Case Reports in Oncology

Case Rep Oncol 2018;11:450–460

DOI: 10.1159/000490458
Published online: July 5, 2018

Case Report

Tolerability and Efficacy of Neoadjuvant Chemotherapy with a Tri-Weekly Interval Methotrexate, Doxorubicin, Vinblastine, and Cisplatin Regimen for Patients with Locally Advanced Bladder Cancer

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Keywords
Neoadjuvant chemotherapy · Modified MVAC · Muscle-invasive bladder cancer

Abstract
Objective: Compared with standard treatment, a modified tri-weekly MVAC (methotrexate, doxorubicin, vinblastine, and cisplatin) treatment regimen with a high cisplatin dose intensity shows good efficacy and lower toxicity. Thus, we retrospectively investigated the tolerability and efficacy of a modified tri-weekly MVAC neoadjuvant regimen. ***Methods:*** We analyzed 25 patients with locally advanced bladder cancer medicated by a modified tri-weekly MVAC neoadjuvant regimen that omits treatment on days 15 and 22. The efficacy and tolerability were assessed retrospectively. ***Results:*** The numbers of patients in clinical stages 2, 3, and 4 were 13 (52.0%), 1 (4.0%), and 11 (44.0%), respectively. Surgery could be performed on all patients. Five patients (20.0%) had no cancer remaining in their surgical specimens. Remaining non-

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muscle-invasive cancer without metastasis was observed in 7 patients (28.0%), and the total downstaging rate was 44.0%. The 5-year overall and relapse-free survival rates were 79.0 and 75.0%, respectively. The overall relative dose intensity was 0.90. Serious hematologic toxicities rated grade 3 or greater were leukopenia in 6 patients (24.0%) and anemia in 1 patient (4.0%). ***Conclusions:*** Sufficient efficacy and tolerability of a modified tri-weekly MVAC neoadjuvant regimen were suggested. Thus, tri-weekly modified MVAC may be an option for neoadjuvant chemotherapy of advanced bladder cancer.

Introduction

The combination of methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) chemotherapy was established as the standard treatment for advanced urothelial carcinoma (UC) by Sternberg in 1985 [1]. The combination of gemcitabine and cisplatin has been established as an alternative to MVAC, with comparable efficacy and a milder toxicity profile [2]. Nevertheless, both regimens require weekly clinic visits, which can be bothersome for patients with advanced UC. Standard MVAC therapy has significant toxicities, including primarily bone-marrow suppression, nausea, vomiting, and stomatitis. Thus, standard MVAC therapy is difficult to administer completely as scheduled in some patients. A previous Japanese study in the 1990s reported that only 34–41% of all MVAC therapies targeting progressive UC could be performed on schedule [3]. For patients experiencing severe toxicities during standard MVAC, methotrexate and vinblastine on day(s) 15 and/or 22 are often omitted. Thus, there is recognition of the necessity to alter the schedule of standard MVAC. Regarding the effect on UC, the dose rate of doxorubicin and cisplatin have been shown to be important, and attempts to increase the dose intensity of doxorubicin and cisplatin have been ongoing at Memorial Sloan Kettering Cancer Center since 1991 [4]. Evidence of efficacy and safety for a bi-weekly cycle of dose-dense MVAC was reported in 2001 [5]. In recent National Comprehensive Cancer Network guidelines, dose-dense MVAC was shown to be preferred over standard MVAC based on category 1 evidence [6]. In addition, long-term efficacy and safety outcomes of modified MVAC, with the deletion of days 15 and 22 in a 3-week schedule, were reported in 2014 for patients with unresectable or metastatic urothelial cancer [7].

The standard care for clinically localized, muscle-invasive bladder cancer (MIBC) is cystectomy with curative intent. Previous reports have shown that platinum-based neoadjuvant chemotherapy (NAC) improves survival outcomes in MIBC patients [8–10], and NAC has been recommended for locally advanced MIBC [11, 12]. In a cisplatin dose escalation study, it was reported that bi-weekly high-cisplatin-dose-intensity MVAC therapy showed higher efficacy than standard MVAC due to the appearance of sustained type granulocyte colony-stimulating factor (G-CSF) preparation [5, 13], and the high-cisplatin-dose-intensity MVAC regimen was applied to NAC [14]. A recent meta-analysis demonstrated that MVAC might have superior overall survival (OS) compared with gemcitabine and cisplatin in the neoadjuvant setting, and MVAC could be the preferred neoadjuvant regimen [15]. The shorter cycle duration and the significantly lower toxicity rate compared with standard MVAC treatment indicate that a high-cisplatin-dose-intensity MVAC regimen may be the preferred option for NAC [16]. However, the incidence of bladder cancer increases with age (median age of 73 years in the US and mean

age of 68.7 years in Japan) [12, 17]; thus, the cases recommended for neoadjuvant bi-weekly high-cisplatin-dose-intensity MVAC were limited to elderly patients.

Based on this background, tri-weekly MVAC as a clinically tolerable modification that omits the administration of methotrexate and vinblastine on days 15 and 22 has been implemented in our urological division since the 2000s.

In our hospital, a 21-day cycle-modified MVAC (m-MVAC) regimen has been registered as a clinical treatment option for NAC. We considered that our m-MVAC therapy was a convenient regimen with enough effectiveness and tolerability for our patients. Therefore, to evaluate the efficacy and safety of this empirical m-MVAC regimen in more detail, a retrospective examination was planned for the patients undergoing NAC for MIBC.

Patients and Methods

Patient Population and Modified MVAC Regimen

Between May 2007 and February 2014, 32 patients with locally advanced bladder cancer who were treated with m-MVAC NAC ahead of a planned radical cystectomy were collected. Patients who received another chemotherapy regimen (n = 5) or suffered from double cancers (n = 2) were excluded from the analysis. Before using a NAC regimen, the feasibility of m-MVAC was confirmed in 9 patients who received this regimen as adjuvant chemotherapy between 2004 and 2006. The R relative dose intensity (RDI) of these patients was 1.00, and the median length of a hospital stay was 7 days (range 6–10). Of those receiving m-MVAC as NAC, 25 patients who received 1–4 courses of tri-weekly m-MVAC NAC (methotrexate 30 mg/m^2 on day 1; vinblastine 3 mg/m^2, doxorubicin 30 mg/m^2, and cisplatin 70 mg/m^2 on day 2) were eligible. The number of courses was determined at the discretion of the attending physician. The detailed schedules for the m-MVAC regimen and supportive care are shown in online supplemental Table 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000490458).

Efficacy and Toxicity Analysis

All surgical specimens were processed according to standard pathological procedures. Histopathological extensions were reclassified according to the 2009 TNM classification of the Union for International Cancer Control. Postoperative urine cytology and radiological imaging were performed every 3–4 months for 2 years after cystectomy, every 6 months after the third year, and annually after the fifth year. The period from the start of chemotherapy to the day of death or relapse was defined as OS or relapse-free survival (RFS), respectively.

Creatinine clearance (CCr) was predicted according to the Cockcroft and Gault formula. RDI was calculated by total and by each course of 1, 2, 3, and 4 rounds of treatment. The rate and reasons for cases requiring a reduction in the dose of cisplatin or a delay in schedule were analyzed. We assessed the surgical implementation rate and the tolerability of NAC with hematologic and nonhematologic adverse events including nausea and vomiting, myelosuppression, hiccups, or constipation based on the common terminology criteria for adverse events ver4.0 adverse grade before each course of m-MVAC. We focused on the cumulative trend data

for both hematologic examination and cisplatin-induced renal dysfunction. We investigated the number of patients experiencing G-CSF administration or hospitalization.

Statistical Analysis

For statistical analyses, the Kaplan-Meier method was used to calculate OS and RFS. Fisher's exact test was used for the evaluation of incidences. For the assessment of hematologic toxicity, a box plot and a line graph were used. The statistically significant *p* value was set at 0.05. The incident rate with the associated 95% confidence interval (CI) is also shown. All statistical analyses were performed using the statistical software "EZR" [18], which is based on the open-source *R* statistical software v3.0.2.

Results

Patient Characteristics

Between May 2007 and February 2014, 25 patients (24 males and 1 female) with MIBC who received preoperative m-MVAC chemotherapy were analyzed. Patient characteristics are summarized in Table 1. The median patient age was 62 years (range: 37–77). The median 24-h CCr value was 118.8 mL per min (range: 58.8–189.3). The CCr of 24 patients (96.0%) was ≥60 mL per min. Eleven patients (44.0%) clinically had regional lymph node metastasis before chemotherapy, and the number of patients in clinical stages 2, 3, and 4 was 13 (52.0%), 1 (4.0%), and 11 (44.0%), respectively.

Efficacy

All 25 patients were evaluated for therapeutic effect. These results are summarized in Table 2. Five patients (20.0%; 95% CI, 6.8–40.7) had no cancer remaining (pT0) in the surgical cystectomy specimen. Non-MIBC without metastasis was observed in 7 patients (28.0%; 95% CI, 12.1–49.4), and the total downstaging rate was 44.0% (95% CI, 24.4–65.1). In the median follow-up of 1,580 days (range: 242–2,868), 2 patients relapsed and 2 died of cancer. Kaplan-Meier survival curves of OS and RFS are shown in Figure 1. The 5-year survival rates of OS and RFS were 79.0% (95% CI 56–91) and 75.0% (95% CI 52–88), respectively.

Tolerability

All patients underwent radical cystectomy; the surgical implementation rate was 100%. The number of patients, RDI, and the number of patients with reduction or delay by course number of m-MVAC NAC are summarized in Table 3. A total of 24 patients (96.0%) received 2 or more cycles of NAC. One patient discontinued chemotherapy after 1 course at the discretion of the attending physician. The overall RDI was 0.90, and the RDIs for each course of 1, 2, 3, and 4 rounds of treatment were 1.00, 0.96, 0.52, and 0.82, respectively. One patient required a reduction in the dose of cisplatin due to renal impairment. The tri-weekly chemotherapy schedule was delayed in 5 patients. The reasons for schedule delays were as follows: 1 patient for hydronephrosis, 2 patients for scheduled image evaluations, 1 patient for a gross hematuria, and 1 patient for an unknown cause.

Serious hematologic toxicities of grade 3 or greater were leukopenia in 6 patients (24.0%) and anemia in 1 patient (4.0%). There were no thrombocytopenic patients of grade 3 or

greater. Three patients (12.0%) received the G-CSF preparation, and the reasons were febrile neutropenia in 1 patient and granulocytopenia in 2 patients. Figure 2 shows the data trend of each cumulative course of hematologic toxicity. The median and interquartile ranges before each chemotherapy course are shown. Hydronephrosis occurred in 1 patient, but no cisplatin-induced renal dysfunction (24 h CCr <60 mL/min) was observed. One other significant non-hematologic toxicity, grade 3 hiccups, was observed in 1 patient (4.0%). Emergency hospitalization was required for 2 patients (8.0%), for fever and gross hematuria.

Discussion

We showed that the 21-day cycle m-MVAC neoadjuvant therapy for patients with advanced MIBC could be performed with sufficient therapeutic effect and without severe adverse events or postponement of administration. The 5-year OS rate and RFS for this study were 79.0% (95% CI: 56–91) and 75.0% (95% CI: 52–88), respectively, for MIBC with or without lymph node metastasis, which was no worse than the reported standard MVAC neoadjuvant therapy outcome [8, 10]. The 5-year OS rate of the 3-course MVAC neoadjuvant therapy for MIBC without metastasis was reported to be 57% in the Southwest Oncology Group (SWOG) 8710 trial [8]. In the Japan Clinical Oncology Group (JCOG) 0209 trial [10], the 5-year OS rate and PFS of two-course MVAC neoadjuvant NAC for MIBC without metastasis were 72.3 and 67.9%, respectively. For comparison, the ratio of downstaging to pT0 in our cases was 20%, and our data were seen to be inferior to the previously reported data [8, 10]. It was reported that the ratios of downstaging to pT0 were 34.4% in JCOG 0209 [10], 38% in SWOG 8710 [8], and 38% in the high-cisplatin-dose-intensity MVAC regimen [14]. However, those populations were selected for clinical trials, and multi-institutional retrospective studies reported that no residual tumors in cystectomy specimens were identified only in 15.3–21.6% of those administered NAC in a real-world setting in Japan, which are results similar to our study [19, 20]. It is necessary to consider the bias of higher stage characteristics and pathological diagnoses, because the ratio achieving pT0 or pTis was 44% in our cases. We surmise that the effectiveness of m-MVAC might be acceptable compared with other regimens against MIBC. To confirm this effectiveness, however, further investigation is necessary.

Common barriers to the successful administration of NAC were therapy-related toxicity, the presence of underlying renal dysfunction, the time delay to definitive surgery, and the potential for an inadequate treatment effect [21]. In this study, surgery could be performed on all patients. For RDI, only 1 patient decreased cisplatin upon the initiation of chemotherapy due to decreased renal function at baseline, but no other doses were lost. In addition, delay of treatment was observed due to cancer-related symptoms, but for up to 2 courses of treatment, roughly 95% or higher RDI was maintained. Two patients underwent emergency hospitalization for fever and hematuria due to primary disease, and there were no treatment-related deaths.

Our study had some limitations. First, there are limitations inherent to retrospective analysis, and our pool of cases was heterogeneous, having selection bias. Our cases were a single-arm case study, and we could not compare these cases with other NAC regimens used at our institute. Second, the course and indications of NAC was not unified. Third, there are few re-

ports regarding tri-weekly m-MVAC NAC from other institutes [22]. The effectiveness and tolerability of tri-weekly m-MVAC neoadjuvant therapy should be prospectively validated to verify the results of our study.

The advantage of a tri-weekly m-MVAC regimen is convenience, omitting day 15 and 22 with a shortened chemotherapy period and having an adequate chemotherapeutic agent exposure interval, permitting the use of PEGylated G-CSF [23]. Considering these observations, suitable effectiveness and tolerability of the neoadjuvant m-MVAC therapy are suggested. It may be possible to consider tri-weekly m-MVAC therapy as an option for NAC of MIBC.

Acknowledgement

The authors would like to thank all members of the National Cancer Center Hospital, Tokyo, Japan. We thank Dennis T. Rogers, PhD, from Edanz Group (www.edanzediting.com/ac) for editing a draft of the manuscript.

Statement of Ethics

This retrospective analysis has been approved by a suitably constituted ethics committee of our institution and it conforms to the provisions of the Declaration of Helsinki (Research assignment No.: 2014-139 and 2017-168).

Disclosure Statement

The authors declare that they have no conflicts of interest to disclose.

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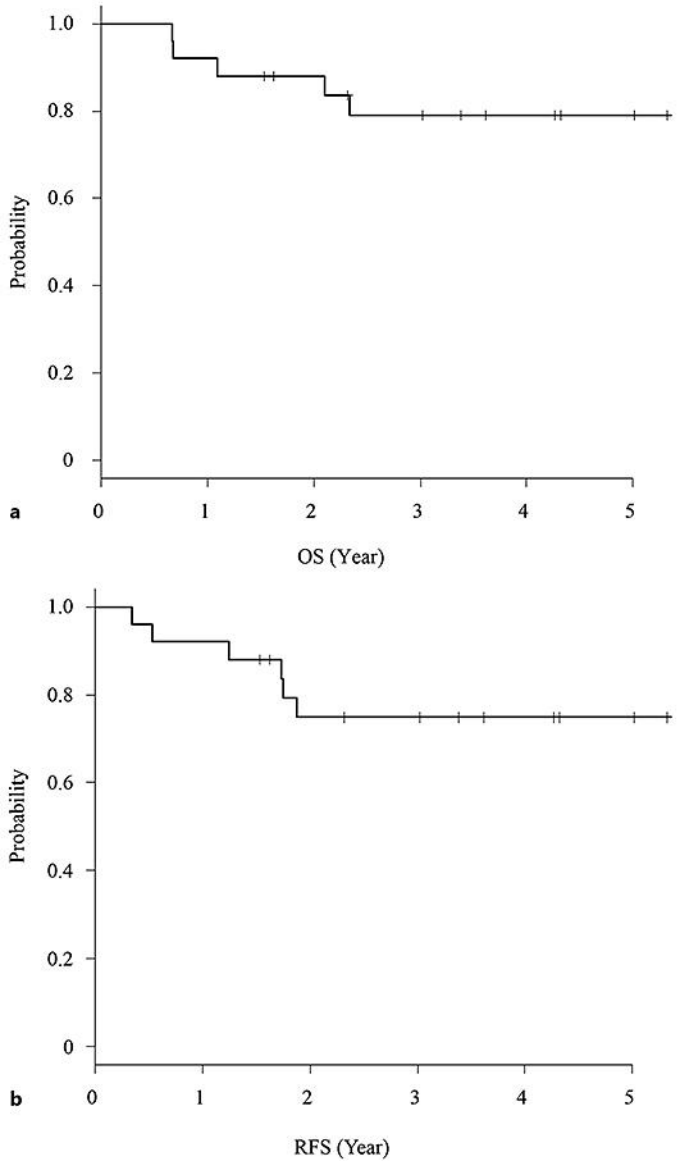

Fig. 1. **a** Kaplan-Meier curves (n = 25 overall survivors). **b** RFS.

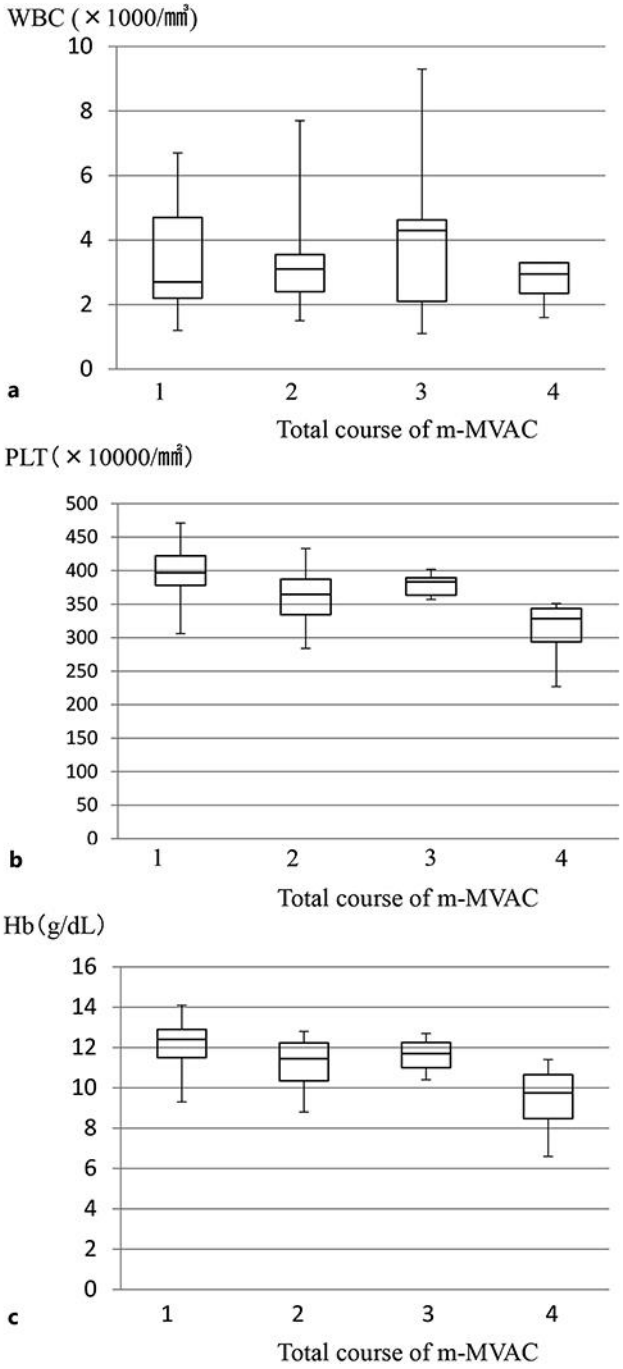

Fig. 2. Box plots and line graphs of individual data points representing hematologic toxicity. **a** White blood cells (WBC). **b** Platelets (PLT). **c** Hemoglobin (Hb).

Table 1. Patient characteristics of 25 patients receiving modified MVAC neoadjuvant therapy

Age, median (range)	62 (37–77)
Gender	
Male	24 (96.0)
Female	1 (4.0)
ECOG PS	
0	23 (92.0)
1	2 (8.0)
cT stage	
T1	4 (16.0)
T2	17 (68.0)
T3	3 (12.0)
T4	1 (4.0)
cN stage	
N0	14 (56.0)
N1	8 (32.0)
N2	2 (8.0)
N3	1 (4.0)
Clinical stage	
T2 N0	13 (52.0)
T3 N0	1 (4.0)
T4 N0	0 (0)
T any N1–3	11 (44.0)
Baseline kidney function	
24 h CCr: 45–59 mL/min	1 (4.0)
24 h CCr: 60–89 mL/min	3 (12.0)
2 h CCr: ≥90 mL/min	21 (84.0)

Values are expressed as *n* (%), unless otherwise indicated. MVAC, methotrexate, vinblastine, doxorubicin, and cisplatin; ECOG PS, Eastern Cooperative Oncology Group performance status; CCr, creatinine clearance.

Table 2. Pathologic response and downstaging in surgical patients following m-MVAC NAC

Pathological clinical stage	
pT0	5 (20.0)
pTis	6 (24.0)
pTa-1	1 (4.0)
pT2	3 (12.0)
pT3–4 or N+	10 (40.0)
Downstaging	
Downstaged	11 (44.0)
No stage change	13 (52.0)
Upstaged	1 (4.0)

Values are expressed as *n* (%). m-MVAC, modified methotrexate, vinblastine, doxorubicin, and cisplatin; NAC, neoadjuvant chemotherapy.

Table 3. RDI of m-MVAC neoadjuvant therapy

Total number of m-MVAC courses received	1 (*n* = 1)	2 (*n* = 18)	3 (*n* = 2)	4 (*n* = 4)	Overall (*n* = 25)
RDI of m-MVAC	1.0	0.96	0.52	0.82	0.90
Number of cases with reduction or delays					
Dose-reduction cases	0	1[a]	0	0	1
Delayed-schedule cases	0	2[b]	2[c]	1[d]	5

[a] Dose reduction was due to renal dysfunction. [b] Delayed schedule was due to an unknown cause in 1 case and hydronephrosis in 1 case. [c] Delayed schedule was due to scheduled image evaluation in 1 case and gross hematuria in 1 case. [d] Delayed schedule was due to scheduled image evaluation. RDI, relative dose intensity; m-MVAC, modified methotrexate, vinblastine, doxorubicin, and cisplatin.