



Original article

Outcome of metastatic urothelial carcinoma treated by systemic chemotherapy: Prognostic factors based on real-world clinical practice in Japan

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Abstract

Aim: To clarify prognostic factors of metastatic urothelial carcinoma treated by systemic chemotherapy in real-world clinical practice in the Japanese population.

Materials and methods: A total of 228 patients with metastatic urothelial carcinoma undergoing systemic chemotherapy between 2000 and 2013 were included in the present multi-institutional study. The gemcitabine plus cisplatin regimen was administered as first-line chemotherapy to 131 patients, whereas methotrexate, vinblastine, doxorubicin, and cisplatin or its modified regimen was given to 71 patients. Of the 228 patients, 119 received at least 2 different regimens and 22 underwent resection of metastases (metastasectomy). Multivariate survival analysis was performed using the Cox proportional hazards model. The characteristics included were age, sex, Eastern Cooperative Oncology Group performance status (PS), primary site, pathology of primary site, hemoglobin levels, lactate dehydrogenase levels, C-reactive protein levels, corrected calcium levels, estimated glomerular filtration rate levels, history of prior chemotherapy, metastatic sites, resection of primary site, number of metastatic organs, and metastasectomy.

Results: The median overall survival (OS) time was 17 months. On multivariate analysis, female sex, good Eastern Cooperative Oncology Group PS at presentation, hemoglobin level ≥ 10 g/dl, and single organ metastasis were significant independent predictors of prolonged OS. For the survival effect of metastasectomy, the median OS time of the 22 patients with metastasectomy was 53 months, which was significantly longer when compared with patients not undergoing metastasectomy (15 mo). After adjustment for the 4 aforementioned prognostic factors, metastasectomy still remained significant (hazard ratio: 0.364, $P = 0.0008$).

Conclusions: Female sex, more favorable PS at presentation, hemoglobin level > 10 g/dl, and single organ metastasis were favorable prognostic factors. In addition, metastasectomy was associated with long-term disease control. © 2016 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Keywords: Metastatic urothelial carcinoma; Systemic chemotherapy; Metastasectomy

1. Introduction

Combinations of gemcitabine plus cisplatin (GC) or methotrexate, vinblastine, doxorubicin, and cisplatin

(MVAC) have become established as the standard first-line regimens for the treatment of metastatic urothelial carcinoma (UC), and initial response rates of approximately 50% to 70% have been reported. However, a large proportion of patients subsequently become refractory to the treatment, and patients resistant to the initial treatment represent a big challenge in daily clinical practice. In the GC era, although the salvage strategy has not been fully

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established, several experimental regimens have been studied, such as paclitaxel-based systemic chemotherapy [1,2]. Furthermore, bone-modifying agents could be added for patients with bone metastases [3], or the resection of metastasis (metastasectomy) has been performed in very selected patients with oligometastasis, aiming to eliminate the disease surgically [4–9]. Clinicians have been devising the treatments case by case, using their limited armamentarium. In the present study, we aimed to clarify prognostic factors of metastatic UC treated by systemic chemotherapy based on real-world clinical practice in the Japanese population.

2. Materials and methods

2.1. Patients

After institutional review board approval, we collected the medical records of 259 patients with metastatic UC undergoing systemic chemotherapy at Hokkaido University Hospital and 6 affiliated community hospitals between 2000 and 2013. First, we excluded the patients undergoing fewer than 2 cycles of systemic chemotherapy ($n = 13$), because, in our experience, the situation that patients discontinued chemotherapy only after 1 cycle strongly suggests that their original health status was not appropriate for initiation of systemic chemotherapy, or rapidly got worsen during the treatment. Because we aimed to clarify prognostic factors in the treatment of systemic chemotherapy in the Japanese population, we excluded those patients. Furthermore excluding the patients undergoing chemotherapy for locally advanced disease or in an adjuvant setting ($n = 9$), those with a histology of pure-small-cell carcinoma ($n = 4$), or those with missing data ($n = 5$), a total of 228 patients were included in the present study.

2.2. Treatments

Although we did not have strict prospective treatment guidelines across our institutions, our general treatment strategy was as follows. Regarding first-line chemotherapy, in the early study period, we started the MEC regimen (methotrexate, epirubicin, and cisplatin), which was relatively common in Japan based on a prospective randomized study whereby a similar response rate and incidence of adverse effects when compared with those after MVAC was observed [10]. In the later period, based on the results of a GC study [11] and government approval in Japan in 2008, the GC regimen was selected as first-line chemotherapy. In patients achieving disease control, we continued the regimen by replacing cisplatin with carboplatin or by prolonging the interval of treatment or both. In patients refractory to first-line chemotherapy, we considered second-line chemotherapy. For metastasectomy, we generally considered it for

patients with oligometastasis, a good performance status (PS) and good response to chemotherapy, as previously reported [4]. In patients with impaired renal function, we considered a dose reduction of chemotherapeutic agents. Usually, as a general rule among our group, we considered dose reduction according to 24-hour Ccr before each cycle. For example, regarding cisplatin, we applied a 75% dose if 24-hour Ccr was between 45 and 60 ml/min/1.73 m² or a 50% dose if between 30 and 45 ml/min/1.73 m². However, this was our general rule and the decision was up to each physician. Recently, a carboplatin-based regimen was also selected first in cases <60 ml/min/1.73 m². Our dose reduction rules regarding other drugs were previously reported [12]. Regarding the body surface area correction, 1.73 m² was currently used.

2.3. Statistical methods

Overall survival (OS) was analyzed from the start of chemotherapy until death or the last follow-up according to the Kaplan-Meier method, using the log-rank test to assess the significance of differences. Regarding the patients undergoing metastasectomy before systemic chemotherapy ($n = 5$), the survival time was calculated from the date of metastasectomy until death or the last follow-up. The Cox proportional hazards model was used to evaluate the relationship between clinical characteristics and survival. The characteristics analyzed were age, sex, ECOG-PS, primary site, pathology of primary site, hemoglobin (Hb) level, lactate dehydrogenase level, C-reactive protein level, corrected calcium level, estimated glomerular filtration rate level, history of prior chemotherapy, resection of the primary site, each metastatic site (lymph node, lung, liver, bone, local recurrence, and visceral metastasis [lung, liver, or bone]), number of metastatic organs, and metastasectomy. All calculations were performed using JMP version 12. A $P < 0.05$ was considered significant.

3. Results

3.1. Characteristics of the patients

Table 1 shows a summary of the patients' characteristics. The median patient age was 67 years (range: 30–83). Approximately one-quarter of the cohort was female patients (54/228, 23.7%). The ECOG-PS was score 0 in 167 patients, score 1 in 38 patients, score 2 in 9 patients, score 3 in 2 patients, and unknown in 12 patients. The primary cancer origin was the bladder in 111, upper urinary tract (UUT) in 98, both in 15, and urethra/prostate in 4. Regarding the metastatic site, 151 patients had disease in the lymph nodes, 86 in the lung, 46 in bone, and 20 in the liver, and local recurrence was noted in 19 (there were overlapping cases). Regarding the baseline renal function, 122 (122/224, 54.5%) patients were considered to be

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