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ORIGINAL ARTICLE

Neoadjuvant chemotherapy improves survival rate in advanced urothelial carcinoma

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Abstract Radical surgery (RS) with adjuvant chemotherapy (AC) or radiotherapy has been conventionally used for patients with advanced urothelial carcinoma (AUC). Recent research has indicated that systemic neoadjuvant chemotherapy (NC) with RS yields better outcomes than RS alone for patients with locally advanced bladder cancer. However, there are no reports indicating whether NC or AC would be beneficial for patients with AUC. The present study compared the survival rate for AUC patients receiving NC or AC. A retrospective analysis was conducted using data for 64 patients with AUC who underwent RS and systemic chemotherapy at our institution between March 2002 and March 2011. Of the 64 patients, 30 received NC before RS and 34 received RS followed by systemic AC. Pathologic stages ($p = 0.002$), grades ($p = 0.018$) and lymphovascular invasion ($p = 0.047$) were significantly lower in the patients who received NC first than in those who received RC first. Furthermore, analysis of the surgical specimens revealed that 26.7% of patients who received NC before RS had complete remission. There were no significant differences in demographic data, surgical complications, and chemotoxicity between the two patient groups. The progression-free survival (PFS) and overall survival (OS) of patients who received initial NC were significantly better than those of patients who received initial RC ($p = 0.002$ and 0.018, respectively). Our results indicate that NC administration before RS significantly improved the PFS and OS of AUC patients, without increasing

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surgical complications and chemotoxicity. Further prospectively controlled trials need to be conducted to confirm the effectiveness of NC for AUC patients.

Introduction

Urothelial carcinoma (UC) is a malignant tumor that originates from the transitional epithelium, including the inner surface of the upper urinary tract (UUT) and bladder. UC, the fifth and ninth most common cancer in men and women, respectively, in the USA, has a variable outcome. Approximately 70,500 cases of UC were reported in the USA in 2010; of these, 14,000 individuals died from the disease, mostly because of progression to advanced UC (AUC) [1,2]. In Taiwan, the rate of UC incidence was 15.4 per 100,000 males in 2008, and the mortality rate associated with UC has shown an increasing trend [3]. Because UC is a chemosensitive tumor, radical surgery (RS) with adjuvant chemotherapy (AC) has been conventionally used for patients with AUC. However, despite new surgical advances and chemotherapeutic regimens, the overall 5-year survival rate for patients with AUC has remained relatively unchanged over recent decades. The 5-year survival rate is 30–50% for pT3 cases and approximately 0–20% for pT4 or lymph node metastasis cases [4].

Recent studies have evaluated the efficacy of neoadjuvant chemotherapy (NC) administered before RS and AC administered after RS in AUC patients. It has been speculated that AC increases the recurrence-free survival rate and improves the outcome for patients with muscle-invasive bladder cancer; however, not all studies have shown a survival benefit [5,6]. The effectiveness of NC with a platinum-based regimen was recently evaluated for patients with locally advanced bladder cancer. These studies showed that the survival rates were better for NC with radical cystectomy than for cystectomy alone [7,8]. However, there are no studies indicating whether NC or AC would be beneficial for patients with AUC. Hence, the aim of the present study was to compare the efficacy of NC and AC in improving the progression-free survival (PFS) and overall survival (OS) of patients with AUC.

Methods

The study was approved by the Institutional Review Broad of our hospital. Between March 2002 and March 2011, 101 patients with AUC underwent RS and systemic chemotherapy at the Kaohsiung Medical University Hospital, Kaohsiung Municipal Ta-Tung Hospital, and Kaohsiung Municipal Hsiao-Kang Hospital. Clinical and histopathological data for the patients were retrospectively reviewed. A smoker was defined as someone who smoked half a pack of cigarettes per day for more than 6 months. Areas endemic for blackfoot disease in south Taiwan (Xuejia, Beimen, Budai, and Yizhu) were included [9].

Patients older than 18 years and who had adequate bone marrow, liver, and renal functions, and locally advanced cancer (T3 or T4) or lymph node metastasis (N1, N2, or N3) according to the Response Evaluation Criteria in Solid Tumors [10] were included in the study. All patients underwent tumor biopsy to confirm the histopathological diagnosis. UC diagnosis and staging were confirmed by independent assessment of all images and specimens by at least two radiologists and pathologists, respectively. Of the 101 patients, 37 were excluded from the study because of diffuse metastasis before RS (15 patients), incomplete chemotherapeutic cycle (10 patients), previous UC (7 patients), a short follow-up period of >3 months (2 patients), or incomplete data (3 patients). The remaining 64 patients were stratified into two groups according to their treatment strategy. The first group (Group I) received three cycles of systemic NC before RS. The second group (Group II) received RS, followed by at least three cycles of systemic AC. RS included cystectomy with bilateral pelvic lymphadenectomy for bladder cancer, and nephroureterectomy with bladder cuff excision and retroperitoneal lymph node dissection for UUT-UC. Various urinary diversions were performed if necessary. RS was performed either openly or laparoscopically, depending on the choice made by the patient and the operating surgeons.

All patients received combination chemotherapy involving a 28-day-cycle gemcitabine and cisplatin regimen: gemcitabine (1000 mg/m^2 body surface area) on Days 1, 8, and 15; and cisplatin (70 mg/m^2) on Day 2 [11]. Before chemotherapy and in the second week of each chemotherapeutic cycle, a complete blood count, serum hepatic and renal function tests, electrolyte titration, and routine urine tests were performed. The chemotherapeutic doses were adjusted if severe toxic effects occurred. Regular follow-up examinations consisted of interval history and physical examination, urinalysis, urine cytology, biochemical analysis, chest radiography, abdominal ultrasound, and abdominal computed tomography. After three cycles of treatment, chemotherapy responses were assessed according to clinical information and imaging findings. Surgical complications and adverse effects of chemotherapy were graded according to the severity grading system of the Memorial Sloan Kettering Cancer Center [12] and the National Cancer Institute Common Toxicity Criteria [13], respectively.

PFS was calculated from the date of the initiation of treatment until the date that UC worsened or recurred. OS was calculated from the date of the diagnosis of UC until the date of death or the last contact when the patients were still alive at the time of follow-up. Demographic and clinicopathologic characteristics were compared between groups using the Pearson χ^2 test or the Student t test. PFS and OS were calculated according to the Kaplan–Meier method using a log-rank test. Statistical analyses were performed using JMP v.8.0 (SAS Institute Inc., Cary, NC, USA) and SPSS v.15.0 (SPSS Inc., Chicago, IL, USA) statistical

software. For all statistical analyses, a p value < 0.05 was considered statistically significant.

Results

The median patient age was 66.94 (±8.91) years (range 36–82), and the median follow-up period was 21 months (range 3–58). The demographic characteristics are listed in Table 1. Of the 64 patients, 30 (47%) underwent NC before RS (Group I) and 34 (53%) underwent RS followed by AC (Group II). There were no differences in patient age, gender, area inhabited, smoking status, and pre-treatment evaluation between the two groups. With regard to tumor features, baseline clinical cancer multiplicity, size, location, stage, and biopsy grade were also similar (Table 1). Severe or lethal surgical complications and chemotoxicity were rare. The Grade 1–3 surgical complication rates, including extensive blood loss (40% vs. 44%, $p = 0.739$), cardiopulmonary thromboembolism (7% vs. 12%, $p = 0.480$), gastrointestinal adverse effects (17% vs. 24%, $p = 0.493$), nosocomial infection (23% vs. 18%, $p = 0.572$), and poor wound healing (13% vs. 18%, $p = 0.634$), were similar between the two groups (Table 2). The adverse effects of chemotherapy noted in Groups I and II included granulocytopenia (27% vs. 38%, $p = 0.323$); thrombocytopenia (37% vs. 41%, $p = 0.711$); anemia (33% vs. 44%, $p = 0.376$), gastrointestinal effects (33% vs. 35%, $p = 0.869$), neuropathy (7% vs. 6%, $p = 0.897$), malaise (23% vs. 41%, $p = 0.126$), and hepatotoxicity (43% vs. 26%, $p = 0.155$). None of these differences was statistically significant. However, nosocomial infections occurred significantly more frequently in Group II (17% vs. 50%, $p = 0.042$). A particularly noteworthy finding was the response rate to chemotherapy. Although there was no significant difference between the two groups, the response rate to chemotherapy was better in Group I than in Group II (77% vs. 56%, $p = 0.080$; Table 1).

Pathologic features are listed in Table 3. There were significant reductions in pathologic stage ($p = 0.002$) and grade ($p = 0.018$) and lymphovascular invasion ($p = 0.047$) in patients who received NC first. Furthermore, 26.7% of patients in Group I who had pathologic stage pT0 showed complete remission (CR), whereas none of the patients in Group II did. The median follow-up period was 24 months (range 3–58) and 19 months (range 3–49) for Groups I and II, respectively. Two patients (3%) were lost to follow-up and 25 cancer-related deaths (39%) occurred. At the time of the analysis, 37 patients (58%) remained alive with regular follow-up. The 2-year PFS rate for Group I and II

Table 1 Clinical characteristics of the study population.

Characteristic	NC before RS ($n = 30$)	AC after RS ($n = 34$)	p
Sex			0.315
Female	13 (43)	19 (56)	
Male	17 (57)	15 (44)	
Age (y)	65.30 ± 8.77	68.38 ± 8.91	0.169
BMI (kg/m^2)	23.49 ± 3.23	22.34 ± 5.32	0.306
Lived in BFD	10 (33)	13 (38)	0.683
Smoking	11 (37)	13 (38)	0.897
Pre-treatment data			
WBC (10^3/μL)	7.47 ± 2.33	7.38 ± 1.85	0.869
Hemoglobin (g/dL)	12.90 ± 1.93	12.19 ± 1.75	0.124
Platelets (10^3/μL)	250.37 ± 70.99	279.32 ± 84.89	0.147
Serum GOT (mg/dL)	26.90 ± 9.04	24.65 ± 9.41	0.334
Serum creatinine (mg/dL)	1.04 ± 0.36	1.03 ± 0.26	0.930
Multiplicity	12 (40)	11 (32)	0.525
Tumor size (cm)	4.14 ± 1.84	4.09 ± 2.42	0.924
Tumor location			0.064
Upper urinary tract	9 (30)	18 (53)	
Bladder	21 (70)	16 (47)	
Clinical stage			
cTNM Stage 3	10 (33)	17 (50)	
cTNM Stage 4	20 (67)	17 (50)	0.176
Biopsy grade			0.928
High	29 (97)	33 (97)	
Low	1 (3)	1 (3)	
Chemotherapy response			0.080
Positive	23 (77)	19 (56)	
Negative	7 (23)	15 (44)	

Data are presented as n (%) or mean ± SD.
AC = adjuvant chemotherapy; BFD = blackfoot disease-endemic area; BMI = body mass index; GOT = glutamic oxaloacetic transaminase; NC = neoadjuvant chemotherapy; RS = radical surgery; WBC = white blood cell count.

Table 2 Surgical complications and chemotoxicity in patients receiving neoadjuvant chemotherapy or adjuvant chemotherapy.

Observation	NC before RS ($n = 30$)	AC after RS ($n = 34$)	p
RS complication			
Extensive blood loss	12 (40)	15 (44)	0.739
Thromboembolism	2 (7)	4 (12)	0.480
GI adverse effect	5 (17)	8 (24)	0.493
Nosocomial infection	7 (23)	6 (18)	0.572
Poor wound healing	4 (13)	6 (18)	0.634
Chemotherapy toxicity			
Granulocytopenia	8 (27)	13 (38)	0.323
Thrombocytopenia	11 (37)	14 (41)	0.711
Anemia	10 (33)	15 (44)	0.376
GI upset	10 (33)	12 (35)	0.869
Neuropathy	2 (7)	2 (6)	0.897
Malaise	7 (23)	14 (41)	0.126
Nosocomial infection	5 (17)	17 (50)	0.042
Hepatotoxicity	13 (43)	9 (26)	0.155

Data are presented as n (%).
AC = adjuvant chemotherapy; GI = gastrointestinal; NC = neoadjuvant chemotherapy; RS = radical surgery.

patients was 63% and 34%, respectively. Additional data showed that the 2-year OS rate for Group I and II patients was 72% and 44%, respectively. Our data indicate that patients who were administered NC before RS had significantly better PFS and OS ($p = 0.002$ and 0.018, respectively; Figs. 1 and 2).

Discussion

AUC, an incurable terminal disease, accounts for 3% of all cancer-related mortality in the USA [1]. Conventionally,

Table 3 Pathologic characteristics of patients receiving neoadjuvant chemotherapy or adjuvant chemotherapy.

Observation	NC before RS ($n = 30$)	AC after RS ($n = 34$)	p
Pathologic stage			0.002
pTNM $\leq$ Stage 2	18 (60)[a]	5 (15)	
pTNM $\geq$ Stage 3	12 (40)	29 (85)	
Surgical margin			0.821
Positive	3 (10)	4 (12)	
Negative	27 (90)	30 (88)	
Grade			0.018
High	20 (67)	33 (97)	
Low	10 (33)	1 (3)	
LV invasion			0.047
Positive	12 (40)	22 (65)	
Negative	18 (60)	12 (35)	

Data are presented as n (%).
AC = adjuvant chemotherapy; LV = lymphovascular; NC = neoadjuvant chemotherapy; RS = radical surgery.
[a] Eight cases (26.7%) showed complete remission (pT0).

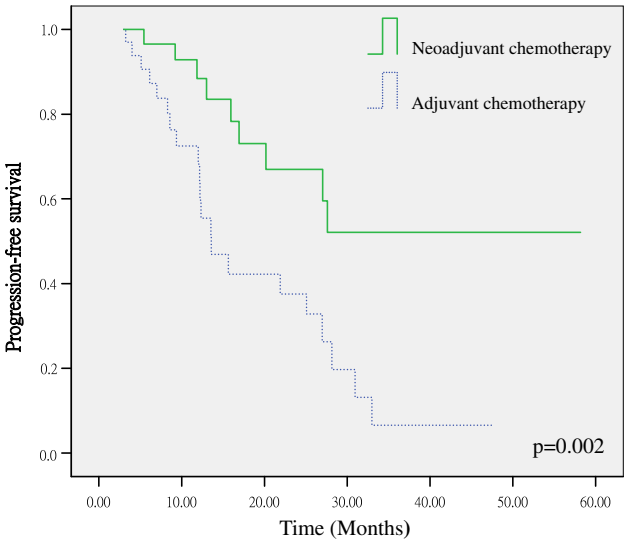

Figure 1. Progression-free survival for patients with advanced urothelial carcinoma in the neoadjuvant chemotherapy (solid line) and adjuvant chemotherapy (dotted line) groups ($p = 0.002$).

RS has been the mainstay of treatment for AUC for decades, but the standard has recently been challenged for many reasons, including the fact that optimal cytoreductive surgeries cannot be performed in some patients and that motility is mainly related to distant spread. With improvements in therapeutic dose adjustment and interventions for adverse effects, AC or NC has been recommended for patients with AUC. Although AC after RS is suggested for patients at high risk of recurrence and metastasis, there is no clear consensus on the impact of AC on the survival of AUC patients [5,6]. NC, which causes adequate tumor shrinkage of unresectable tumors, early control of metastatic disease, and reduction of occult

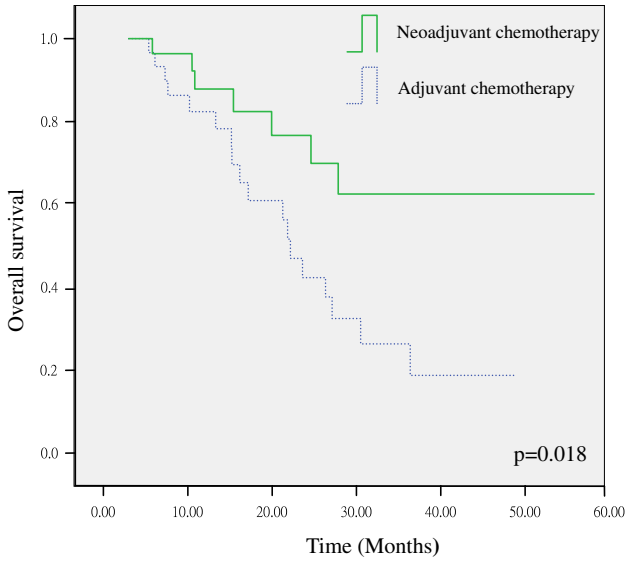

Figure 2. Overall survival for patients with advanced urothelial carcinoma in the neoadjuvant chemotherapy (solid line) and adjuvant chemotherapy (dotted line) groups ($p = 0.018$).

micrometastases, is considered another therapeutic choice for AUC patients. However, the use of NC before RS in AUC patients has not yet been standardized because of the potential for disease progression from delay of curative surgery and the increased risk of surgical complications. Community-based studies have been conducted to ascertain the beneficial effects of NC for patients with advanced bladder cancer [7,8,14] and UUT [15]. Few recent trials have directly compared the efficacy of NC and AC in patients undergoing RS.

Our results revealed a significant reduction in pathologic stage in AUC patients who received NC, and these patients showed a 60% incidence of pT2 or lower disease. Furthermore, of the 30 patients in Group I, 8 (26.7%) were pathologically free of cancer (CR, pT0). Grossman et al. observed a CR rate of 38% in 126 patients with locally advanced bladder UC who received NC [7]. Matin et al. found that NC was associated with a 14% CR rate and a significant rate of downstaging in UUT-UC [15]. A study by Schultz et al. revealed a CR rate after NC in patients with clinical T2/T3a of 43%, but only 9% in patients with clinical T3b/T4 tumors [16]. This is consistent with our finding that more than half (62.5%) of the CR patients after NC had a lower clinical stage (cTNM stage 3).

Compared to AC after RS, NC administration before RS improved PFS and OS for patients with AUC. With regard to the risk factors for survival, previous studies have revealed that the primary prognostic factor was pathologic grade and stage [6,8,17–19]. While low-grade disease was associated with a 5-year OS rate that approached 94%, high-grade disease conferred a poor survival rate of approximately 28% [20]. Another study conducted at our hospital showed that the 5-year survival rate was approximately 50% in UTT-UC patients with pT3 lesions and was less than 5% in patients with pT4 or node-positive disease [19]. In addition, pathologic CR was a good surrogate for predicting longer relapse-free survival and OS. Compared to patients with residual cancer after NC, those with CR appeared to have excellent survival rates [8]. This is consistent with our results indicating that PFS and OS were significantly associated with tumor pathologic stages ($p = 0.001$ and 0.002) and grade ($p = 0.004$ and 0.012) (data not shown). Lymphovascular invasion might be another independent prognostic factor and could be a useful tool during disease treatment and follow-up [21]. There was a significant reduction in lymphovascular invasion in Group I patients who received NC first, and this might have played a role in the variability of survival between the two groups.

Several mechanisms to explain the impact of NC on survival have been discussed. Because positive surgical margins and the lack of optimal RS were found to be correlated with dismal outcomes [8], NC was considered to result in adequate tumor shrinkage and better conditions for optimal RS, leading to better survival results. Another advantage of NC for survival may be early control of occult micrometastases. Thoeny et al. observed a high rate of micrometastases (25%) in urologic cancer patients with preoperatively negative imaging findings, particularly those with locally advanced cancer [22]. Current morphologic assessments conducted using computerized tomography or magnetic resonance imaging of lymph nodes are based on size and shape and are unable to detect smaller metastases in normal-sized nodes [22]. The consequences of missing micrometastasis are inaccurate preoperative risk stratification and treatment strategies, resulting in further distal metastasis. Since the motility of UC is mainly related to distant spread, early control of occult micrometastasis in AUC is considered to play a role in survival improvement. Besides early tumor control, another plausible reason for the use of NC, at least for UUT-AUC patients, may be the strong dose of the cisplatin-based chemotherapy. The potential risk of nephrotoxicity for a solitary kidney may discourage oncologists from administering sufficient cisplatin-based AC after nephroureterectomy. A multifactorial analysis by Barlow et al. showed that 52% of patients who underwent radical nephrectomy for renal cell carcinoma had new-onset chronic kidney disease more than 3 months after surgery [23]. In our study, there was a trend towards a poor response rate to chemotherapy in the RS followed by AC group. This may be attributed to an inadequate dose of AC and a delay in the control of distant spread.

Although the occurrence of myelosuppression or gastrointestinal effects during chemotherapy was noted in more than one-third of the patients in our study, all the patients recovered and there were no life-threatening toxic effects or deaths. Our study showed that the combination of gemcitabine and cisplatin can be administered safely before or after RS to patients with AUC, and this was because of selection of patients with adequate renal function, attentive adjustment of drug doses, careful monitoring of chemotoxicity, and appropriate interventions for adverse effects. NC did not influence the risk of surgical complications and did not increase the risk of adverse effects related to chemotherapy. Nevertheless, a higher percentage of nosocomial infections was observed for AC, which may have been caused by unnecessary antibiotic therapy, prolonged hospital stay, compromised nutritional or immune status after RS in AUC patients, and decreased nephron mass and reduced drug excretion after nephroureterectomy in UUT-AUC patients.

There are some limitations to our study. First, the exact clinical stage of AUC was not confirmed by imaging. A challenge in NC for AUC lies in accurate preoperative staging. Predicting whether patients have organ-confined UC or a high recurrence risk is difficult before RS. Hellenthal et al. reported that uncertainty rates for stage prediction made on the basis of preoperative imaging and tumor grade at biopsy and urinary cytology were approximately 30–40%, and hence ~61% of clinical high-risk AUC patients received NC unnecessarily [24]. To identify patients who might benefit from NC, genetic variation [25] and molecular markers are being investigated for the detection of micrometastases in UC [26,27]. However, to date, none of the markers has sufficient clinical and statistical data to support its validation and to help clinical decision making. Second, this study was a retrospective review, and the numbers of UUT-AUC patients with initial NC were small because of the rare occurrence. In addition, variability in the techniques used during RS and the doses used during chemotherapy was inevitable. Therefore, our empirical results might have a selection bias. Further randomized, double-blind, multicenter, and prospectively controlled trials are needed to clarify the validity of NC for AUC.

Conclusion

To the best of our knowledge, this study reports on the largest group of patients with AUC who received NC or AC in Taiwan, which is one of the areas with the highest rate of UC incidence. Compared with RS followed by AC, NC administration before RS increased PFS and OS for patients with AUC. NC was also associated with a 26.7% CR rate and significant downstaging of AUC. These results suggest that NC has a positive impact and might provide strong and potentially curative cancer control in patients with unresectable AUC. However, more such studies with larger sample sizes and longer follow-ups are needed to clarify the role of NC in the therapeutic management of AUC.

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