POSSIBLE SURVIVAL BENEFIT OF HIGH-DOSE-INTENSITY METHOTREXATE, VINBLASTINE, DOXORUBICIN, AND CISPLATIN COMBINATION THERAPY (HD-MVAC) OVER CONVENTIONAL MVAC IN METASTATIC UROTHELIAL CARCINOMA PATIENTS

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Eight patients with metastatic urothelial carcinoma received high-dose (HD)-MVAC therapy, which consisted of methotrexate (30 mg/m^2) on day 1, vinblastine (3 mg/m^2) on day 2, doxorubicin (30 mg/m^2) on day 2 and cisplatin (70 mg/m^2) on day 2 (14-day cycle). Patients were treated with granulocyte colony-stimulating factor (G-CSF) (100 μg) subcutaneously from day 4 to 10. For comparison, 7 patients with metastatic urothelial carcinoma who received conventional (C)-MVAC (28-day cycle) were enrolled in this study. Overall survival in the HD-MVAC group was significantly better than that in the C-MVAC group ($p = 0.012$, log rank test). The overall response rate for measurable metastatic lesions was similar in both groups (HD-MVAC, 62.5% vs C-MVAC, 57.1%, $p = 0.622$). The patients in the HD-MVAC group were able to receive significantly more courses than the C-MVAC group (HD-MVAC, median 3 courses vs. C-MVAC, 2 courses, $p = 0.045$, Student's t test). The frequency of grade 3/4 toxicities was not statistically different between the 2 groups. HD-MVAC therapy rather than C-MVAC therapy may be advocated as a first-line chemotherapy for metastatic patients, since HD-MVAC is associated with a shorter period required for each course, a lower frequency of dose reduction and a possible benefit in terms of overall survival.

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Key words : MVAC, Chemotherapy, G-CSF, Metastatic tumor, Urothelial carcinoma

INTRODUCTION

Conventional combination chemotherapy consisting of methotrexate, vinblastine, doxorubicin and cisplatin (C-MVAC), which was developed in 1985[1], has been universally considered the standard treatment for advanced urothelial carcinoma patients, with response rates of more than 50%, 3-year survival of 20% to 25%, and median survival past 1 year is consistently reported[2–4]. Furthermore, the long-term, disease-free survival rate of metastatic urothelial carcinoma treated with C-MVAC is only 3.7% at 6 years[5]. Although C-MVAC has shown considerable efficacy in advanced urothelial carcinoma, there remains room for improvement. In addition to poor long-term survival rate, the toxicities including neutropenia, mucositis, nausea, and neurological toxicities of this combination are significant and problematic.

Sternberg et al. reported the results of high-dose-intensity methotrexate, vinblastine, doxorubicin, and cisplatin combination therapy (HD-MVAC) in 2001[6]. The duration of the HD-MVAC therapy is shortened from 28 to 14 days by omitting methotrexate and vinblastine administration on day 15 and 22 of the C-MVAC. Moreover, a granulocyte colony-stimulating factor (G-CSF) is given for 7 consecutive days beginning on day 4 after administration of the HD-MVAC anti-cancer agents. Sternberg et al. showed that by applying the HD-MVAC protocol, it was possible to deliver twice the dose of cisplatin and doxorubicin in half the time with less toxicity, and improvement was seen in progression-free survival, complete response rates, and toxicity.

In view of the reported superiority of HD-MVAC over C-MVAC, we used HD-MVAC therapy on 8 Japanese patients with metastatic urothelial carcinoma. In this study, we retrospectively assessed the efficacy and toxicity of HD-MVAC as first-line chemotherapy, in comparison with C-MVAC in our institute.

PATIENTS AND METHODS

From 1994 to 2004, 15 patients with metastatic urothelial carcinoma were treated in our institute and enrolled in this study. Demographic data of the 15 patients are shown on Table 1 (Table 1). As first-line chemotherapy, we administered C-MVAC to 7 patients from 1994 to 2001 and HD-MVAC to 8 patients from 2001 to 2004. Eight patients previously received total

Table 1. Demographic data of 15 metastatic urothelial carcinoma patients

Patient characteristics	Conventional MVAC	HD-MVAC
n	7	8
Sex		
Male	6	7
Female	1	1
Age		
>69	3	3
60–69	2	2
50–59	0	2
<50	2	1
Performance status		
0	5	7
1–2	1	1
3–4	1	0
Hemoglobin concentration before chemotherapy		
>12	2	3
8–12	4	4
<8	1	1
Primary tumor site		
Bladder	3	3
Ureter or renal pelvis	4	4
Prostatic duct	0	1
Prior surgery		
Total cystectomy	3	2
Nephroureterectomy	3	2
Total cystectomy + nephroureterectomy	1	2
No surgery	0	2
Grade		
2	2	0
3	5	7
Unknown	0	1
Primary tumor stage		
<pT2	1	0
pT3	5	7
pT4	0	0
Unknown	1	1
Metastatic sites		
Lymph node	5	3
Lung	1	3
Liver	0	2
Bone	1	0

cystectomy for bladder carcinomas, 8 patients received nephroureterectomy for renal pelvic or ureteral carcinomas and 2 patients had an inoperable bladder carcinoma. No patients received any previous systemic chemotherapy before the C-MVAC or HD-MVAC treatment. Three of the 8 patients in the HD-MVAC group and 1 of the 7 patients in the C-MVAC group received second-line chemotherapy. Two patients had grade 2 tumors, 12 patients had grade 3 tumors and the grade of 1 patient was not determined. The treatment schedules of C-MVAC and the HD-MVAC are shown in Table 2 (Table 2).

Table 2. Regimens of conventional MVAC and HD-MVAC

	Conventional MVAC	HD-MVAC
Days/cycle	28	14
Methotrexate 30 mg/m^2	Days 1, 15, 22	Day 1
Vinblastine 3 mg/m^2	Days 2, 15, 22	Day 2
Doxorubicin 30 mg/m^2	Day 2	Day 2
Cisplatin 70 mg/m	Day 2	Day 2
G-CSF (100 μg/body)	WBC <2,000	Days 4 – 10, continuously

The treatment schedules of C-MVAC and HD-MVAC are shown in Table 2 (Table 2). Patients on C-MVAC (28-day cycle) received methotrexate and doxorubicin three times per cycle while those on HD-MVAC (14-day cycle) received those drugs once per cycle. Patients on C-MVAC received G-CSF when grade 3 neutropenia (WBC <2,000/dl) was observed while those on HD-MVAC received G-CSF routinely for 7 consecutive days beginning on day 4 regardless of the level of neutropenia.

Patients continued to receive treatment for a maximum of six cycles unless they developed progressive disease or unacceptable toxicity. Toxicity was assessed using the National Cancer Institute-Common Toxicity Criteria Version 2.0[7]. Overall survival was measured from day 1 of the first course until death, and progression-free survival was measured from day 1 of the first course until death or progression.

Patients were evaluated for tumor size using a computed tomography (CT) every 2 cycles, and the response was confirmed at least 4 weeks after the completion of chemotherapy. Complete response (CR) was defined as the disappearance of all of the disease determined by 2 observations. Partial response (PR) was achieved if total tumor size decreased by at least 50% in 2 dimensions or 30% in diameter. Progressive disease (PD) occurred if the size of at least 1 measurable lesion increased by at least 25% or if new lesions appeared.

Overall survival and progression-free survival were calculated using the Kaplan-Meier method and compared using the log-lank test. Overall response rate and frequency of grade 3/4 toxicities were compared using Fisher's exact test. Dose of G-CSF and frequency of cycles were compared using Student's t test. P values were 2 sided and statistical significance was set at 0.05.

RESULTS

Patients treated with HD-MVAC and C-MVAC received a total of 26 cycles and 14 cycles, respectively. The patients in the HD-MVAC group could receive significantly more cycles than those in the C-MVAC group (HD-MVAC, median 3 cycles vs C-MVAC, 2 cycles, $p=0.045$, Student's t test). The median length

of follow-up period was 16.5 months in the HD-MVAC group and 8 months in the C-MVAC group (p=0.004, Student's t test).

The overall response rate for measurable metastatic lesions was not statistically different in both groups (HD-MVAC, 62.5% (CR : 12.5%) vs C-MVAC, 57.1% (CR : 0%), p=0.622, Fisher's exact test). In the HD-MVAC group, 3 of the 5 patients with metastatic ureteral or pelvic cancer achieved PR while 2 of the 3 patients with metastatic bladder or prostatic ductal cancer achieved CR and PR. In the C-MVAC group, all 4 patients with metastatic ureteral or pelvic cancer achieved PR while none of the 3 patients with metastatic bladder cancer achieved CR or PR. Median survival was 16.5 months in patients treated with HD-MVAC and 8 months in those treated with C-MVAC. Survival rates at 6, 12 and 18 months were 100, 87 and 37%, respectively, in the HD-MVAC group and 71, 14 and 0%, respectively, in the C-MVAC group. Median progression-free survival was 5 months in patients treated with HD-MVAC and 1 month in those treated with C-MVAC. Progression-free rates at 6, 12 and 18 months were 12.5, 12.5 and 0%, respectively, in the HD-MVAC group and 14.3, 0 and 0%, respectively, in the C-MVAC group. Overall survival of patients in the HD-MVAC group is significantly better than that in the C-MVAC group (p = 0.012, log rank test) (Fig. 1). Progression-free survival was not statistically different

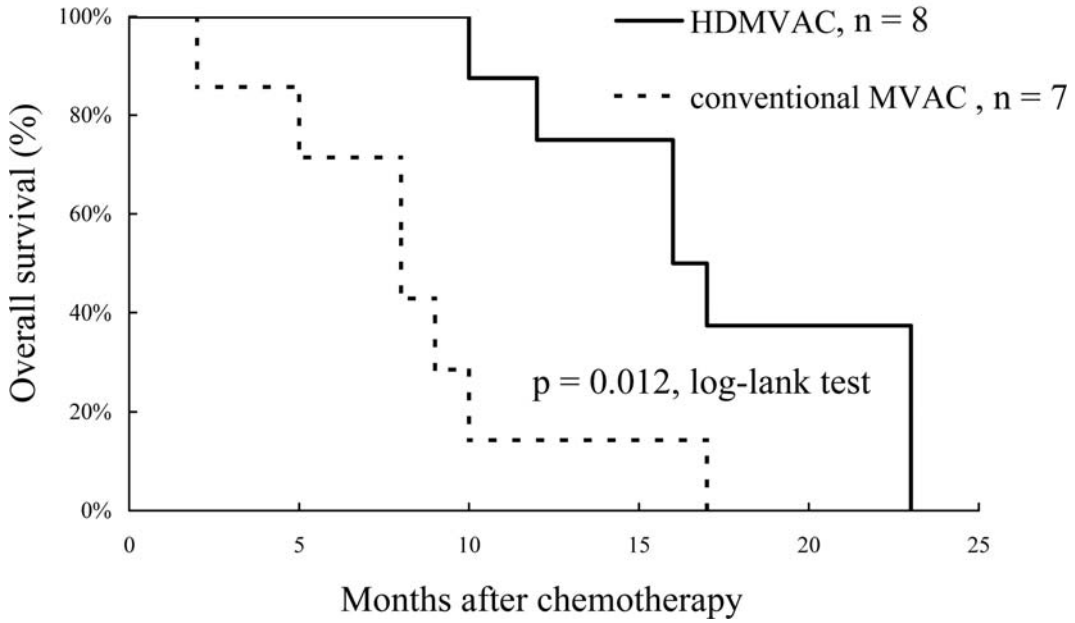

Fig. 1. Overall survival of patients in the HD-MVAC group is significantly better than that in the C-MVAC group (p=0.012, log rank test).

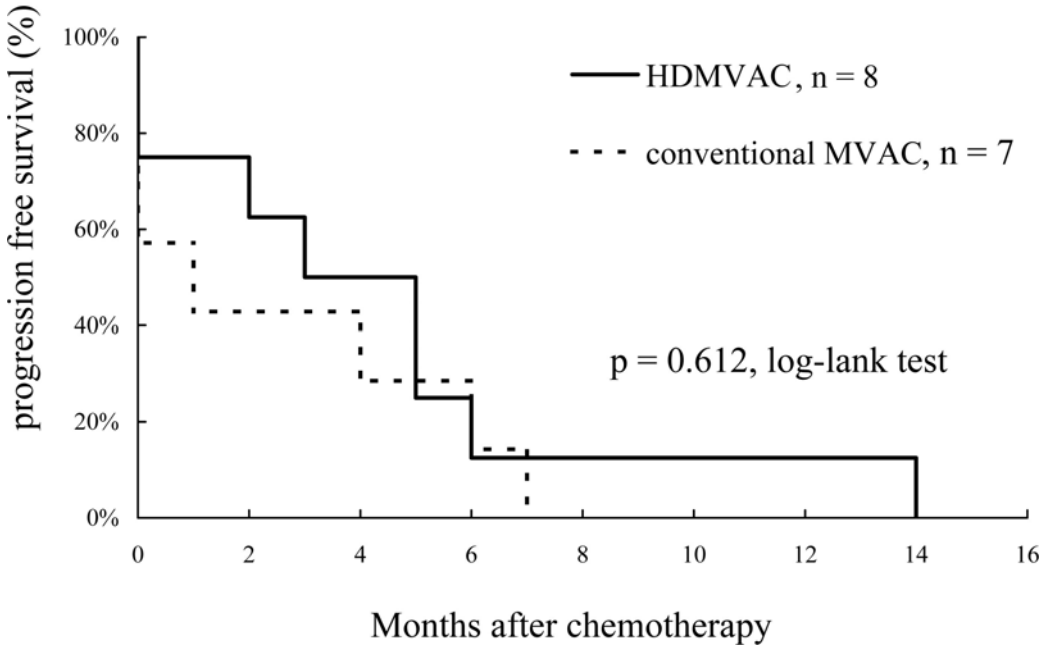

Fig. 2. Progression-free survival of patients was not statistically different between the HD-MVAC group and the C-MVAC group (p=0.612, log rank test).

Table 3. Incidence of grade 3/4 toxicities

Toxicity	Conventional MVAC (n=7)		HD-MVAC (n=8)		p value (Grade 3+4)
Grade	3	4	3	4	
Neutropenia	3	2	2	2	0.377
Anemia	2	2	0	3	0.405
Thrombocytopenia	2	1	3	0	0.622
Nausea and/or vomiting	2	1	0	0	0.077
Diarrhea	0	0	2	0	0.267
Mucositis	3	0	4	0	0.595

between the 2 groups (p=0.612, log rank test) (Fig. 2).

In the HD-MVAC group, 87.5% (7/8) of patients did not require any dose adjustments compared with 57.1% (4/7) in the C-MVAC group (p=0.230, Fisher's exact test). The treatment schedule was completed with all 26 courses in the HD-MVAC group, while administration of methotrexate and vinblastine on day 15 and/or 22 was skipped in 4/14 (28.6%) courses in the C-MVAC group. However, we delayed the initiation of the next course after 11/26 (42.3%) courses in the HD-MVAC group.

A total dose of G-CSF administered in each cycle was greater in the HD-MVAC group than the C-MVAC group (median of 700 μg vs. 208.5 μg, p=0.050, Student's t test). The frequency of the entire grade 3/4 toxicities observed was not significantly different between the 2 groups. Grade 3/4 vomiting tended to be observed more frequently in the C-MVAC than in the HD-MVAC group (p=0.076, Fisher's exact test). Fifty units of platelet concentrates were required in 3 patients for grade 3/4 thrombocytopenia in the C-MVAC group and no patient received platelet administration in the HD-MVAC group. No significant difference was observed in the incidence of grade 3/4 thrombocytopenia (p=0.622). Table 3 shows the toxicity in both groups (Table 3).

DISCUSSION

Although C-MVAC has been recognized as a standard therapy of metastatic urothelial carcinoma since Sternberg et al. initially reported the results of the C-MVAC regimen in 1985[1], several problems have remained such as severe toxicity, a relatively long period required for one cycle and lack of confirmative evidence for improvement of prognosis. To overcome these problems, Sternberg et al. reported on the HD-MVAC regimen[6] and showed that complete response rate and progression-free survival were significantly better in the HD-MVAC group compared to the C-MVAC group (21% vs 9%, p=0.009; and p=0.037, respectively). While the overall response rate and overall survival were similar in both groups (p=0.06 and 0.122, respectively), they showed that the HD-MVAC regimen had less toxicity and a shorter period required for each course. Taking the possible benefit of HD-MVAC into account, we changed the standard regimen of chemotherapy for metastatic patients from C-MVAC to HD-MVAC.

In our series, overall survival in patients who received HD-MVAC in 2001–2004 was significantly better than that of C-MVAC performed before 2001, while progression-free survival and response rate were not different between the 2 groups. The reason for the discrepancy between our results and those of the previous study remains unclear. Our study was not randomized and was retrospective. In addition, the number of patients entered was much smaller, and therefore the significant results may be caused by selection bias or may be a result of the small sample size. Another possible reason is that 3 of the 8 patients in the HD-MVAC group received second-line combination chemotherapy consisting of gemcitabine, docetaxel and carboplatin (GDC)[8], while only 1 of the 7 patients in the C-MVAC group received the same second-line chemotherapy. However, only 1 of the 3 patients who received GDC therapy after HD-MVAC obtained complete response for 6 months and no response was observed in 2 of the 3. One patient who received GDC therapy after C-MVAC obtained a partial response. Therefore, it remains unknown whether the second-line chemotherapy might have a significant influence on the overall survival of the patients in the HD-MVAC group.

Previous reports have illustrated that median survival rates and 1-year survival rates of patients with metastatic urothelial carcinoma who were treated with C-MVAC were 12.0–13.8 months and 50–57%, respectively[1–6,9,10]. In our C-MVAC group series, median survival was 8 months and survival rates at 6, 12 and 18 months were 71, 14 and 0%, respectively. Our results seemed to be inferior to these of the previous reports using the C-MVAC. In our series, dose reduction was necessary because of severe neutropenia in 3 of the 7 patients in the C-MVAC group and this could be the reason for the inferior results. C-MVAC therapy without standard administration of G-CSF might be associated with severe toxicities in patients with metastatic urothelial carcinoma.

Patients in the HD-MVAC group were able to receive a significantly greater number of cycles than those in the C-MVAC group. No significant difference was observed in the incidence of grade 3/4 neutropenia (p=0.377, Fisher's exact test). Although the dose of G-CSF in our HD-MVAC regimen (100 μg/body/day) was less than

that of the previous description (240 $\mu g/m^2/day$)[6], these results suggested that continuous administration of the relatively low dose of G-CSF successfully controlled neutropenia, which is the strongest dose-limiting factor. Our results suggest the advantage of the HD-MVAC regimen over C-MVAC. Because continuous administration of G-CSF might be a problem in terms of cost, further investigation for dose reduction of G-CSF is warranted.

CONCLUSION

HD-MVAC therapy rather than C-MVAC therapy may be advocated as a first-line chemotherapy for metastatic urothelial carcinoma patients, since HD-MVAC is associated with a shorter period required for each course, lower frequency of dose reduction, and possible benefit in terms of overall survival. In addition, HD-MVAC was not associated with a higher frequency of grade 3/4 toxicities when compared with C-MVAC.

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和文抄録

転移性尿路上皮癌患者に対する High-Dose-Intensity MVAC 療法と Conventional MVAC 療法との比較検討

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目的：転移性尿路上皮癌に対する初期治療としての High-Dose-Intensity MVAC 療法（HD-MVAC）の効果と有害事象を後ろ向きに評価し，従来の MVAC 療法（C-MVAC）と比較する．

対象と方法：転移性尿路上皮癌患者 8 例に対し，14 日サイクルの HD-MVAC 療法を行った．内容は methotrexate（30 mg/m^2）day 1，vinblastine（3 mg/m^2）day 2，doxorubicin（30 mg/m^2）day 2，cisplatin（70 mg/m^2）day 2 とした．顆粒球コロニー刺激因子（G-CSF）100 μg を day 4～10 まで連日皮下注射した．HD-MVAC と比較するため，従来の28日サイクルの C-MVAC を受けた 7 例をこの研究に割り付けた．

結果：HD-MVAC 療法群患者の生存期間は C-MVAC 療法群患者に比べ，有意に長かった（p＝0.012，log rank test）．評価可能病変に対する全奏効率は 2 群間で差がなかった（HD-MVAC，62.5% vs C-MVAC，57.1%，p＝0.622）．HD-MVAC 群患者は C-MVAC 群患者に比較し，有意に多くのコース数を受けることが出来た（HD-MVAC，中央値 3 コース vs C-MVAC，2 コース，p＝0.045，Student's t test）．グレード 3/4 の有害事象の出現率は 2 群間で差がなかった．

結論：HD-MVAC 療法は C-MVAC 療法よりも転移性尿路上皮癌に対する初期化学療法として推奨されるかもしれない．HD-MVAC は各コースの治療期間を短縮できるほか，抗癌剤投与量の減量の頻度を抑制し，生存期間を延長する可能性がある．

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