



Neoadjuvant chemotherapy with gemcitabine and cisplatin followed by selective bladder preservation chemoradiotherapy in muscle-invasive urothelial carcinoma of bladder

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Purpose: To assess the safety and efficacy of gemcitabine and cisplatin as neoadjuvant chemotherapy followed by selective bladder preservation chemoradiotherapy in muscle-invasive bladder cancer (MIBC).

Materials and Methods: Patients with clinical T2-T4aN0M0 MIBC eligible for radical cystectomy and cisplatin-based chemotherapy were treated with gemcitabine 1,000 mg/m² on days 1, 8 and 15, and cisplatin 70 mg/m² on day 1 every 28 days for 3 cycles. After clinical re-staging with computed tomography scans and cystoscopy, patients with clinical complete response (CR) were eligible to proceed without cystectomy and receive bladder preservation chemoradiotherapy involving weekly cisplatin 10 mg/m² and up to 70.2 Gy of radiation. The primary endpoint of the present prospective phase II study was metastasis-free survival (MFS).

Results: Between Oct 2017 and Nov 2019, a total of 138 MIBC patients were enrolled and treated with neoadjuvant gemcitabine/cisplatin. Neoadjuvant chemotherapy was well-tolerated, with fatigue, nausea, and pruritus being the most commonly observed adverse events. After completion of planned neoadjuvant chemotherapy, 54 patients with a clinical CR and 10 patients who did not have CR but refused surgery received bladder preservation chemoradiotherapy. With a median follow-up duration of 34 months (95% confidence interval [CI], 32%–36%), the 3-year MFS rate in 64 chemoradiotherapy patients was calculated to be 70% (95% CI, 58%–82%).

Conclusions: Neoadjuvant chemotherapy followed by selective bladder preservation chemoradiotherapy based on the clinical CR was feasible and efficacious in the treatment of MIBC.

Keywords: Bladder cancer; Concurrent chemoradiotherapy; Neoadjuvant chemotherapy

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INTRODUCTION

Urothelial carcinoma arising from urinary bladder is the second most frequently occurring genitourinary malignancy after prostate cancer, and is one of the main causes of cancer-related death in Korea [1]. Bladder urothelial carcinoma presents as superficial (i.e., non-muscle-invasive bladder cancer; NMIBC), muscle-invasive bladder cancer (MIBC), or metastatic disease. In patients with MIBC, neoadjuvant cisplatin-based chemotherapy followed by radical cystectomy has been considered the standard treatment [2]. Neoadjuvant chemotherapy was reported to have promising efficacy in terms of tumor downstaging, with 15% to 30% achieving pathologic complete response (CR) [3,4]. However, radical cystectomy and urinary diversion significantly affects quality of life of patients [5].

If a patient is considered cystectomy-ineligible, concurrent chemoradiotherapy can be offered as an alternative. Although not confirmed in randomized controlled trials (RCTs), bladder preservation strategies involving maximal transurethral resection of bladder tumor (TURBT) followed by chemoradiotherapy resulted in the outcomes similar to those from surgery [6,7]. Due to the better quality of life and the chance of preserving the patient's own bladder, bladder preservation without affecting survival is becoming an attractive strategy in MIBC treatment [8]. In the present study, we investigated where neoadjuvant chemotherapy followed by bladder preservation chemoradiotherapy is feasible in patients with MIBC. Our results could be useful to define the best treatment strategy for MIBC according to the clinical response to neoadjuvant chemotherapy.

In early 2017, we established a multidisciplinary MIBC team within our institute, comprised of urologists, medical oncologists, radiation oncologists, radiologists, and a pathologist. The team developed the present study protocol of neoadjuvant chemotherapy with pre- and post-chemotherapy imaging and cystoscopic clinical staging. Patients who achieved a clinical CR were eligible to proceed without surgery but receive bladder preservation chemoradiotherapy.

MATERIALS AND METHODS

This was a single-center, prospective, phase II study. Patients with clinical stage T2-T4aN0M0 MIBC were enrolled. Eligible patients had to be medically appropriate to undergo radical cystectomy and eligible for cisplatin [9]. Patients had an Eastern Cooperative Oncology Group performance status 0 or 1, no prior systemic chemotherapy for MIBC, and normal major organ functions. Key exclusion criteria included

distant and/or lymph node metastases, concurrent upper tract (renal pelvis or ureter) urothelial carcinoma, and the presence of other malignancies. The study protocol was reviewed and approved by the Samsung Medical Center (Seoul, Korea) Institutional Review Board (approval number: SMC IRB No. 2017-10-008) and conducted in accordance with ethical principles per the Declaration of Helsinki. The study was registered in advance (ClinicalTrials.gov, NCT03061630) and all patients gave written informed consent.

1. Study design

All patients underwent TURBT before enrollment to confirm T2-T4a MIBC. Pathologic specimen was examined by a dedicated pathologist (GYK). Imaging studies with computed tomography (CT) scans or magnetic resonance imaging of the abdomen and pelvis, and chest CT were evaluated by a radiologist (CKK). Neoadjuvant chemotherapy consisted of cisplatin 70 mg/m² on day 1, and gemcitabine 1,000 mg/m² on days 1, 8, and 15 every 28 days. All patients received standard supportive regimen per institutional guidelines including hydration and antiemetics. The prophylactic use of hematopoietic growth factors was not allowed during treatment, except for the patients with febrile neutropenia or grade 4 myelosuppression. Chemotherapy was continued up to three cycles, withdrawal of consent, progressive disease (PD), or unacceptable toxicity. Clinical response was evaluated with CT scans, or by the same tests that were initially used to stage the tumor, urine cytology and cystoscopy, and then discussed within the multidisciplinary team. Clinical CR was defined as no visible tumor on imaging studies as well as on urine cytology and cystoscopy. Patients with clinical CR after neoadjuvant chemotherapy were eligible to proceed without cystectomy and receive chemoradiotherapy. Patients whose primary tumors did not achieve a clinical CR underwent radical cystectomy. In patients who received radical cystectomy, pathological stage was evaluated on surgical specimens on primary tumor and lymph nodes. Those with PD received second-line chemotherapy.

Concurrent chemoradiotherapy was started at 2 to 4 weeks after the last dose of chemotherapy. If chemoradiotherapy would be delayed, one more cycle of gemcitabine/cisplatin chemotherapy was allowed. Chemoradiotherapy consisted of image-guided intensity-modulated radiotherapy and concurrent weekly cisplatin 10 mg/m². Radiotherapy was delivered using 10 MV photon beams with a four-field box technique, for 5 days each week over 6 to 7 weeks. The fraction size was 1.8 or 2.0 Gy. The initial irradiation were delivered into the whole pelvis or whole bladder. The portals were reduced after 44 to 46 Gy (median, 45 Gy), and a follow-up CT study was performed. Boost treatment included

Table 1. Baseline patient characteristics

Variable	All patients (n=138)	Chemoradiotherapy (n=64)
Age (y)	68 (40–86)	66 (40–85)
Sex		
Male	119 (86.2)	53 (82.8)
Female	19 (13.8)	11 (17.2)
Disease status		
Previous NMIBC	21 (15.2)	6 (9.4)
MIBC at diagnosis	117 (84.8)	58 (90.6)
Baseline T Stages		
T2	71 (51.4)	35 (54.7)
T3	52 (37.7)	26 (40.6)
T4a	15 (10.9)	3 (4.7)
ECOG performance status		
0	99 (71.7)	45 (70.3)
1	39 (28.3)	19 (29.7)
Smoking history		
Current or former smoker	102 (73.9)	51 (79.7)
Never smoker	36 (26.1)	13 (20.3)

Values are presented as median (range) or number (%). NMIBC, non-muscle-invasive bladder cancer; MIBC, muscle-invasive bladder cancer; ECOG, Eastern Cooperative Oncology Group.

an initial tumor bed with a 1 to 15 cm margin. The total irradiation doses to tumor bed were ranged from 54 to 70.2 Gy (median, 66 Gy) depending on surrounding normal tissues. All patients were followed every 3 months for 2 years after completion of chemoradiotherapy, and every 6 months afterward.

2. Statistical analysis

The primary endpoint of the present phase II study was metastasis-free survival (MFS), which was calculated from the day of informed consent to the day that a patient experienced distant and/or lymph node metastasis, or to the date of death, whichever came first. Secondary endpoints included clinical CR and safety. This study was not designed as a comparative study because we did not know the rate of clinical CR or what percentages of patients would receive chemoradiotherapy at the time of study design. However, on the basis of our previous data [10], we assumed a 70% 3-year MFS rate with neoadjuvant chemotherapy followed by chemoradiotherapy in MIBC patients. We hypothesized that at least half of patients would achieve clinical CR after neoadjuvant chemotherapy, and an observed 3-year MFS rate of <50% would suggest lack of activity. It was determined that at least 118 patients treated with neoadjuvant chemotherapy would provide 90% power and one-sided significance of 5%. All patients (intent-to-treat) were included in the evaluation

Table 2. Maximum grade adverse events with neoadjuvant chemotherapy involving gemcitabine and cisplatin (n=138)

Adverse event	All grades	Grades 3 or 4
Fatigue	59 (42.8)	0 (0.0)
Nausea	59 (42.8)	3 (2.2)
Vomiting	15 (10.9)	0 (0.0)
Skin rash	35 (25.4)	0 (0.0)
Pruritus	44 (31.9)	0 (0.0)
Alopecia	22 (15.9)	0 (0.0)
Diarrhea	11 (8.0)	0 (0.0)
Constipation	24 (17.4)	0 (0.0)
Anorexia	28 (20.3)	0 (0.0)
Neuropathy	11 (8.0)	0 (0.0)
Urinary tract infection	3 (2.2)	3 (2.2)
Neutropenia	41 (29.7)	8 (5.8)
Thrombocytopenia	48 (34.8)	15 (10.9)
Anemia	55 (39.9)	19 (13.8)

Values are presented as number (%).

of the endpoints. Statistical tests were performed by using R packages (<https://r-project.org>). All of the follow-ups and data were concluded on April 2021.

RESULTS

Between Oct 2017 and Nov 2019, a total of 138 MIBC patients were enrolled and treated with neoadjuvant gemcitabine/cisplatin. Most (86.2%) were male and the median age was 68 years. Clinical characteristics of all patients are listed in Table 1. Patients received a median of 3 (range, 1–4) cycles of gemcitabine/cisplatin neoadjuvant chemotherapy. Among 138 patients who started treatment, 10 patients cannot completed planned cycles. The main reasons for discontinuing chemotherapy included withdrawal (n=6), local progression leading to TURBT (n=3), and adverse event (n=1). Fifteen patients received 4 cycles of chemotherapy because of the availability of surgical or radiotherapy facilities. One patient developed urosepsis during the first cycle of chemotherapy. Otherwise, gemcitabine/cisplatin neoadjuvant chemotherapy was generally well tolerated, with main adverse events being self-limiting fatigue, nausea, and pruritus (Table 2). There were no treatment-related deaths. After completion of planned neoadjuvant chemotherapy, 128 patients underwent disease evaluation using CT scans, urine cytology, and cystoscopy (Fig. 1). Clinical CR was noted in 54 patients (39.1%; 95% confidence interval [CI], 31%–47%). No correlation was observed between the baseline T stages and response. One patient exhibited liver metastases on CT scans and was considered to have a PD. The patient subsequently received

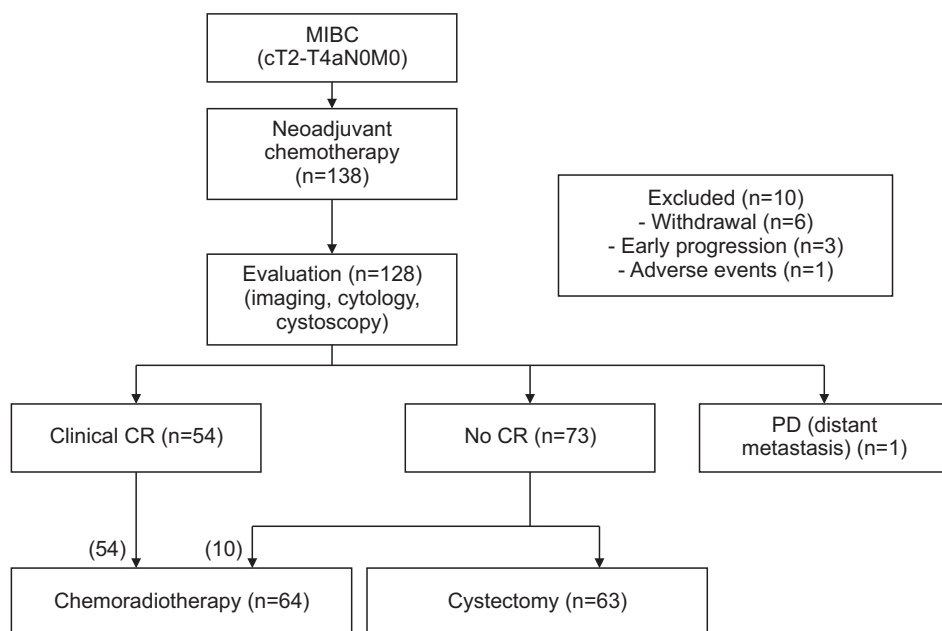


Fig. 1. Study flow for all patients. Bladder preservation chemoradiotherapy was provided to 54 and 10 patients who achieved a clinical CR after neoadjuvant chemotherapy, and those without CR, respectively. MIBC, muscle-invasive bladder cancer; CR, complete response; PD, progressive disease.

second-line atezolizumab.

All 54 patients with clinical CR received bladder preservation chemoradiotherapy. Among 73 patients who did not have CR or PD, 63 patients received radical cystectomy and the remaining 10 patients refused surgery. After multidisciplinary team discussion, they were treated with TURBT plus chemoradiotherapy. The median time from the last dose of neoadjuvant chemotherapy to the starting date of chemoradiotherapy was 21 days (range, 14–28 days). Chemoradiotherapy was well-tolerated, and all 64 patients completed the treatment as planned.

Although 63 radical cystectomy patients did not have clinical CR following neoadjuvant chemotherapy, 12 (19.0%) patients had pathologic CR, and 27 (42.8%) achieved pathologic downstaging (<pT1). Of note, 36 (57.1%) patients still had MIBC despite neoadjuvant chemotherapy, and lymph node positivity was found in 6 patients. No patients received adjuvant chemotherapy following cystectomy. With a median follow-up duration of 34 months (95% CI, 32%–36%), 47 of 138 patients experienced metastases, leading to a 3-year MFS rate of 65% (95% CI, 58%–73%; Fig. 2A). A median MFS was not reached. In 64 patients who were treated with bladder preservation chemoradiotherapy, recurrences were noted in 28 patients, including 13 with distant and/or lymph node metastases (3-year MFS rate 70%; 95% CI, 58%–82%; Fig. 2B). In an exploratory multivariate analysis, although statistically insignificant, the MFS appeared to be affected by the achievement of clinical CR (hazard ratio, 0.32; 95% CI, 0.04–2.44; p=0.273). In 17 patients with a local-only recurrence after chemoradiotherapy, salvage cystectomy were performed

in 6 patients, leading to a bladder preservation rate of 90%.

DISCUSSION

In early 2017, we established a multidisciplinary MIBC team within our institute, comprised of urologists, medical oncologists, radiation oncologists, radiologists, and a pathologist. The team developed the present study protocol of neoadjuvant chemotherapy with pre- and post-chemotherapy imaging and cystoscopic clinical staging. Patients who achieved a clinical CR were eligible to proceed without surgery but receive bladder preservation chemoradiotherapy. In the present innovative, multidisciplinary, combined modality phase II study, 39% of MIBC patients achieved a clinical CR after neoadjuvant chemotherapy involving gemcitabine and cisplatin. Patients with a clinical CR and an additional 10 patients who did not have a clinical CR but wanted to preserve their urinary bladder were treated with chemoradiotherapy, while others received radical cystectomy. In 64 chemoradiotherapy patients, the probability of surviving metastasis-free by 36 months (i.e., 3-year MFS rate) was encouraging as 70%. The outcomes obtained here compared favorably to those reported in studies involving neoadjuvant chemotherapy for MIBC [11].

Although radical cystectomy remains the standard of care in MIBC, and retrospective studies demonstrated inferior survival for patients treated with chemoradiotherapy for MIBC when compared to surgery [12], this might be likely due to confounding factors including different patients and their co-morbidities, as well as clinical stages. There is no

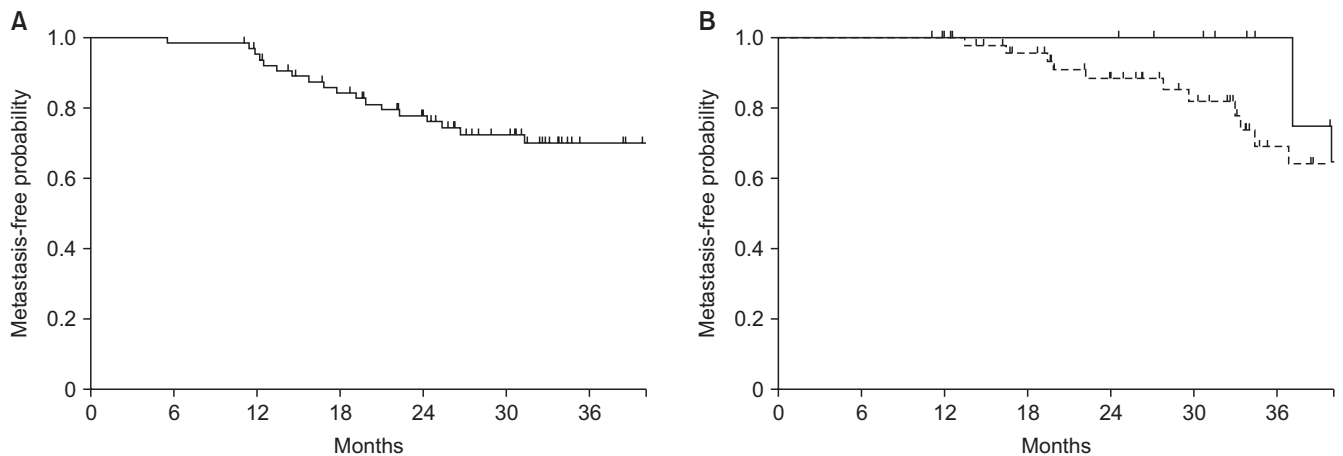


Fig. 2. Kaplan–Meier curves for metastasis-free survival (MFS) in all enrolled patients (A) and in 64 patients (B) who were treated with bladder preservation chemoradiotherapy. (B) Solid line denotes 10 patients without a clinical complete response and dotted line denotes 54 patients who achieved a clinical complete response after neoadjuvant chemotherapy.

RCT comparing radical cystectomy with bladder preservation chemoradiotherapy. Selective bladder Preservation Against Radical Excision (SPARE) trial tried to randomize patients with clinical CR at cystoscopy following neoadjuvant chemotherapy into surgery and radiotherapy [13], but was closed early due to poor accrual. RCTs are widely accepted as the definitive method for comparing the efficacy of specific treatments. However, RCTs involve a range of potential confounding factors including patient perceptions, experiences and preferences, and the views of treating doctors. Patients have preferences for treatments under evaluation and may decline to consent to randomization. When treatments cannot be blinded, patients often find it difficult to accept being randomly allocated to their non-preferred treatment, surgical versus non-surgical options in particular [14]. Thus, patient preferences may introduce bias, and result in patients refusing to consent to enter a RCT. MIBC patients are often vulnerable as the median age at diagnosis is >70 years which implies an aging target population, with multiple co-morbidities. Bladder preservation treatment might have been offered to non-surgical candidates, medically unfit to undergo radical surgery or those to by themselves demand bladder preservation. Moreover, with the introduction of a multidisciplinary team approach in the treatment of MIBC, the treatment decision becomes more complex than before when multiple specialties involved in delivering different components of treatment.

Our patients were treated with chemoradiotherapy after completion of three cycles of gemcitabine/cisplatin neoadjuvant chemotherapy. Although the idea of neoadjuvant chemotherapy followed by concurrent chemoradiotherapy is dated [15,16], its benefit remains unclear. On the premise

of tolerable chemotherapy regimen, studies suggested that patients with downstaging by neoadjuvant chemotherapy could benefit from bladder preservation chemoradiotherapy [11,17], as well as from radical cystectomy [3,4,18]. In order to improve the outcomes of neoadjuvant chemotherapy, the addition of immune checkpoint inhibitors to cisplatin-based chemotherapy is a promising strategy. The therapeutic landscape for metastatic urothelial carcinoma has already been expanded with the approval of several PD-1/PD-L1 inhibitors [19]. In palliative setting, multiple clinical trials are ongoing to explore the combination of immune checkpoint inhibitors and platinum-based chemotherapy expecting synergistic effect and reducing the risk of developing resistance. Therefore, another phase II trial involving the combination of immune checkpoint inhibitor and neoadjuvant gemcitabine/cisplatin for patients with MIBC (<https://cris.nih.gov/kcr/KCT0003804>) is under way.

More than a few limitations of the study deserve mention. Although this was a prospective study, lack of randomization dilutes the findings, as stated above. It is presently unclear whether bladder preservation chemoradiotherapy is superior or, at least equivalent, to radical cystectomy for patients with clinical CR after neoadjuvant chemotherapy. Secondly, evaluation of response to therapy with imaging studies, urine cytology and cystoscopy might lead to inaccurate tumor staging, as studies suggested a discrepancy between T stages at TURBT and subsequent radical cystectomy [20]. Another concern that has not been mentioned so far is the impact that different treatment strategies could have on the quality of life. We did not collect data on quality of life or specific comorbidities of patients. However, a long term differences of functions and quality of life between

cystectomy and bladder preservation are evident [21], despite major advances in surgical techniques. Finally, a 3-year MFS rate of 70% suggested that adjuvant therapy is required to maximize outcomes [22].

CONCLUSIONS

In conclusion, the strategy of neoadjuvant chemotherapy followed by selective bladder preservation chemoradiotherapy based on the clinical CR was feasible in the treatment of MIBC. Neoadjuvant chemotherapy involving gemcitabine and cisplatin was well tolerated and did not compromise the administration of subsequent treatments. It is conceivable that addition of other active and tolerable agents (immune checkpoint inhibitors, for example) to neoadjuvant chemotherapy could improve the efficacy for treating MIBC without compromising tolerability.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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AUTHORS' CONTRIBUTIONS

Research conception and design: Won Park, Byong Chang Jeong, and Se Hoon Park. Data acquisition: Hyun Hwan Sung, Wan Song, Byong Chang Jeong, and Se Hoon Park. Data analysis and interpretation: Hyun Hwan Sung, Ryul Kim, Chan Kyo Kim, Ghee Young Kwon, Won Park, and Se Hoon Park. Drafting the manuscript: Hyun Hwan Sung, Hana Kim, Ryul Kim, and Se Hoon Park. Critical revision of the manuscript: all authors. Statistical analysis: Hana Kim, Ryul Kim, and Se Hoon Park. Supervision: Byong Chang Jeong and Se Hoon Park. Administrative, technical, or material support: Se Hoon Park. Approval of the final manuscript: all authors.

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