

Clinical Outcomes of Three or More Courses of First-line Chemotherapy for Metastatic Urothelial Carcinoma

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Abstract. *Background/Aim:* The current standard of care for first-line treatment of locally advanced or metastatic urothelial carcinoma (UC) is platinum-based combination chemotherapy. Recently, immune checkpoint inhibitors have been reported to be effective for UC. Knowing whether immunotherapy or chemotherapy is suitable as first-line treatment is beneficial for patients. A retrospective study was conducted on the clinical outcomes of Japanese patients who received three or more courses of first-line chemotherapy for metastatic UC to assess the outcome of conventional treatments in real clinical situation. *Patients and Methods:* Patients who received first-line chemotherapy between August 2009 and December 2019 were included. Progression-free survival (PFS) and overall survival (OS) were assessed. *Results:* The median PFS and OS were 7.1 and 27.1 months, respectively, for patients with no disease progression at the end of three courses. Of 28 patients, 25 (89.3%) received second-line drug therapy and 10 (35.7%) received focal therapy for disease control. Patients with focal therapy had significantly longer OS than those without focal therapy ($p=0.019$, log-rank test). *Conclusion:* OS of metastatic UC at our Institution is relatively long, suggesting that aggressive second-line drug therapy and focal therapy may have contributed to such result.

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Bladder cancer is the ninth most common malignancy worldwide, of which about 5% of newly diagnosed cases have metastases with poor prognosis (1). The current standard of care for first-line treatment of locally advanced or metastatic urothelial carcinoma (UC) is platinum-based combination chemotherapy. The initial effects of gemcitabine plus cisplatin (GC) and the combination of methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) therapy for bladder cancer are favourable to a certain extent, and their complete response (CR) rates and partial response (PR) rates are 12.2% and 11.9% and 37.2% and 33.8%, respectively (2). However, the median overall survival (OS) is poor with 14.0 and 15.2 months for GC and MVAC, respectively, and the 5-year OS rates are 13.0% and 15.3%, respectively (3).

Recently, immune checkpoint inhibitors (ICI) have been reported to be effective for UC. The median OS of first-line treatment with atezolizumab, an anti-PD-L1 antibody, in cisplatin-ineligible patients was reported to be 15.9 months (IMvigor210), and that of first-line treatment with pembrolizumab, an anti-PD-1 antibody, in cisplatin-ineligible patients, was reported to be 11.3 months (KEYNOTE-052) (4, 5). The addition of atezolizumab to platinum-based chemotherapy as first-line treatment has also been reported to prolong progression-free survival (PFS) in patients with metastatic UC (IMvigor130) (6). The efficacy of avelumab, an anti-PD-L1 antibody, for maintenance therapy after platinum-based first-line chemotherapy has been reported and may be one of the effective treatment options (JAVELIN Bladder 100) (7).

The JAVELIN Bladder 100 trial compared avelumab maintenance with best supportive care (BSC) for patients with no disease progression after four to six courses of first-line chemotherapy. OS was longer in patients with avelumab maintenance than in patients with BSC only. This result may be due to the benefit of starting avelumab immediately after first-line chemotherapy instead of waiting for disease progression. In clinical practice, if first-line chemotherapy is

Table I. Patient characteristics.

| | Median (range) or n (%) |
|---|-------------------------------|
| Total number of patients | 28 |
| Age, years | 69 (52-83) |
| Male/female | 16 (57)/12 (43) |
| Primary tumor site, upper urinary tract/bladder | 16 (57)/12 (43) |
| ECOG-PS, 0-1/2-4 | 25 (89)/3 (11) |
| Number of first-line chemotherapy | 4.5 (3-14) |
| Regimen at the start of treatment, GC/GCarbo/MVAC | 15 (54)/9 (32)/4 (14) |
| Metastatic sites, liver/lung/bone/lymph node | 7 (25)/12 (43)/6 (21)/21 (75) |
| Visceral metastasis | 16 (57) |
| Number of metastatic organs, 1/2/3 | 11 (39)/14 (50)/3 (11) |
| Albumin at first-line chemotherapy start | 3.6 (2.0-4.6) |
| NLR at first-line chemotherapy start | 3.7 (1.5-13.7) |

ECOG-PS: Eastern Cooperative Oncology Group Scale of Performance States; GC: gemcitabine and cisplatin; GCarbo: gemcitabine and carboplatin; MVAC: methotrexate, vinblastine, doxorubicin and cisplatin; NLR: neutrophil-lymphocyte ratio.

effective and tolerable, it may continue for more than six courses. Continuous maintenance chemotherapy for chemosensitive tumors have been reported to be able to lead to survival benefits for patients with metastatic UC (8). Also, even if the patients are not in progressive disease (PD) according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, they may change to second-line treatment if the tumor tends to increase. The efficacy of second-line immunotherapy or chemotherapy for metastatic UC has been reported (9, 10). Moreover, resection or radiation for primary lesion or metastatic lesion has also reported (11-13). Although metastatic UC has a poor prognosis, aggressive multidisciplinary treatment after first-line chemotherapy may improve clinical outcomes.

Several studies have been performed on the prognostic factors of immunotherapy, and it is possible to find which patients are suitable for immunotherapy as first-line therapy. One study has reported a risk score for first-line ICI, and the Eastern Cooperative Oncology Group Scale of Performance States (ECOG-PS) ≥ 2 , albumin < 3.5 g/dl, neutrophil-to-lymphocyte ratio (NLR) > 5 and liver metastases are associated with worse OS (14). The prediction of good prognosis for pembrolizumab as second-line treatment for UC was reported as pretreatment low NLR and an NLR with no large increase after 1 month of treatment (15). In addition, prognostic nutritional index before pembrolizumab initiation was also reported to be a significant and independent prognostic factor for survival in metastatic UC patients (16). Knowing whether immunotherapy or chemotherapy is suitable as first-line treatment is beneficial for patients. Exploring the differences between prognostic factors of immunotherapy and chemotherapy is important.

A retrospective study was conducted on the clinical outcomes of Japanese patients who received three or more

courses of first-line chemotherapy for metastatic UC to assess the outcome of conventional treatments in a real-world clinical situation. Whether the poor prognostic factors for immunotherapy apply to chemotherapy and whether the OS of patients who received aggressive treatment instead of BSC is longer have been investigated.

Patients and Methods

Metastatic UC patients who received first-line platinum-based chemotherapy at Kanazawa University between August 2009 and December 2019 have been retrospectively evaluated. All patients had histologically or cytologically confirmed UC of the renal pelvis, ureter or bladder. Patients who received three or more courses of first-line chemotherapy and had no disease progression [i.e. CR, PR or stable disease (SD)] at the end of three courses were included. Patients who received adjuvant or neoadjuvant chemotherapy within the preceding 12 months were excluded from the study. OS and PFS were analysed using the clinical records. OS and PFS were calculated as the time from the first day of first-line chemotherapy administration to death or the last follow-up and progression to PD according to RECIST, respectively. Clinical variables included patient age, sex, primary tumour lesion, ECOG-PS, number of first-line chemotherapy courses, metastatic site and laboratory data including blood cell counts and serum albumin concentration. Survival curves were measured using the Kaplan–Meier method, and differences in OS were evaluated using the log-rank test. All data analyses were performed using SPSS for windows (SPSS Inc., Chicago, IL, USA), and a p -value of < 0.05 was used to indicate statistical significance. This study was approved by the institutional review board of Kanazawa University Hospital.

Results

Patient characteristics. A total of 34 cases have been evaluated by RECIST, of which 6 (17.6%) had PD at the end of three courses. Table I shows the demographics and baseline characteristics of 28 patients who had no disease

Table II. Details of focal therapy for disease control.

| Case | Pre- or post-chemotherapy | Primary lesion | First-line regimen | Target lesion | Detail of focal therapy |
|------|---------------------------|----------------|--------------------|----------------------------|---|
| 1 | Pre | Bladder | GC | Primary lesion, bone | External irradiation |
| 2 | Post | Renal pelvis | GC | Primary lesion | Nephroureterectomy |
| 3 | Post | Renal pelvis | GC | Primary lesion, lymph node | External irradiation |
| 4 | Post | Renal pelvis | GCarbo | Liver | Radiofrequency ablation |
| 5 | Post | Renal Pelvis | GCarbo | Lung | External irradiation |
| 6 | Post | Renal Pelvis | MVAC | Primary lesion, lymph node | External irradiation |
| 7 | Post | Ureter | GC | Primary lesion | External irradiation |
| 8 | Post | Ureter | GCarbo | Primary lesion | External irradiation |
| 9 | Post | Bladder | GC | Lymph node | Lymphadenectomy |
| 10 | Post | Bladder | GC | Primary lesion Liver | External irradiation Radiofrequency ablation |

GC: Gemcitabine and cisplatin; GCarbo: gemcitabine and carboplatin; MVAC: methotrexate, vinblastine, doxorubicin and cisplatin.

progression at the end of three courses. The median number of first-line chemotherapy courses was 4.5 cycles, five cases (17.9%) had received seven or more courses, and the maximum number of first-line chemotherapy courses was 13 cycles. Nineteen (67.9%) patients received cisplatin-based chemotherapy at the start of first-line chemotherapy. A total of 16 cases (57.1%) had visceral metastases, of which seven (25.0%) had liver metastases.

Ten patients (35.7%) received focal therapy for disease control before or after first-line chemotherapy. Details of focal therapy are shown in Table II. External beam radiotherapy was performed in seven cases, radiofrequency ablation was performed in two cases and primary lesion or lymph node resection was performed in two cases. Twenty-five patients (89.3%) received second-line chemotherapy or immunotherapy.

The therapeutic effect was CR in 1 case, PR in 11 cases and SD in 16 cases at the end of three courses. Figure 1 shows the PFS and OS of patients. Median PFS and OS were 7.1 and 27.1 months, respectively. A comparison of OS between patients with fewer than six courses and those with six or more courses of first-line chemotherapy showed 36.2 and 23.0 months, respectively. Moreover, OS was compared for ECOG-PS, albumin, NLR and liver metastases. OS of patients with ECOG-PS 0-1 and PS ≥ 2 was 27.1 and 15.2 months, respectively ($p=0.834$, log-rank test). OS of patients with albumin level of 3.5 g/dL or more and below 3.5 g/dl was 36.2 and 15.2 months, respectively ($p=0.100$ log-rank test). OS of patients with an NLR of 5 or more and below 5 was 36.2 and 23.0 months, respectively ($p=0.886$, log-rank test). OS of patients with and without liver metastasis was 31.4 and 15.2 months, respectively ($p=0.780$, log-rank test). Figure 2 shows a comparison of OS of patients with and without focal therapy for disease control. OS was significantly longer in patients with focal therapy than in those without focal therapy ($p=0.019$, log-rank test).

Discussion

Chemotherapy with GC has been widely selected as the first-line treatment since it became the standard for UC (2). Recently, the advent of ICI has provided new treatment options. Various reports have been made on the effectiveness of ICI, including first-line treatment of cases unsuitable for cisplatin, second-line treatment and maintenance therapy after first-line chemotherapy (4-7). However, no conclusions have been reached as to what treatment strategy is best for metastatic UC yet.

In this study, the OS of patients with metastatic UC who had more than SD after three courses of first-line chemotherapy was 27.1 months. In the JAVELN Bladder 100 trial, patients were assigned to the avelumab maintenance therapy with BSC group or the BSC-only group at intervals of 4-10 weeks after four to six courses of primary chemotherapy. The OS in the avelumab maintenance therapy with BSC group was 21.4 months, and the OS in the BSC-only group was 14.3 months (7). Although it is not possible to directly compare this study and the JAVELIN Bladder 100 trial because of the differing start time of OS measurement, we compared these by subtracting the time to start measuring OS in JAVELIN Bladder 100 from that in this study. Specifically, we subtracted the duration of primary chemotherapy (112-168 days for 4-6 courses over 28 days per course) and the time to randomization [4-10 weeks (28-70 days)], for a total of 140-238 days. The result was 19.3-22.5 months, which was equivalent to that of the avelumab with the BSC group. The results may have been related to the high rate of focal treatment for disease control and the high rate of second-line chemotherapy without large intervals in this study.

Although there are some reports showing that focal therapies, including metastasectomy, radiation therapy and radiofrequency therapy are effective for metastatic UC, the role of focal therapy and its impact on survival remains controversial. Several studies on metastasectomy reported that patients who underwent

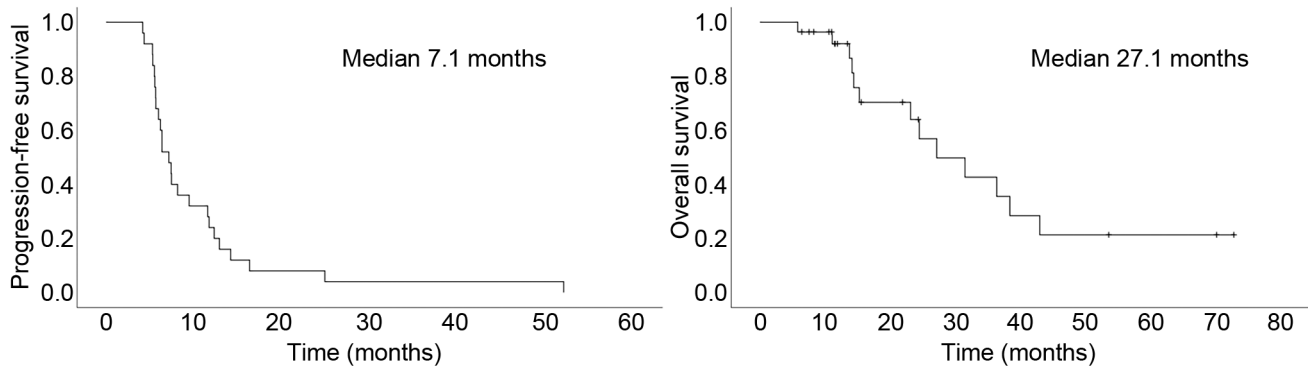


Figure 1. Progression-free survival (PFS) and overall survival (OS) of patients who received three or more courses of first-line chemotherapy and had no disease progression at the end of three courses.

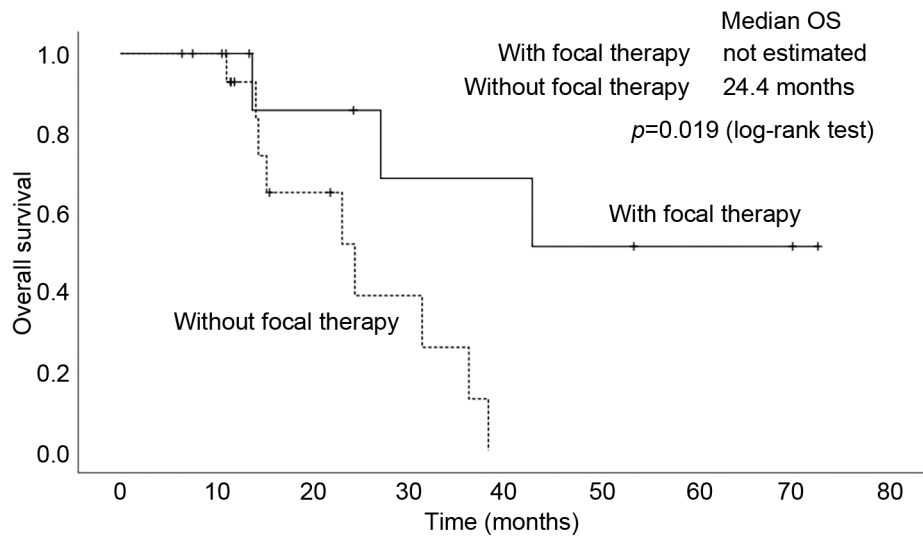


Figure 2. A comparison of overall survival (OS) of patients with and without focal therapy for disease control.

metastasectomy achieved a median OS of 23-50 months, and the 5-year OS rate was 28-33% (12, 17, 18). These studies reported that combination chemotherapy might have contributed to this good result. In one study comparing patients who underwent chemotherapy plus nephroureterectomy for metastatic UC with those who received chemotherapy alone, it was found that chemotherapy plus nephroureterectomy was associated with a significant OS benefit (11). In another report of radiation therapy for metastatic lesion, irradiation of lymph nodes, adrenal glands, lungs and omental metastases resulted in a median OS of 29 months and a 6-year OS rate of 33% (13). As described above, some reports have indicated that focal therapy is effective for metastatic UC and that it should be considered as one of the treatment strategies.

The abscopal effect is a phenomenon by which systemic antitumor response is observed outside of the primary site of

local irradiation and combining radiotherapy, which could provide an opportunity to boost abscopal response rates (19). Immunotherapy has been reported to enhance the abscopal effect (20). Actually, the combination of radiation therapy and ICI has been reported to show abscopal effect in patients with metastatic UC (21). Currently, there are many ongoing clinical trials combining immunotherapy and radiotherapy (19). Focal treatment, especially radiation therapy including palliative radiotherapy, may become more important as a strategy for treating metastatic UC in the age of immunotherapy.

Approximately 90% of patients in this study received second-line medication, which may have led to prolongation of OS. Pembrolizumab has been considered a second-line standard treatment based on the results of phase 3 RCT, KEYNOTE-045 (9). Although we reported that OS of combination chemotherapy was comparable with that of pembrolizumab

(10), pembrolizumab may be better suited for second-line treatment than chemotherapy because some patients treated with pembrolizumab showed durable response and pembrolizumab induced less adverse effects than did chemotherapy. A new drug called enfortumab vedotin, which is an antibody-drug conjugate that targets Nectin-4, demonstrated a clinically meaningful response rate in patients with locally advanced or metastatic UC who were previously treated with chemotherapy and immunotherapy (22). Various studies are progressing on first-line treatment and second-line treatment of metastatic UC, and selecting the optimal treatment based on the results is necessary.

Choosing between chemotherapy and immunotherapy as the first-line treatment for metastatic UC is an issue to be resolved. In this study, the previously reported poor prognostic factors of ICI including ECOG-PS ≥ 2 , albumin < 3.5 g/dl, NLR >5 and liver metastases have been investigated (14). No significant difference was found, but all factors showed short OS even in first-line chemotherapy. The poor prognostic factors in patients who received cisplatin-based salvage chemotherapy for metastatic UC have been reported as liver metastasis, poor performance status and higher leukocyte counts (23). Further research is necessary for the discovery of new prognostic markers by treatment selection. The latest meta-analysis indicated that first-line ICI combination therapies confer a superior oncological benefit compared to standard chemotherapy in platinum-based chemotherapy-eligible metastatic UC patients (24). ICI-chemotherapy combination therapy may be an important strategy until useful prognostic markers are discovered.

The limitations of the study were its retrospective nature and the small sample size. Patients had received various regimens as second-line chemotherapy, and the modality of focal treatment was also different depending on the cases.

New treatment strategies are about to be added for metastatic UC, for which treatment options were scarce. This study suggests that aggressive focal treatment improves treatment outcomes. It has become possible to provide treatment that is easy to continue from the viewpoint of QOL, including avelumab maintenance therapy, and there is a possibility that further prolongation of OS can be expected by combining aggressive focal treatment. The result of large-scale research on the combination of immunotherapy and focal treatment for metastatic UC is desired.

Conflicts of Interest

The Authors have no conflicts of interest to declare.

Authors' Contributions

Study conception and design: Kouji Izumi, Shohei Kawaguchi. Acquisition of data: Renato Naito, Suguru Kadomoto, Hiroaki Iwamoto, Hiroshi Yaegashi, Masashi Iijima, Analysis and interpretation of data: Shohei Kawaguchi, Takahiro Nohara, Kazuyoshi Shigehara,

Yoshifumi Kadono. Drafting of the manuscript: Shohei Kawaguchi. Project supervision: Atsushi Mizokami.

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