Japanese Journal of Clinical Oncology, 2025, 55(4), 421–427
https://doi.org/10.1093/jjco/hyaf001
Advance access publication date 15 January 2025
Original Article

JJCO Japanese Journal of Clinical Oncology
OXFORD

Optimization of dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin therapy for Japanese patients with urothelial carcinoma

Taketo Kawai[1,2,3,‡], Yoshiaki Kurokawa[2,‡], Satoru Taguchi[2,*], Kazuki Honda[2], Kazuki Maki[2], Yoshiki Ambe[2], Naoki Saegusa[2], Masahiro Yamamoto[2], Jimpei Miyakawa[2,4], Yuumi Tokura[3], Hazuki Inoue[3], Takehiro Tanaka[5], Katsuhiko Nara[5], Tomoyuki Kaneko[3], Yoichi Fujii[2], Jun Kamei[2], Shigenori Kakutani[2], Yuta Yamada[2], Aya Niimi[2], Daisuke Yamada[2], Tappei Takada[5], Tohru Nakagawa[3], Haruki Kume[2]

[1]Department of Urology, International University of Health and Welfare Ichikawa Hospital, 6-1-14 Konodai, Ichikawa, Chiba 272-0827, Japan
[2]Department of Urology, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan
[3]Department of Urology, Teikyo University School of Medicine, 2-11-1 Kaga, Itabashi-ku, Tokyo 173-8605, Japan
[4]Department of Urology, Kyorin University School of Medicine, 6-20-2 Shinkawa, Mitaka, Tokyo 181-8611, Japan
[5]Department of Pharmacy, The University of Tokyo Hospital, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan

*Corresponding author. Department of Urology, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan. E-mail: satorutaguchi33@gmail.com. X: f@SatoruTaguchi

‡Taketo Kawai and Yoshiaki Kurokawa Contributed equally to this work.

Abstract

Background: Dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin (dd-MVAC) regimen has been established as a systemic chemotherapy for patients with urothelial carcinoma. However, it is rarely used in Japan owing to the challenges associated with managing the related adverse events. This study aimed to optimize the dd-MVAC protocol for Japanese patients.

Methods: Criteria were developed to adjust the doses of anticancer drugs used in dd-MVAC. In this regimen, the initial cycle of methotrexate and cisplatin was administered at 75% of the full dose. Patients who did not experience significant toxicities during the first cycle subsequently received the full dose starting from the second cycle. Additionally, the doses of methotrexate and cisplatin were adjusted according to the Cockcroft-Gault creatinine clearance. Based on these criteria, patients with urothelial carcinoma underwent dd-MVAC between August 2018 and May 2023, and all patients were scheduled to undergo six cycles.

Results: A total of 86 patients received dd-MVAC, with 36, 15, and 35 patients receiving it as neoadjuvant, adjuvant, and salvage chemotherapy, respectively. Fifty-nine patients (68.6%) completed the six scheduled cycles. Grade $\geq$ 3 toxicities of Common Terminology Criteria for Adverse Events were observed in 76 (88.4%) patients; however, most were manageable. In the neoadjuvant cohort, the pathological complete response rate was 52.2% among patients with clinical N0 lower tract urothelial carcinoma. High levels of alkaline phosphatase at the initiation of treatment were correlated with failure to complete six cycles of dd-MVAC.

Conclusion: Adjusting the dd-MVAC regimen based on renal function and significant adverse events may result in a high completion rate of scheduled treatments in Japanese patients with urothelial carcinoma.

Keywords: dose-dense MVAC; urothelial carcinoma; Japanese patients; treatment completion rate

Introduction

Dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin (dd-MVAC) is an established regimen for systemic chemotherapy in urothelial carcinoma, with intensified treatment through a 2-week cycle in association with prophylactic granulocyte colony-stimulating factor (G-CSF) administration compared with the conventional 4-week cycle of MVAC. In 2001, Sternberg et al. demonstrated that dd-MVAC prolongs overall survival compared with conventional MVAC in advanced urothelial carcinoma [1, 2]. Furthermore, the 2022 VESPER trial revealed that dd-MVAC provided better local control, extended overall survival, and progression-free survival than gemcitabine and cisplatin (GC) therapy in perioperative chemotherapy for muscle-invasive bladder cancer [3, 4]. Consequently, dd-MVAC is recommended as the first-line regimen for primary chemotherapy in advanced urothelial carcinoma and perioperative chemotherapy for muscle-invasive bladder cancer according to the European Association of Urology (EAU) and National Comprehensive Cancer Network (NCCN) guidelines [5, 6].

However, in terms of adverse events (AEs), dd-MVAC with G-CSF support showed lower rates of leukopenia

Received 23 September 2024; **editorial decision** 2 January 2025; **accepted** 3 January 2025
© The Author(s) 2025. Published by Oxford University Press.
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (https://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

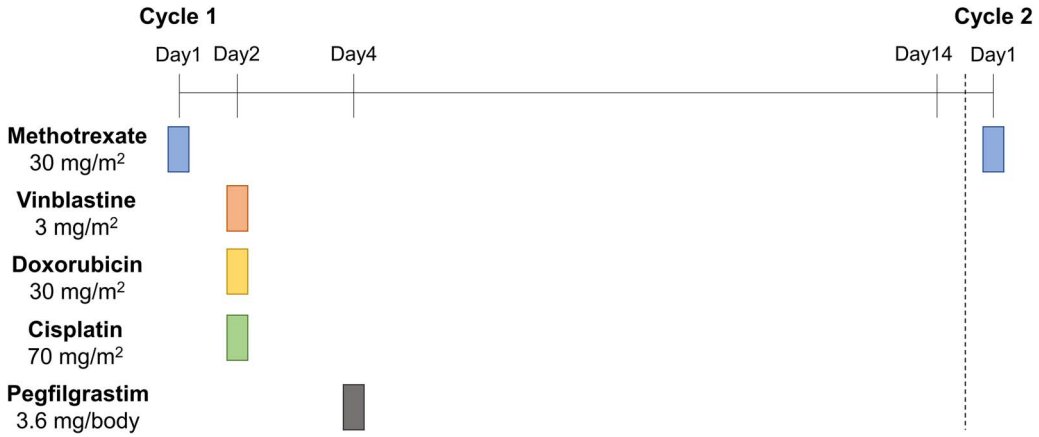

Figure 1. Treatment schedule of dd-MVAC. Dd-MVAC = dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin.

and febrile neutropenia than conventional MVAC [2], but higher incidences of anemia, asthenia, and gastrointestinal symptoms than GC [3]. In particular, Japanese patients, who are generally less robust than the Western patients, experience more AEs with conventional MVAC [7, 8]; thus, dd-MVAC acceptance has been limited and it is rarely used in Japan [9, 10]. Nevertheless, given the superior efficacy of dd-MVAC as demonstrated in the VESPER trial, promoting its use in Japanese patients is of utmost priority.

This study aimed to optimize the dd-MVAC protocol in Japanese patients by adjusting drug dosages based on evaluation of specific criteria.

Patients and methods

Patients

This retrospective study included patients with urothelial carcinoma treated with dd-MVAC at the University of Tokyo Hospital and Teikyo University Hospital between August 2018 and May 2023. The study was approved by the Institutional Review Boards of the Graduate School of Medicine and Faculty of Medicine, The University of Tokyo (approval number: 2024246NI), as well as that of Teikyo University School of Medicine. Informed consent was obtained using the opt-out approach.

Protocol of dd-MVAC

The chemotherapy schedule was as follows: methotrexate 30 mg/m^2 on day 1, vinblastine 3 mg/m^2 on day 2, doxorubicin (or pirarubicin for some patients) 30 mg/m^2 on day 2, cisplatin 70 mg/m^2 on day 2, and pegfilgrastim 3.6 mg/body on day 4, administered every 2 weeks for a total of six cycles (Fig. 1). However, AEs such as gastrointestinal symptoms often necessitated the termination of treatment in several patients after the first cycle of full dose administration (data not shown). Consequently, a dose reduction protocol was established, wherein the first cycle of methotrexate and cisplatin was administered at 75% of the full dose. Only patients who did not experience significant AEs in the first cycle then proceeded with the full dose from the second cycle onward (Fig. 2). Following the criteria established by Kintzel et al. [11], the doses of methotrexate and cisplatin were adjusted according to the Cockcroft-Gault creatinine clearance. Additionally, if any of the following AEs occurred in the previous cycle: non-hematologic toxicity of Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or higher, hematologic toxicity of CTCAE grade 4, febrile neutropenia, or hemorrhagic thrombocytopenia, all chemotherapeutic agents were reduced by 20% (Fig. 2). As a general rule, patients were hospitalized until day 3, and managed on an outpatient basis from day 4 onward. Eligibility criteria included a general condition judged tolerable by the attending physician, creatinine clearance $\geq$30 ml/min, white blood cells $\geq$2500/μl, platelets $\geq 10 \times 10^4/\mu$l, and hemoglobin $\geq$8.0 g/dL. A delay of up to 14 days was considered acceptable if blood tests on day 0 showed bone marrow suppression that did not meet eligibility criteria. Efficacy was evaluated using computed tomography (contrast-enhanced, if possible) at the end of the 3rd and 6th cycles in all cases. Chemotherapy was discontinued if disease progression was confirmed or if the patient's general condition deteriorated owing to AEs. Disease progression was assessed according to the Response Evaluation Criteria in Solid Tumours version 1.1.

Data collection

The clinicopathological characteristics of patients at the start of dd-MVAC therapy, treatment delivery, toxicities, and pathological responses in the neoadjuvant cohort were extracted from the medical records. The relative dose intensity of the chemotherapeutic agents was calculated based on the dose and interval between cycles. Toxicities were assessed using CTCAE version 5.0.

Statistical analyses

The correlation between the clinicopathological factors of patients at the start of dd-MVAC and the inability to complete six cycles was analyzed using nominal logistic regression analysis. The cutoff values for laboratory data were defined as the upper or lower limits of normal at each institution. The correlation between clinicopathological factors at the start of dd-MVAC was analyzed using the Mann–Whitney U test for continuous variables and either the chi-squared test or Fisher's exact test for categorical variables. All statistical analyses were conducted using the JMP Pro version 16.0.0 software (SAS Institute, Cary, NC, USA). Statistical significance was defined as $P < .05$.

Results

Patients' characteristics

The clinical characteristics of patients at the start of dd-MVAC are shown in Table 1. The cohort comprised 86 patients,

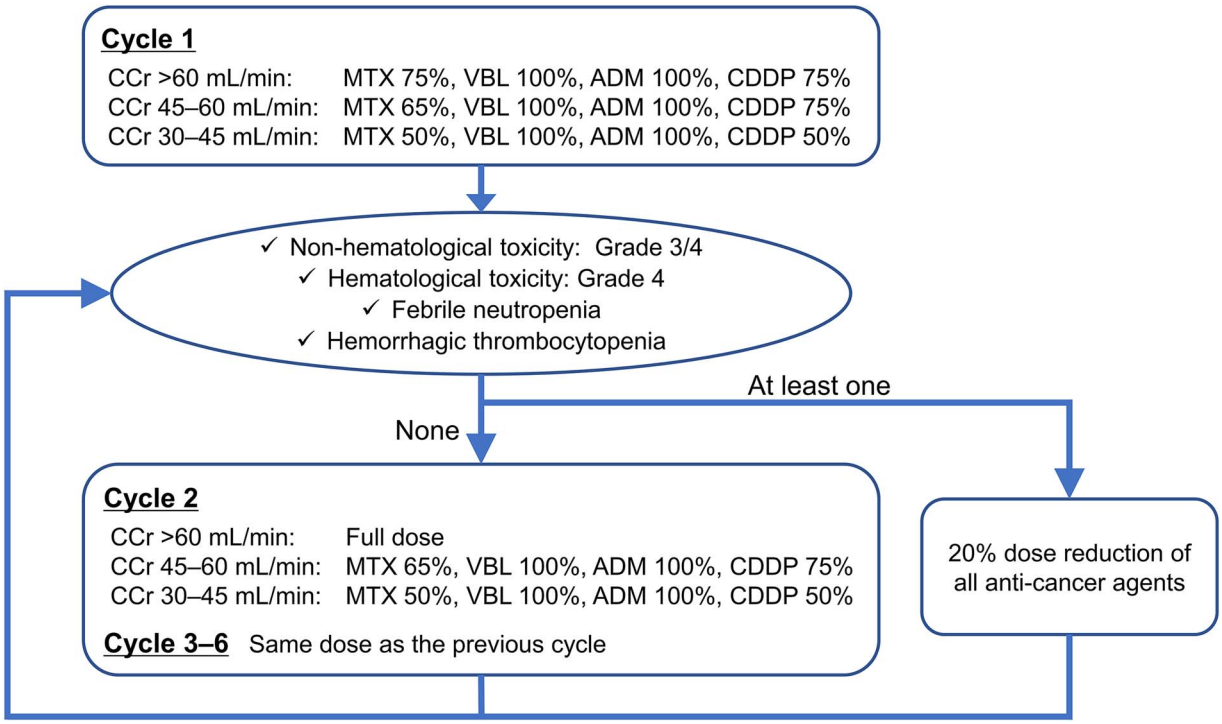

Figure 2. Dose reduction criteria based on renal function and adverse events in previous cycles.

including 56 men (65.1%) and 30 women (34.9%), with a median age of 71 years (range: 43–84 years). Primary lesions were located in the lower, upper, or both urinary tracts in 50 (58.1%), 34 (39.5%), and 2 (2.3%) patients, respectively. The chemotherapy regimens were neoadjuvant, adjuvant, and salvage in 36 (41.9%), 15 (17.4%), and 35 (40.7%) patients, respectively. The breakdown of the treatment settings for the 42 patients without metastasis were as follows: 24 patients in the neoadjuvant setting (with the remaining 12 having regional lymph node metastasis), 15 patients in the adjuvant setting, and 3 patients in the salvage setting (cases where curative resection was deemed impossible). The median creatinine clearance was 56.4 ml/min (interquartile range: 48.0–78.1 ml/min).

Treatment delivery

As shown in Table 2, 59 patients (68.6%) completed the scheduled six cycles of dd-MVAC. Among the 27 patients who could not complete the treatment, 14 discontinued due to non-hematological AEs, 8 due to disease progression, 3 due to hematological AEs, and 2 due to other reasons. Twenty-six patients (30.2%) were able to escalate to the full dose therapy. The mean relative dose intensities were 61.1% for methotrexate, 83.3% for vinblastine, 83.3%, for doxorubicin, and 63.4% for cisplatin.

Toxicities

Table 3 details the profile of CTCAE grade ≥ 3 toxicities, with grade ≥ 3 in 76 (88.4%) and grade ≥ 4 toxicities in 47 (54.7%) patients. Herein, grade ≥ 3 and grade ≥ 4 hematologic toxicities occurred in 75 (87.2%) and 47 (54.7%) patients, respectively, with 34 (39.5%) requiring red blood cell transfusions, 16 (18.6%) requiring filgrastim administration, and 7 patients (8.1%) requiring platelet transfusions. Grade ≥ 3 non-hematologic toxicity occurred in 33 patients (38.4%), with anorexia in 14 patients (16.3%) and fatigue in 13 patients (15.1%) being relatively frequent. Grade ≥ 4 non-hematologic toxicity occurred in 4 patients (4.7%, sepsis, lower gastrointestinal hemorrhage, lung infection, and thromboembolic event). Most AEs were manageable; however, one progressed to grade 5 toxicity due to lower gastrointestinal hemorrhage.

Pathological responses in the neoadjuvant cohort

The pathological responses in the neoadjuvant cohort (n = 36) are shown in Table 4. The pathological complete response rate and downstaging rate were 36.1% and 61.1%, respectively. Among patients with clinical N0 lower tract urothelial carcinoma, the pathological complete response rate and downstaging rate were 52.2% and 65.2%, respectively.

Analysis of factors involved in failure to complete six cycles

The results of the correlation analysis between clinicopathological factors at the start of dd-MVAC and the inability to complete six cycles are presented in Table 5. Serum alkaline phosphatase (ALP) levels >113 U/L [= upper limit of normal] (odds ratio [OR], 5.96; 95% confidence interval [CI], 1.90–18.7; P = .002), C-reactive protein >0.3 mg/dL (OR, 2.84; 95% CI, 1.11–7.25; P = .029), and Eastern Cooperative Oncology Group Performance Status (ECOG-PS) of ≥1 (OR, 3.72; 95% CI, 1.14–12.1; P = .029) were significantly correlated with the failure to complete six cycles of dd-MVAC in the univariate analysis. However, creatinine clearance had no correlation with treatment completion. In the multivariate analysis, ALP levels >113 U/L were significantly correlated with the failure to complete six cycles of dd-MVAC (OR, 5.07; 95% CI, 1.54–16.7; P = .008).

In the neoadjuvant cohort, no factors were associated with treatment completion (Supplementary Table 1). In

Table 1. Patients' characteristics at the start of dd-MVAC (n = 86).

Factors	Values
Age, years, median (range):	71 (43–84)
Sex, *n* (%):	
Male	56 (65.1)
Female	30 (34.9)
BMI, kg/m^2, median (range):	23.1 (14.6–33.2)
ECOG Performance Status, *n* (%):	
0	72 (83.7)
1	13 (15.1)
2	1 (1.2)
Comorbidity, *n* (%):	
Hypertension	36 (41.9)
Diabetes mellitus	10 (11.6)
Hyperlipidemia	27 (31.4)
Cardiovascular diseases	11 (12.8)
History of smoking, *n* (%):	
Never	28 (32.6)
Past	41 (47.7)
Current	17 (19.8)
Primary site, *n* (%):	
Lower urinary tract	50 (58.1)
Upper urinary tract	34 (39.5)
Both	2 (2.3)
Histology of primary site, *n* (%):	
Pure UC	69 (80.2)
UC with squamous differentiation	9 (10.5)
UC, plasmacytoid variant	4 (4.7)
UC, sarcomatoid variant	2 (2.3)
UC with glandular differentiation	1 (1.2)
Pure AC	1 (1.2)
Metastasis, *n* (%):	
No	42 (48.9)
Yes	44 (51.2)
Lymph node	32 (37.2)
Lung	16 (18.6)
Bone	9 (10.5)
Liver	6 (7.0)
Setting of chemotherapy, *n* (%):	
Neoadjuvant	36 (41.9)
Adjuvant	15 (17.4)
Salvage	35 (40.7)
Laboratory data, median (IQR):	
White blood cells ($10^3/\mu$l)	6.4 (5.4–7.8)
Hemoglobin (g/dL)	11.9 (10.7–13.3)
Platelets ($10^4/\mu$l)	25.9 (22.0–32.9)
Albumin (g/dL)	3.8 (3.5–4.1)
Total bilirubin (mg/dL)	0.5 (0.4–0.7)
Aspartate transaminase (U/L)	18 (16–22)
Alanine transaminase (U/L)	13 (11–17)
Lactate dehydrogenase (U/L)	204 (180–237)
Alkaline phosphatase (U/L)	86 (68–108)
Corrected calcium (mg/dL)	9.2 (9.1–9.5)
C-reactive protein (mg/dL)	0.20 (0.06–0.82)
Creatinine (mg/dL)	0.90 (0.70–1.15)
Clearance of creatinine (ml/min)	59.5 (48.0–78.1)

dd-MVAC = dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin; BMI = body mass index; ECOG = Eastern Cooperative Oncology Group; UC = urothelial carcinoma; AC = adenocarcinoma; IQR = interquartile range.

Table 2. Treatment delivery of dd-MVAC (n = 86).

Parameters	Values
Cycles of dd-MVAC, *n* (%):	
6	59 (68.6)
5	7 (8.1)
4	2 (2.3)
3	9 (10.5)
2	4 (4.7)
1	5 (5.8)
Reasons for not completing 6 cycles, *n* (%):	
Non-hematological adverse events	14 (51.9)
Progression disease	8 (29.6)
Hematological adverse events	3 (11.1)
Other reasons	2 (7.4)
Days per course, mean ± SD:	15.8 ± 2.2
Increase to full dose	
Yes	26 (30.2)
No	60 (69.8)
Relative dose intensity, %, mean ± SD:	
Methotrexate	61.1 ± 19.6
Vinblastine	83.3 ± 15.4
Doxorubicin	83.3 ± 15.4
Cisplatin	63.4 ± 19.2

dd-MVAC = dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin; SD = standard deviation.

Table 3. CTCAE grade ≥ 3 toxicities (n = 86).

Events	Grade ≥ 3	Grade ≥ 4
Any toxicity, *n* (%):	76 (88.4)	47 (54.7)
Hematological toxicity, *n* (%):		
Any	75 (87.2)	47 (54.7)
Neutropenia	60 (69.8)	46 (53.5)
Leukopenia	54 (62.8)	23 (26.7)
Anemia	42 (48.8)	1 (1.2)
Thrombocytopenia	32 (37.2)	8 (9.3)
Febrile neutropenia	11 (12.8)	1 (1.2)
Required treatment		
Red blood cell transfusion	34 (39.5)	
Filgrastim administration	16 (18.6)	
Platelet transfusion	7 (8.1)	
Non-hematological toxicity, *n* (%):		
Any	33 (38.4)	4 (4.7)
Anorexia	14 (16.3)	0 (0)
Fatigue	13 (15.1)	0 (0)
Thromboembolic event	5 (5.8)	1 (1.2)
Lung/bronchial infection	4 (4.7)	1 (1.2)
Constipation	3 (3.5)	0 (0)
Nausea/vomiting	3 (3.5)	0 (0)
Fever	3 (3.5)	0 (0)
Sepsis	2 (2.3)	2 (2.3)
Infusion site extravasation	2 (2.3)	0 (0)
Peripheral sensory neuropathy	2 (2.3)	0 (0)
Lower gastrointestinal hemorrhage	1 (1.2)	1 (1.2)*
Others**	6 (7.0)	0 (0)

*Grade 5 toxicity. **Including one case each of acute renal dysfunction, diarrhea, mucositis oral, pulmonary fibrosis, pyelonephritis, and skin cellulitis. CTCAE = Common Terminology Criteria for Adverse Events.

contrast, ALP levels >113 U/L were associated with treatment completion in the salvage cohort (Supplementary Table 2; OR, 4.29; 95% CI, 0.96–19.2; P = .049).

Analysis of factors involved in elevated ALP levels

The results of the correlation analysis between elevated ALP levels (>113 U/L) and other clinicopathological factors at the start of dd-MVAC are presented in Supplementary Table 3. Elevated ALP levels were significantly correlated with bone metastasis (P < .001), salvage setting (P = .006), liver metastasis (P = .013), any metastasis (P = .028), and history of cardiovascular diseases (CVD) (P = .039).

Discussion

The present study demonstrated that dd-MVAC could be efficiently administered at a high completion rate even in

Table 4. Pathological responses in the neoadjuvant cohort (n = 36).

Parameters	All cases n = 36	cN0 cases n = 24	cN1–2 cases n = 12	P value
Complete response (ypT0 N0), n (%):				
All	13/36 (36.1)	12/24 (50.0)	1/12 (8.3)	0.025*
LTUC	13/31 (41.9)	12/23 (52.2)	1/8 (12.5)	0.095
UTUC	0/5 (0)	0/1 (0)	0/4 (0)	1.00
Non-muscle invasive (<ypT2 N0), n (%):				
All	19/36 (52.8)	14/24 (58.3)	5/12 (41.7)	0.48
LTUC	18/31 (58.1)	14/23 (60.9)	4/8 (50.0)	0.69
UTUC	1/5 (20.0)	0/1 (0)	1/4 (25.0)	1.00
Organ-confined disease (<ypT3 N0), n (%):				
All	21/36 (58.3)	16/24 (66.7)	5/12 (41.7)	0.18
LTUC	20/31 (64.5)	16/23 (69.6)	4/8 (50.0)	0.41
UTUC	1/5 (20.0)	0/1 (0)	1/4 (25.0)	1.00
Down-staging, n (%):				
All	22/36 (61.1)	15/24 (62.5)	7/12 (58.3)	1.00
LTUC	21/31 (67.7)	15/23 (65.2)	6/8 (75.0)	1.00
UTUC	1/5 (20.0)	0/1 (0)	1/4 (25.0)	1.00

[a]Statistically significant. LTUC = lower tract urothelial carcinoma; UTUC = upper tract urothelial carcinoma.

Table 5. Analysis of factors at the initiation involved in failure to complete 6 cycles of dd-MVAC therapy.

Factors	Reference	Univariate		Multivariate	
		OR (95% CI)	P value	OR (95% CI)	P value
Age	Continuous	1.82 (0.21–15.9)	0.59		
Sex, female	Male	0.71 (0.27–1.89)	0.49		
Body mass index	Continuous	0.73 (0.07–8.02)	0.79		
ECOG Performance Status, ≥1	0	3.72 (1.14–12.1)	0.029*	2.92 (0.81–10.5)	0.100
Comorbidity					
Hypertension, yes	No	0.75 (0.29–1.90)	0.54		
Diabetes mellitus, yes	No	0.51 (0.10–2.58)	0.42		
Hyperlipidemia, yes	No	1.14 (0.43–3.01)	0.79		
Cardiovascular diseases, yes	No	1.29 (0.34–4.85)	0.70		
History of smoking, past	Never	0.68 (0.23–1.98)	0.48		
History of smoking, current	Never	1.88 (0.54–6.48)	0.32		
Primary site, upper tract or both	Lower tract	1.17 (0.47–2.93)	0.74		
Histology, not pure UC	Pure UC	0.62 (0.18–2.10)	0.44		
Metastasis, yes	No	1.61 (0.69–4.34)	0.31		
Lymph node metastasis, yes	No	0.99 (0.39–2.54)	0.98		
Lung metastasis, yes	No	1.94 (0.64–5.93)	0.24		
Bone metastasis, yes	No	3.12 (0.77–12.7)	0.11		
Liver metastasis, yes	No	4.96 (0.85–29.0)	0.076		
Setting of chemotherapy, adjuvant	Neoadjuvant	0.75 (0.17–3.27)	0.70		
Setting of chemotherapy, salvage	Neoadjuvant	2.25 (0.82–6.17)	0.12		
Laboratory data					
White blood cells, $>8.6 \times 10^3/\mu l$[a]	$\leq 8.6 \times 10^3$	3.09 (0.85–11.2)	0.087		
Hemoglobin, <LLN[b]	≥LLN	1.47 (0.53–4.05)	0.46		
Platelets, $>34.8 \times 10^4/\mu l$[a]	$\leq 34.8 \times 10^4$	2.06 (0.71–6.01)	0.18		
Albumin, <4.1 g/dL[c]	≥4.1	2.26 (0.74–6.85)	0.15		
Total bilirubin, >1.5 mg/dL[a]	≤1.5	NA	0.99		
Aspartate transaminase, >30 U/L[a]	≤30	4.96 (0.85–29.0)	0.076		
Alanine transaminase, >ULN[d]	≤ULN	NA	0.99		
Lactate dehydrogenase, >222 U/L[a]	≤222	1.02 (0.37–2.76)	0.98		
Alkaline phosphatase, >113 U/L[a]	≤113	5.96 (1.90–18.7)	0.002*	5.07 (1.54–16.7)	0.008*
Corrected calcium, >10.1 mg/dL[a]	≤10.1	0.41 (0.05–3.67)	0.42		
C-reactive protein, >0.3 mg/dL	≤0.3	2.84 (1.11–7.25)	0.029*	2.77 (1.00–7.70)	0.050
Creatinine, >ULN[e]	≤ULN	0.92 (0.36–2.36)	0.86		
Creatinine clearance, <60 ml/min	≥60	0.84 (0.34–2.09)	0.71		

*Statistically significant. [a]ULN. [b]13.7 g/dL for men and 11.6 g/dL for women. [c]LLN. [d]42 U/L for men and 23 U/L for women. [e]1.07 mg/dL for men and 0.79 mg/dL for women. dd-MVAC = dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin; OR = odds ratio; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; UC = urothelial carcinoma; LLN = lower limit of normal; NA = not applicable; ULN = upper limit of normal.

Japanese patients, who generally have lower physical strength than the Western population, by regulating the dosage of anticancer drugs according to renal function and AEs. Specifically, by initiating the first cycle with reduced doses of methotrexate and cisplatin allowed for identifying the patient groups that were more vulnerable to toxicity, thereby enabling the continuation of chemotherapy without undue strains. Regarding renal function, it was found that the protocol could

be implemented with a Cockcroft-Gault creatinine clearance of ≥30 ml/min without impacting the completion rate of the six cycles. We established dose reduction criteria for methotrexate and cisplatin according to renal function, based on Kintzel's criteria [11]. Although renal function-based dose reduction of cisplatin is not widely accepted, and current guidelines allow for split-dose cisplatin administration in patients with impaired renal function [12], the two-week cycle of dd-MVAC raised concerns that split-dose administration on days 1 and 8 might delay recovery from myelosuppression. Therefore, a dose-reduction protocol for cisplatin was adopted in this study. Nephrology guidelines recommend dose reduction of cisplatin for patients with renal insufficiency and a creatinine clearance of 30–60 ml/min [13, 14]. Among these recommendations, the standardized protocol based on Kintzel's criteria is particularly widely utilized [13, 14]. In Japan, dose-reduced GC therapy has been commonly used for patients with urothelial carcinoma and impaired renal function, with reports demonstrating therapeutic efficacy comparable to that of standard GC or gemcitabine/carboplatin regimens [15, 16]. By incorporating a flexible dose-reduction regimen for methotrexate and cisplatin based on renal function, this study's protocol expanded the eligibility criteria to include a broader range of renal function compared to the EAU guidelines, which recommend dd-MVAC for patients with a GFR >50–60 ml/min [12]. This is particularly beneficial for patients with upper tract urothelial carcinoma and other groups with compromised renal function, allowing the administration of a regimen without reduced intensity. The dose intensity of CDDP across all patients decreased to 63.4%; however, when limited to patients with a creatinine clearance ≥60 ml/min (n = 42), it was 73.8%, corresponding to 25.8 mg/m^2/week (data not shown). This exceeds the dose intensity of 23.3 mg/m^2/week observed with the three-week GC regimen. Furthermore, the pathological complete response rate for neoadjuvant therapy was 52.2% in patients with clinical N0 lower tract urothelial carcinoma, which is comparable to the 42% reported in the VESPER trial under similar conditions.

In contrast, CTCAE grade ≥ 3 toxicities were observed in 88% of the patients, with hematologic toxicities in 87% patients. These frequency rates are significantly higher than that reported in the VESPER trial (52%). This discrepancy may be attributed to the greater susceptibility of Japanese patients to chemotherapy-related AEs as well as differences in the dose of pegfilgrastim used. Choueiri et al. reported that using 6 mg/body of pegfilgrastim with dd-MVAC resulted in grade ≥ 3 AEs in only 10% of patients [17]. In contrast, the present study utilized a 3.6 mg/body dose of pegfilgrastim approved by Japanese insurance, which may explain the high incidence of grade ≥ 3 neutropenia at 70%. Although pegfilgrastim was used to shorten hospitalization, prophylactic daily administration of filgrastim, as in the original Sternberg protocol or the VESPER trial, may be more suitable in Japan. Despite the high frequency of grade ≥ 3 hematologic toxicities, they were manageable with red blood cell or platelet transfusions and additional filgrastim administration, contributing to a non-completion rate of only 11% after six cycles. Notably, non-hematologic toxicities accounted for 52% of the factors resulting in non-completion, highlighting the importance of managing non-hematologic toxicities, such as decreased appetite and fatigue.

Multivariate analysis indicated that pretreatment ALP level > 113 U/L was correlated with non-completion of the six cycles of dd-MVAC. Analysis by treatment setting revealed a correlation between ALP levels and non-completion of treatment in the salvage cohort. ALP is a group of enzymes that catalyze the hydrolysis of phosphate esters in an alkaline pH environment, generating inorganic phosphate, and its activity is found in various tissues, including bone, liver, intestine, and placenta. Elevated serum ALP levels are often observed in patients with bone or liver metastases [18]. In the present study, elevated ALP levels correlated with bone and liver metastases, indicating a higher prevalence of advanced cancer. Among the 11 patients with high ALP levels who could not complete six cycles of dd-MVAC, 4 patients experienced disease progression during treatment (data not shown). In the remaining six patients it was due to non-hematologic toxicities (loss of appetite in 2, septic shock in 2, fatigue in 1, and gastrointestinal bleeding in one patient), and in one patient due to progression of another cancer. Notably, 8 of these 11 patients were in the salvage setting, suggesting their overall vulnerability. Additionally, prospective cohort studies have linked elevated ALP levels to an increased CVD risk [19]. In this study, elevated ALP levels were correlated with a history of CVD, although it was unclear whether CVD itself influenced the dd-MVAC protocol completion.

This study followed six cycles of the VESPER trial protocol. However, other prospective and retrospective studies have mostly used three to four cycles [17, 20–23]; the NCCN guidelines recommend three to six cycles [6], whereas the EAU guidelines recommend four to six cycles [12]. Considering the higher frequency of AEs in Japanese patients, it may be necessary to investigate the feasibility of reducing the number of cycles to four in future studies.

This study had several limitations. First, this was a retrospective study with a relatively small sample size. Second, there may have been selection bias because only relatively robust patients deemed eligible for dd-MVAC by their physicians were included, with only one patient having an ECOG-PS score of 2 or higher. Third, while this study explored factors associated with the completion of six cycles of dd-MVAC, it included patients undergoing neoadjuvant, adjuvant, and salvage therapies, resulting in significant heterogeneity between these groups and limiting the reliability of the analysis. Fourth, as the study focused on AEs and completion rates, the inclusion of different settings hindered a thorough evaluation of therapeutic effects. Future studies with longer observation periods are required to evaluate the therapeutic effects within each specific setting.

Conclusion

Dose-adjusted dd-MVAC based on renal function and adverse events has achieved a high treatment completion rate in Japanese patients with urothelial carcinoma. Although the frequency of grade 3 or higher adverse events was high, most events were manageable. Elevated pre-treatment ALP levels correlated with a decreased completion rate.

Acknowledgements

We thank Editage (www.editage.com) for English language editing.

Supplementary data

Supplementary data are available at *Japanese Journal of Clinical Oncology* online.

Conflict of interest statement

The authors declare no conflict of interest.

Funding

We received no funding/grant support for this study.

Abbreviation

dd-MVAC, dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin; G-CSF, granulocyte colony-stimulating factor; GC, gemcitabine and cisplatin; EAU, European Association of Urology; NCCN, National Comprehensive Cancer Network; AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; LTUC, lower tract urothelial carcinoma; UTUC, upper tract urothelial carcinoma; ALP, alkaline phosphatase; OR, odds ratio; CI, confidence interval; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; CVD, cardiovascular diseases.

References

1. Sternberg CN, de Mulder PH, Schornagel JH. *et al.* European Organization for Research and Treatment of cancer genitourinary tract cancer cooperative group. Randomized phase III trial of high-dose-intensity methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) chemotherapy and recombinant human granulocyte colony-stimulating factor versus classic MVAC in advanced urothelial tract tumors: European Organization for Research and Treatment of cancer protocol no. 30924. *J Clin Oncol* 2001;**19**:2638–46.
2. Sternberg CN, de Mulder P, Schornagel JH. *et al.* EORTC Genitourinary cancer group. Seven year update of an EORTC phase III trial of high-dose intensity M-VAC chemotherapy and G-CSF versus classic M-VAC in advanced urothelial tract tumours. *Eur J Cancer* 2006;**42**:50–4. https://doi.org/10.1016/j.ejca.2005.08.032.
3. Pfister C, Gravis G, Fléchon A. *et al.* VESPER trial investigators. Randomized phase III trial of dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin, or gemcitabine and cisplatin as perioperative chemotherapy for patients with muscle-invasive bladder cancer. Analysis of the GETUG/AFU V05 VESPER trial secondary endpoints: Chemotherapy toxicity and pathological responses. *Eur Urol* 2021;**79**:214–21. https://doi.org/10.1016/j.eururo.2020.08.024.
4. Pfister C, Gravis G, Fléchon A. *et al.* VESPER trial investigators. Dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin or gemcitabine and cisplatin as perioperative chemotherapy for patients with nonmetastatic muscle-invasive bladder cancer: Results of the GETUG-AFU V05 VESPER trial. *J Clin Oncol* 2022;**40**:2013–22. https://doi.org/10.1200/JCO.21.02051.
5. EAU Guidelines. *Muscle-invasive and metastatic bladder cancer*. PO Box 30016 NL-6803 AA Arnhem, the Netherlands: EAU guidelines office. https://uroweb.org/guidelines/muscle-invasive-and-metastatic-bladder-cancer Accessed June 1, 2024, https://doi.org/10.1016/j.euo.2024.05.010.
6. NCCN Clinical Practice Guidelines in Oncology. Bladder cancer. Version 3. In: *National comprehensive cancer network, 3025 chemical road, suite 100, Plymouth meeting, PA 19462*. 2024; https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf Accessed June 1, 2024.
7. Maeda T, Takahashi A, Hirobe M. *et al.* Adverse events of MVAC chemotherapy in patients with advanced urothelial cancer of the bladder. *Hinyokika Kiyo* 2007;**53**:213–9.
8. Kuroda M, Kotake T, Akaza H, Hinotsu S, Kakizoe T, the Japanese Urothelial Cancer Research Group. Efficacy of dose-intensified MEC (methotrexate, epirubicin and cisplatin) chemotherapy for advanced urothelial carcinoma: A prospective randomized trial comparing MEC and M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin). Japanese urothelial cancer research group. *Jpn J Clin Oncol* 1998;**28**:497–501. https://doi.org/10.1093/jjco/28.8.497.
9. Taguchi S, Kawai T, Nakagawa T. *et al.* Improved survival in real-world patients with advanced urothelial carcinoma: A multicenter propensity score-matched cohort study comparing a period before the introduction of pembrolizumab (2003-2011) and a more recent period (2016-2020). *Int J Urol* 2022;**29**:1462–9. https://doi.org/10.1111/iju.15014.
10. Kita Y, Otsuka H, Ito K. *et al.* Japan urological oncology group. Real-world sequential treatment patterns and clinical outcomes among patients with advanced urothelial carcinoma in Japan. *Int J Urol* 2024;**31**:552–9. https://doi.org/10.1111/iju.15411.
11. Kintzel PE, Dorr RT. Anticancer drug renal toxicity and elimination: Dosing guidelines for altered renal function. *Cancer Treat Rev* 1995;**21**:33–64. https://doi.org/10.1016/0305-7372(95)90010-1.
12. Cathomas R, Lorch A, Bruins HM. *et al.* The 2021 updated European Association of Urology guidelines on metastatic urothelial carcinoma. *Eur Urol* 2022;**81**:95–103. https://doi.org/10.1016/j.eururo.2021.09.026.
13. Latcha S. Pharmacokinetics of chemotherapeutic agents in kidney disease. In: Perazella MA, editor. *Onco-nephrology curriculum. Chap. 12*. Washington, DC: American Society of Nephrology, 2016; 1–9.
14. Horie S, Oya M, Nangaku M. *et al.* Guidelines for treatment of renal injury during cancer chemotherapy 2016. *Clin Exp Nephrol* 2018;**22**:210–44. https://doi.org/10.1007/s10157-017-1448-z.
15. Murakami T, Kikuchi E, Ide H. *et al.* Oncological outcomes of dose reductions in cisplatin due to renal dysfunction for patients with metastatic urothelial carcinoma. *BJUI Compass* 2021;**2**:322–30. https://doi.org/10.1002/bco2.81.
16. Sugimoto K, Taguchi S, Kishitani K. *et al.* Comparison of full-dose gemcitabine/cisplatin, dose-reduced gemcitabine/cisplatin, and gemcitabine/carboplatin in real-world patients with advanced urothelial carcinoma. *BMC Urol* 2022;**22**:177. https://doi.org/10.1186/s12894-022-01139-9.
17. Choueiri TK, Jacobus S, Bellmunt J. *et al.* Neoadjuvant dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin with pegfilgrastim support in muscle-invasive urothelial cancer: Pathologic, radiologic, and biomarker correlates. *J Clin Oncol* 2014;**32**:1889–94. https://doi.org/10.1200/JCO.2013.52.4785.
18. Jiang T, Zeng Q, He J. Do alkaline phosphatases have great potential in the diagnosis, prognosis, and treatment of tumors? *Transl Cancer Res* 2023;**12**:2932–45. https://doi.org/10.21037/tcr-23-1190.
19. Liu K, Yu Y, Yuan Y. *et al.* Elevated levels of serum alkaline phosphatase are associated with increased risk of cardiovascular disease: A prospective cohort study. *J Atheroscler Thromb* 2023;**30**:795–819. https://doi.org/10.5551/jat.63646.
20. van de Putte EE, Mertens LS, Meijer RP. *et al.* Neoadjuvant induction dose-dense MVAC for muscle invasive bladder cancer: Efficacy and safety compared with classic MVAC and gemcitabine/-cisplatin. *World J Urol* 2016;**34**:157–62. https://doi.org/10.1007/s00345-015-1636-y.
21. Peyton CC, Tang D, Reich RR. *et al.* Downstaging and survival outcomes associated with neoadjuvant chemotherapy regimens among patients treated with cystectomy for muscle-invasive bladder cancer. *JAMA Oncol* 2018;**4**:1535–42. https://doi.org/10.1001/jamaoncol.2018.3542.
22. Zargar H, Shah JB, van Rhijn BW. *et al.* Neoadjuvant dose dense MVAC versus gemcitabine and cisplatin in patients with cT3-4aN0M0 bladder cancer treated with radical cystectomy. *J Urol* 2018;**199**:1452–8. https://doi.org/10.1016/j.juro.2017.12.062.
23. Ruplin AT, Spengler AMZ, Montgomery RB, Wright JL. Downstaging of muscle-invasive bladder cancer using neoadjuvant gemcitabine and cisplatin or dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin as single regimens or as switch therapy modalities. *Clin Genitourin Cancer* 2020;**18**:e557–62. https://doi.org/10.1016/j.clgc.2020.02.010.

© The Author(s) 2025. Published by Oxford University Press. This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (https://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com
Japanese Journal of Clinical Oncology, 2025, 55(4), 421–427
https://doi.org/10.1093/jjco/hyaf001
Original Article