Original Article

Impact of Adjuvant Systemic Chemotherapy on Invasive Urothelial Cell Carcinoma of the Upper Urinary Tract

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Background: The objective of this study was to retrospectively investigate the effectiveness of adjuvant methotrexate, epirubicin, and cisplatin (MEC) combination chemotherapy for invasive urothelial cell carcinoma (UCC) of the upper urinary tract.

Materials and Methods: Between 1988 and 1996, 65 patients diagnosed with invasive UCC of the upper urinary tract underwent radical operation at one institution. Among them, 58 patients identified from medical records were enrolled in this study. Fifteen patients had lymph node–positive disease and 43 patients did not. Thirty-six patients received MEC chemotherapy and 22 patients were observed after surgery. Cox proportional hazards models were used to determine the impacts of clinicopathological findings on survival. A subgroup analysis of patients with lymph node-positive disease was conducted to evaluate disease-free survival and overall survival rates.

Results: The median interval between operation and chemotherapy was 5.6 weeks (range, 3-13) and the median follow-up period was 36 months (range, 2-105) after surgery. Disease-free and overall survival rates were 59% and 64%, respectively, at 3 years. Only lymph node status was significantly associated with disease-free and overall survival on multivariate analysis. On subgroup analysis of patients with lymph node-positive disease, 9 patients who underwent adjuvant chemotherapy had superior disease-free survival compared to 6 patients who did not undergo adjuvant chemotherapy (p=0.0434).

Conclusion: These findings showed that the prognosis of invasive UCC of the upper urinary tract is significantly associated with nodal status. Adjuvant MEC chemotherapy is feasible and has a positive impact on survival of patients with lymph node-positive disease. Based on these findings, we can select patients with nodal involvement for adjuvant chemotherapy, which may extend the median survival and reduce the rate of cancer death.

Key words: urinary tract, urothelial cell carcinoma, adjuvant chemotherapy

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Introduction

Urothelial cell carcinoma (UCC) of the upper urinary tract is not a common disease, accounting for only 5-10% of urothelial tumors [1]. Nephrouretectomy with bladder cuff excision has been the gold standard of treatment. Approximately 50% of patients with muscle invasion die due to

disseminated disease within 2 years of presentation despite advances in surgery and radiotherapy [2, 3]. Failure is presumed due to occult systemic spread [3]. Therefore, it has been suggested that survival can be improved only with the development of more effective systemic therapeutic regimens. Although UCC of the urinary tract is a chemotherapeutically responsive tumor [4], the options for treatment of local and distant metastases were previously limited and there was poor prognosis. However, the management of extensive urothelial cancer has improved with the identification of effective chemotherapeutic agents [5]. Sternberg et. al. reported a 69% overall response rate to M-VAC (methotrexate, vinblastin, doxorubicin, and cisplatin) chemotherapy regimen for advanced urothelial cancer at Memorial Sloan-Kettering Hospital [6] . Toxicity was significant, however, with 20% rate of WBC nadir sepsis, 4% treatment-related death, 31% renal toxicity and 41% mucositis [6]. Several single-arm studies and three randomized trials of adjuvant therapy against observation alone after surgery have been conducted. Interpretation of results has been limited due to small sample size, early closing of trials and selection bias. Those studies are not definitive, but suggest that adjuvant chemotherapy benefits patients with pathological stage T3b, T4 or Nodal positive disease in terms of disease-free and, perhaps, overall survival [7, 8, 9] . Suzuki et al. also reported that adjuvant chemotherapy with M-VAC/methotrexate, epirubicin and cisplatin (MEC) after radical cystectomy or nephrouretecotmy improves disease-free survival rates in patients with pathological lymph node-positive urothelial cancer [10]. However, it still remains unknown whether adjuvant systemic chemotherapy improves the prognosis of invasive UCC of the upper urinary tract.

The outcome of MEC adjuvant systemic chemotherapy and its positive impact on survival, observed in this study, may allow for the selection of patients who would benefit the most from this multimodal approach.

Material and Methods

From January 1988 to December 1996, a total of 65 patients diagnosed with invasive UCC of the upper urinary tract underwent radical operation at one institution. There were 58 patients identified from medical records who met eligibility criteria and were enrolled in this retrospective study. The eligibility criteria included: (i) pathological stage T2 or higher, based on 1997 tumor, nodes and metastasis (TNM) system for histopathological tumor staging of upper urinary tract cancer; (ii) pathologically defined nodal disease, regardless of the pathological stage of the primary tumor; (iii) lack of evidence of macroscopic residual disease and distant metastases; and (iv) good performance status (PS 0 or 1). Routine lymphadenectomy included the unilateral retroperitoneal lymph nodes of the renal pelvis and upper and middle segments of the ureter. We excluded patients with distant metastasis and patients who had received neo-adjuvant chemotherapy or preoperative radiation therapy.

Before initiation of chemotherapy, patients provided signed informed consent. Their decision to receive adjuvant chemotherapy was made after discussion with their physician. All patients with adjuvant systemic chemotherapy were admitted in 3-week cycles. However, when necessary, initiation of the next course was delayed until after recovery of the leukocyte count to at least 3000/mm^3 and the platelet count to at least 100000/mm^3. Granulocyte-colony stimulating factor (G-CSF) was administered when necessary to increase the leukocyte count. On day 1, 30 mg/m^2 methotrexate and 30 mg/m^2 epirubicin were administered intravenously (I.V.). Then, cisplatin (70 mg/m^2 I.V.) was given 24 hours later with additional I.V. fluid to maintain sufficient urinary output. All patients were administered 200 mg mannitol or 40 mg furosemide before and after the infusion of cisplatin. Antiemetics including 5-HT_3 receptor antagonist and steroids were used when deemed necessary by the investigator. Before each cycle of chemotherapy, 24-hour urine creatinine clearance (CCr) was measured to modify the cisplatin dosage accordingly. Full dosage cisplatin was administered when CCr was 60 ml/per minute or more and 80% of the dose was given when CCr was 30 to 60 ml/per minute. CCr of less than 30 ml/per minute

occurred in 4 patients who were given 200mg/m^2 carboplatin as a substitute for cisplatin.

Follow-up examination of the patients included physical examination with laboratory test, cystoscopy, chest X ray, computed tomography (CT), and cytological examination of urine. Bone scintigraphy and chest CT were performed if indicated clinically.

Disease-free survival and overall survival times were recorded from the date of radical surgery to the date of documented recurrence or death, as were all causes of death. Patients who did not relapse, or who were alive with/without cancer were censored. Cox proportional hazard models were used to determine the prognostic significance of clinical and pathological findings with disease-free survival and overall survival as the end-points. Significant tests were based on the test scores of Cox proportional models. For stepwise variable selection a *p*-value of 0.05 or less was required. Survival curves were obtained using the Kaplan-Meier method and were compared using log-rank test. A *p*-value of less than 0.05 was considered statistically significant and all *p*-values were two-sided.

Results

Patient and tumor characteristics are shown in Table 1. The mean age at operation was 65.1 years (range 31-87 years). Thirty-four of the patients were men and 24 were women. The mean follow-up period was 43.8 months (median, 36 months; range 2-105 months). The pathological grades of operated

Table 1. ***Characteristics of patients with invasive UCC of upper urinary tract***

Gender	N
Male	34
Female	24
Age (years)	
Range	31-87
Mean±S.D	64.8±10.7
Primary tumor origin	
Renal pelvis	34 (60%)
Ureter	24 (40%)
Histological Subtype	
Pure TCC	53 (92%)
Mixed tumor	5 (8%)
Tumor grade	
Ⅱ	15
Ⅲ	43
Pathologic Stage	
PT_2	7
PT_{3a}	20
PT_{3b}	27
PT_4	4
Lymph node	
N^-	43
N^+	15

Table 2. ***Multivariate analysis of factors associated with survival in 58 patients***

Factors	Variables	Disease-free survival		Overall survival	
		P-value	Risk ratio (95% CI)	P-value	Risk ratio (95% CI)
Gender	Male/Female	0.750	0.8755 (0.385-1.989)	0.672	1.224 (0.481-3.114)
Age	≧65 / <65	0.3733	1.469 (0.629-3.428)	0.086	2.53 (0.877-7.301)
Tumor grade	Ⅲ/Ⅱ	0.466	1.467 (0.523-4.114)	0.251	2.128 (0.587-7.717)
Nodal disease	N^+/N^0	0.0215	3.513 (1.204-10.250)	0.0153	4.955 (1.349-16.765)
Adjuvant chemotherapy	$C/T^- / C/T^+$	0.934	2.389 (0.864-6.612)	0.898	2.717 (0.856-8.627)
Primary site	Pelvis/Ureter	0.265	2.3897 (0.864-6.612)	0.4383	1.538 (0.517-4.572)

specimens were grade 2 in 15 patients and grade 3 in 43 patients. Pathological stages (pTs) were T2 in 7, T3a in 20, T3b in 27 and T4 in 4 patients. Fifteen patients had node-positive disease and 43 patients had node-negative disease. Thirty-six patients underwent adjuvant chemotherapy after surgery (1-6 cycles, median 4 cycles) and the remaining 22 patients did not. The median interval from surgery to adjuvant chemotherapy was 1 month (range 1-2.5 months).

Disease-free and overall survival rates for all 58 patients were, respectively, 59 % and 64 % at 3 years, and 45% and 49% at 5 years. Gender, age, tumor pathological grade, lesion side, primary tumor site, lymph node status, and adjuvant chemotherapy were included on multivariate analysis. The most significant risk factor for predicting both disease-free and overall survival was lymph node status (p=0.0225 and 0.0153). (Table2).

In 15 patients with lymph node-positive disease, we analyzed whether adjuvant chemotherapy has a positive survival benefit. The characteristics of node-positive patients are presented in Table 3. There were similar distributions for gender, age and tumor pathological stage among the chemotherapy and observation-only groups Disease-free and overall survival rates for 9 patients who received adjuvant chemotherapy were 38% and 48% at 3 years, respectively, whereas disease-free and overall survival rates for 6 patients who did not receive adjuvant chemotherapy were 0% and 19%, respectively. There was a significant difference in disease-free survival between patients who received adjuvant chemotherapy and those who did not (p=0.0424) (Fig.1). There was better overall survival in adjuvant chemotherapy group, however, this difference was not statistically significant (p=0.0729) (Fig.2).

Discussion

Surgical resection has been considered the definitive local therapy for organ-confined UCC of the bladder and upper urinary tract. However, patients with locally advanced disease are at substantial risk of both local and distant relapse [11]. If there is high risk of recurrence, patients are usually assigned postoperative adjuvant chemotherapy to delay tumor relapse and improve survival rate. Analysis of pathologic factors for

Table 3. ***Baseline characteristics of patients with lymph-node positive disease***

	N=9 Adjuvant chemotherapy	N=6 Surgery alone	p-value
Gender Male Female	 5 4	 3 3	 0.608@
Age (years) Range Mean	 50.87 65.44	 50.82 61.8571	 0.545#
Tumor grade Ⅱ Ⅲ	 2 7	 1 5	 1.0@
Primary site pelvis ureter	 7 2	 4 2	 0.622@
Pathological stage PT_2 PT_{3a} PT_{3b} PT_4	 1 6 2 0	 0 5 0 1	 0.864%

@ Fisher exact test
 # Student t test
% Wilcoxon Rank-sum test

predicting cancer specific survival among patients who have received radical cystectomy for UCC of urinary bladder and prostate shows that poor cancer specific survival is related to muscle invasive disease, positive nodes, evidence of vascular or lymphatic invasion and positive surgical margins [12]. However, there is controversy as to whether all patients who undergo radical surgery for invasive UCC of the upper urinary tract should be routinely treated with postoperative chemotherapy.

Evaluation of data from two large series of patients who underwent radical cystectomy has confirmed pathological stage as a major predictor of relapse. Nodal status, microscopic involvement of surgical margins and histological grade have been found to influence cancer-specific survival on multivariate analysis[13]. These prognostic factors are of equivalent importance in patients with upper urinary tract UCC[14]. In this study, we showed that the prognosis of invasive upper urinary tract UCC is significantly associated with nodal status. Adjuvant chemotherapy did not affect the survival of all patients. However, on subgroup analysis of patients with node-positive disease, adjuvant chemotherapy had a positive survival benefit.

Skinner et al. randomly compared cystectomy plus four cycles of adjuvant chemotherapy (CISA: cisplatin, cyclophosphamide and adriamycin) with radical cystectomy alone in local advanced TCC[8]. Their findings demonstrated a significant disease-free survival advantage for the adjuvant treatment group in the 5 years after cystectomy. However, overall survival was not significantly prolonged. In a subgroup of patients with only one positive

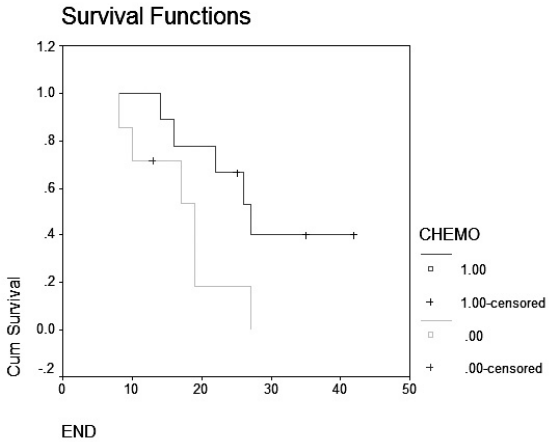

Fig. 1 3-year disease-free survival curve demonstrates benefit in adjuvant chemotherapy group. (Kaplan-Meier method, log-rank test, p=0.0424)

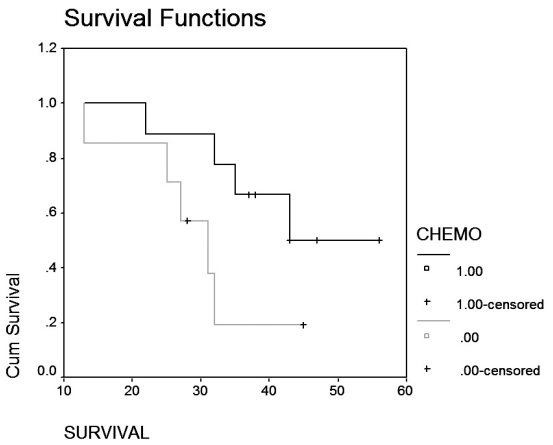

Fig. 2 3-year overall survival curve does not demonstrate benefit in adjuvant chemotherapy group. (Kaplan-Meier method, log-rank test, p=0.0729)

lymph node, those in the adjuvant chemotherapy group had superior disease-free and overall survival rates when compared with patients in the cystectomy alone group[8]. Stockle et al. compared 80 patients who underwent three cycles of adjuvant M-VAC or MVEC with 86 patients who underwent cystectomy alone, and found a highly significant difference in disease-free survival[15]. That study also demonstrated that adjuvant chemotherapy achieves the highest therapeutic benefit in patients with pN1 disease[15].

UCC is a malignancy in which a number of single agents with different mechanisms of action are effective. Patients with UCC at high risk of relapse after radical surgery can have a reasonable chance at long-term survival with systemic adjuvant chemotherapy. However, such treatment is often associated with toxicity. The benefits of such treatment should be addressed in a large randomized controlled trial[16]. Most of the older agents have limited activity, but several combinations are quite active. The most common regimens over the past years have been cyclophosphamide, doxorubicin, and cisplatin (CAP, CISA); cisplatin, methotrexate, and vinblastine (CMV, MCV) and M-VAC. M-VAC therapy, proposed by the Memorial Sloan Kettering Cancer Center in 1985, was once widely accepted as a standard regimen[6]. However, it is associated with adverse drug reactions such as bone marrow suppression and stomatitis. The MEC regimen modified from M-VAC regimen demonstrates comparable effect with less drug reaction[17]. We have used this regimen as adjuvant regimen for invasive or metastatic urothelial caner since 1987. Several new agents have recently been identified, including docetaxel, paclitaxel, gemcitabine, piritrexim, and ifosfamide. In comparison with older agents, these new agents demonstrate activity in both first- and second-line therapy, favorable toxicity profiles, metabolism of renal function, and complete response of metastatic disease to a single agent. Randomized trials have shown that they are an acceptable alternative to the M-VAC regimen. These new regimens have much lower toxicity than those previously used, but with comparable survival[18].

There are several limitations to our study. First, it is not a randomized controlled trial. Patients decided to receive adjuvant chemotherapy after being well informed and providing consent. Second, there were only a small number of study subjects, especially on subgroup analysis, making it difficult to distinguish between a real effect and random variations. Lastly, the study was conducted in one center. Thus, it is not suitable to extrapolate the findings to the general population.

Conclusion

In conclusion, from our limited study subjects, adjuvant chemotherapy with MEC after radical nephrouretectomy improves disease-free survival rates in patients with pathological lymph node positive UCC. However, large randomized controlled trial may be needed to verify this finding..

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