75%) of T3a patients. Response of three patients with T3b was IR.

Ten (63%) of 16 patients relapsed. The median time to relapse for these 10 patients was 12.5 months (range, 6–34 months). Relationship between relapse, clinical stage and histological grade of the tumor was assessed (Table 2). Recurrence of superficial bladder cancer was observed in 1 patient with T2G2, 2 with T2G3 and 2 with T3aG2, whereas invasive bladder cancer developed in 1 with T3aG3 and 2 with T3bG3. cCR had been attained in one of three patients with recurrence of invasive bladder cancer. Distant or lymph node metastases developed in 1 patient with T3aG3 and 1 with T3bG3.

The median survival for all patients was 48 months. Eleven (69%) of the 16 patients are alive with a functional bladder at a median follow-up of 48 months+ (range, 12–75 months+) and residual 5 patients died of disease at a median duration of 38 months (range, 13–73 months). Five dead patients had T3a–3bG3 tumors, and the response of these patients was cCR in 1 patient and IR in 4 patients.

DISCUSSION

Neoadjuvant chemotherapy has been performed for the treatment of the bladder cancer with the hope of improving primary tumor control following down-staging, allowing for organ preservation in patients with complete response to chemotherapy and increasing disease-specific survival by destroying occult distant micrometastases (11). While the overall response rate was 56% in our study, it was 69% in patients with T2–3a tumors and no response was observed in patients

with T3b tumors. Our results indicate that patients with T2–3a bladder tumors have a tendency to respond to chemotherapy and other investigator suggested that bladder preservation was a reasonable goal for patients with T2–3a tumors who responded completely to chemotherapy (12). In highly selected patients, those with T2 and T3a tumors, bladder preservation can be achieved (13), but patients managed by bladder-saving surgery need close surveillance since they remain at risk for development of new or persistent invasive tumors (12). Out of 10 patients with recurrence in our study, 5 patients with T3a–3bG3 tumors had recurrences of invasive bladder tumors or metastatic diseases. In view of tumor recurrence, bladder preservation is not suitable for patients with T3a–3bG3 tumors. Also, recurrence of invasive tumor in a patient with T3aG3 tumor who attained a cCR and received transurethral resection may indicate the underestimation in extent of disease after neoadjuvant chemotherapy. Absence of cystoscopic evidence of disease after chemotherapy does not always mean that residual invasive bladder cancer still is not present (12) and as many as 40% of patients who have stage T0 disease endoscopically have residual muscle-infiltrating disease at cystectomy (14–17). In addition, it also means that, at present, the clinical information available to the physician to assess the presence or absence of residual bladder cancer accurately as a prelude to any decision regarding bladder preservation is inadequate and that the decision to withhold definitive surgical therapy based on the results of a negative transurethral biopsy is likely to lead to local failure in a significant number of patients (18). Improvement in survival remains the most important endpoint of neoadjuvant chemotherapy, but it is unclear whether a favorable response to chemotherapy induces survival benefit or whether responding tumors have an inherently more favorable course (12). Herr *et al.* noted that approximately 25 to 30% of the patients had metastatic disease 18 to 24 months after chemotherapy and transurethral resection by the review of 4 recent studies (12). While our study showed a low incidence of metastasis after neoadjuvant chemotherapy, the contribution of this treatment modality to the outcome was not assessed because of small number of patients. Five-year survival rates of bladder cancer patients with stages T2 and T3a who were treated with TUR alone were reported to be 57–59%, 14–23%, respectively (18). The outcome of patients in our study was favorable compared to the results of surgery alone (18), but effect of neoadjuvant chemotherapy to micrometastatic lesions remain unclear from the findings in our study because this study was not a controlled one.

While bladder preservation may be possible in selected patients with T2–3a disease, they have a risk for recurrence of invasive bladder cancer. It is inconclusive whether neoadjuvant chemotherapy improves the survival of patients with invasive bladder cancer and any durable benefits of neoadjuvant chemotherapy remain to be demonstrated by the long-term follow-up of controlled study.

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