JJCO Japanese Journal of Clinical Oncology

Japanese Journal of Clinical Oncology, 2018, 48(8) 771–776
doi: 10.1093/jjco/hyy094
Advance Access Publication Date: 25 June 2018
Original Article

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Outcome and prognostic factors in metastatic urothelial carcinoma patients receiving second-line chemotherapy: an analysis of real-world clinical practice data in Japan

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Received 13 March 2018; Editorial Decision 2 June 2018; Accepted 13 June 2018

Abstract

Objectives: The objective of the present study was to investigate the survival outcome and prognostic factors of metastatic urothelial carcinoma patients treated with second-line systemic chemotherapy in real-world clinical practice.

Methods: Overall, 114 patients with metastatic urothelial carcinoma undergoing second-line systemic chemotherapy were included in this retrospective analysis. The dominant second-line chemotherapy was a paclitaxel-based combination regimen (60%, 68/114). We assessed the progression-free survival and overall survival times using the Kaplan–Meier method. The Cox proportional hazards model was applied to identify the factors affecting overall survival.

Results: The median progression-free survival and overall survival times were 4 and 9 months, respectively. In the multivariate analysis, an Eastern Cooperative Oncology Group performance status score greater than 0 at presentation, C-reactive protein level ≧1 mg/dl and poor response to prior chemotherapy were adverse prognostic indicators. Patients with 0, 1, 2 and 3 of those risk factors had a median overall survival of 17, 12, 7 and 3 months, respectively.

Conclusions: The Eastern Cooperative Oncology Group performance status at presentation, C-reactive protein level and response to prior chemotherapy were prognostic factors for metastatic urothelial carcinoma patients undergoing second-line chemotherapy. In the future, this information might help guide the choice of salvage treatment, such as second-line chemotherapy or immune checkpoint inhibitors, after the failure of first-line chemotherapy.

Key words: urothelial carcinoma, chemotherapy, second-line, metastatic

Introduction

Cisplatin-based combination chemotherapy has been the standard treatment for metastatic urothelial carcinoma (UC) patients. Although good initial response rates of approximately 50–70% to methotrexate, vinblastine, doxorubicin and cisplatin

(MVAC) or gemcitabine plus cisplatin (GC) have been reported, most patients subsequently become resistant to the first-line therapy, and salvage treatment remains a major challenge in daily clinical practice. To date, a growing body of literature has shown the safety and efficacy of second-line regimens for advanced and metastatic UC patients refractory to first-line chemotherapy, such as a paclitaxel-based salvage regimen (1–3). In Europe, based on the results of a phase III randomized trial showing the efficacy with a significant survival benefit of 2.5 months compared with best supportive care (4), vinflunine is also available as a treatment option, although it has yet to be approved in Japan. Several studies have evaluated prognostic factors in metastatic UC patients treated with second-line chemotherapy. Bellmunt et al. proposed a three-factor prognostic model consisting of the Eastern Cooperative Oncology Group performance status (ECOG PS), hemoglobin (Hb) level and liver metastasis (5). Thereafter, a duration from prior chemotherapy of shorter than 3 months and an albumin level below the lower limit of normal were also reported as adverse prognostic indicators (6,7). However, one of the potential limitations of those prognostic models is that, because they were constructed from phase II or III clinical trial data, where patients were strictly selected for study participation, there might be a gap compared with clinical practice in the real world. In the present study, using a retrospective database constructed from daily clinical practice at seven hospitals in Japan (8), we investigated prognostic factors in metastatic UC patients treated with second-line chemotherapy.

Patients and methods

Patients

The present multi-institutional study was performed with the approval of each institutional review board. We previously reported the outcome of a median overall survival (OS) of 17 months, derived from a total of 228 metastatic UC patients treated with systemic chemotherapy at Hokkaido University Hospital and six affiliated hospitals between 2000 and 2013 (8). Of the 228 patients, 122 undergoing second-line systemic chemotherapy were the subjects of the current study. After excluding 8 patients with missing data, 114 underwent further analysis. In the present study, we defined primary chemotherapy at the beginning of therapy for a metastatic lesion, so adjuvant or neoadjuvant therapy was not considered to be a platinum-based first-line chemotherapy.

Treatment methods

Our general treatment strategy for patients with metastatic UC was described previously (8). Briefly, regarding the first-line chemotherapy, early in the study period (2000–08), we used the MVAC regimen or its modification. After the GC regimen was approved for use in Japan in 2008, we chose that as the first-line chemotherapy regimen. In patients' refractory or intolerant to the first-line chemotherapy, we considered second-line chemotherapy. The selection of the second-line regimen depended on each physician's decision. Overall, the combination of paclitaxel, ifosphamide and nedaplatin (PIN) was the most frequently used regimen (57%, 65/114), because our group was conducting a phase II study of the PIN regimen for the early study period, and it became the most familiar salvage regimen among our group. In patients with a deteriorated renal function, we used the 24-h urinary creatinine clearance value to adjust the dose of chemotherapeutic agents. Our rules on dose modification of chemotherapeutic agents were previously reported (9). The objective response was evaluated by the treating physician according to the Response Evaluation Criteria in Solid Tumors, version 1.1, in most cases.

Data collection

Data were retrospectively collected from the patients' medical charts, including the characteristics at the starting point of second-line chemotherapy, as described below. The progression-free survival (PFS) rate was calculated from the day when the second-line treatment was started to the date of radiological or clinical disease progression. The OS time was analyzed from the start of the second-line chemotherapy until death or the last follow-up examination.

Statistical analyses

The PFS and OS were estimated using the Kaplan–Meier method, and the log-rank test was used to assess the significance of differences. A proportional Cox hazard model was used to identify factors associated with the OS. Variables that were found to be significant in univariate analysis were selected for further evaluation in a multivariable model. We analyzed the following factors: age, sex, ECOG PS, primary site, pathology of the primary site, Hb level, neutrophil-to-lymphocyte ratio (NLR), platelet count, lactate dehydrogenase (LDH) level, C-reactive protein (CRP) level, albumin level, estimated glomerular filtration rate (eGFR), prior chemotherapy response, time since prior chemotherapy, visceral metastasis (lung, liver or bone) and liver metastasis. These were measured just before the start of the second-line chemotherapy. All statistical analyses were conducted using JMP Pro version 13.

P values <0.05 were considered significant.

Results

Patients' characteristics

A summary of the patients' characteristics is shown in Table 1. The median age

at the start of the second-line chemotherapy was 65 years (range: 42–81 years). The ECOG PS score was 0 in 67 patients, 1 in 31 patients, 2 in 7 patients, 3 in 6 patients and unknown in 3 patients. Clinical records revealed that 10 patients (8.8%) had received adjuvant and/or neoadjuvant chemotherapy in the perioperative period. The primary site was resected at the initiation of first-line chemotherapy in 57 patients (50.0%). Regarding the metastatic site, 70 patients (61.4%) had lymph node metastasis, 44 (38.6%) had lung disease, 20 (17.5%) had bone disease, 18 (15.8%) had liver disease and 12 (10.5%) had local recurrence (there were overlapping cases). In terms of the first-line chemotherapy, 62 patients received the GC regimen, whereas MVAC or its modified regimen was given to 45 patients (Methotraxate, epirubicin, cisplatin: $n = 37$, Methotrexate, epirubicin, nedaplatin: $n = 6$, MVAC: $n = 2$). The median interval between the end of the first-line and beginning of the second-line treatment was 2 months (range: 1–74 months). In terms of the second-line chemotherapy, 68 (60%, 68/114) received paclitaxel-based combination regimens. The number of courses of first-line

Table 1. Patients' characteristics

	$n = 114$
Age, year	median 65 (range, 42–81)
Sex male/female	
Male	85 (74.6%)
Female	29 (25.4%)
ECOG performance status	
0	67 (58.8%)
1	31 (27.2%)
2	7 (6.1%)
3	6 (5.3%)
Unknown	3 (2.6%)
Primary site	
Bladder	49 (43.0%)
Upper urinary tract	55 (48.2%)
Both	6 (5.3%)
Urethra/prostate	4 (3.5%)
Adjuvnt and/or neoadjuvant chemotherapy	
Yes	10 (8.8%)
No	104 (91.2%)
Primary site before first-line chemotherapy	
Resected	57 (50%)
Not resected	57 (50%)
Pathology of primary site	
Pure UC	83 (72.8%)
Others	20 (17.5%)
Cytology positive	11 (9.6%)
Baseline laboratory data	
Hemoblobin, g/dl ($n = 114$)	median 10.6 (range,7.1–17.8)
NLR ($n = 99$)	median 3.09 (range, 0.57–46.5)
Platelets ($n = 114$)	median 23 (range, 9–83.4)
LDH, IU/l ($n = 114$)	median 202 (range, 113–1034)
CRP, mg/dl ($n = 113$)	median 0.51 (range, 0.01–17.26)
Albumin, g/dl ($n = 108$)	median 3.8 (range, 2.2–4.7)
eGFR, ml/min/1.73 m^2 ($n = 114$)	median 48.2 (range, 21.8–124.5)
Fit (n, 4 ml/min/1.73 m^2)	29 (25.4%)
Cisplatin-unfit (<60 ml/min/ 1.73 m^2)	85 (74.6%)
Metastatic site	
Lymph node	70 (61.4%)
Lung	44 (38.6%)
Bone	20 (17.5%)
Liver	18 (15.8%)
Local recurrence	12 (10.5%)
Prior chemotherapy	
GC	62 (54.4%)
Gemcitabine, carboplatin	2 (1.8%)
MEC	37 (32.5%)
Methotrexate, epirubicin, nedaplatin	6 (5.3%)
MVAC	2 (1.8%)
PIN	5 (4.4%)
Response to first-line chemotherapy	
CR	9 (7.9%)
PR	49 (43.0%)
SD	25 (21.9%)
PD	30 (26.3%)
Not evaluable	1 (0.9%)
Time from prior chemotherapy, months	median 2 (range, 1–71)
Second-line regimens	
PIN	65 (57.0%)
Gemcitabine, carboplatin	15 (13.2%)
GC	15 (13.2%)
Gemcitabine	8 (7.0%)
MEC	4 (3.5%)
Methotrexate, epirubicin, nedaplatin	2 (1.8%)
Paclitaxel, carboplatin	2 (1.8%)
Gemcitabine, docetaxel	1 (0.9%)
Gemcitabine, nedaplatin	1 (0.9%)
Gemcitabine, paclitaxel	1 (0.9%)

eGFR, estimated glomerular filtration rate; CR, complete response; CRP, C-reactive protein; LDH, lactate dehydrogenase; MEC, methotrexate, epirubicin and cisplatin; MVAC, methotrexate, vinblastine, doxorubicin and cisplatin; NE, not evaluable; NLR, neutrophil-to-lymphocyte ratio; PD, progressive disease; PIN, paclitaxel, ifosphamide and nedaplatin; PR, partial response; SD, stable disease; UC, urothelial carcinoma.

and second-line chemotherapy in our cohort was a median of 4 (range: 1–14) and 3 (range: 1–17), respectively. Furthermore, 26 patients underwent third-line and 2 underwent forth-line chemotherapy, respectively.

Survival outcomes and prognostic factors

Figure 1 shows PFS and OS curves for 114 patients. The median PFS and OS times were 4 and 9 months (95% confidence interval: 3.5–5 and 8–12), respectively (Fig. 1). Table 2 summarizes the responses to the second-line chemotherapy. The objective response rate was 28.1%, with a complete response (CR) in 8 patients (7.0%) and partial response (PR) in 24 (21.1%). The results of the uni and multivariate analyses of the prognostic characteristics at the time of the second-line chemotherapy starting point are shown in Table 3. In the univariate analysis, the ECOG PS, Hb level, NLR, platelet count, CRP level, albumin level, prior chemotherapy response and the presence of liver metastasis were significant predictors of OS. According to the multivariate analysis, the ECOG PS score at presentation, CRP level and prior chemotherapy response were significant independent predictors of prolonged OS. In addition, the ECOG PS score at presentation and CRP level were also significant independent predictors of prolonged PFS (Supplementary data, Table 1). We constructed a prognostic model that included these three independent prognostic factors. There were significant differences in OS among the four categories (Fig. 2). The median OS for patients with 0, 1, 2 and 3 risk factors was 17, 12, 7 and 3 months, respectively.

Discussion

In the present study, based on a database retrospectively constructed from daily clinical practice at seven hospitals in Japan (8), we evaluated the outcome of salvage treatment for metastatic UC patients. Overall, the median PFS and OS times for metastatic UC patients who received second-line systemic chemotherapy were 4 and 9 months, respectively, being in line with previous results derived from several phase II and III studies (2,3,10,11). A multivariate model revealed that a good ECOG PS, CRP level <1 mg/dl and good response to prior chemotherapy were independent predictors

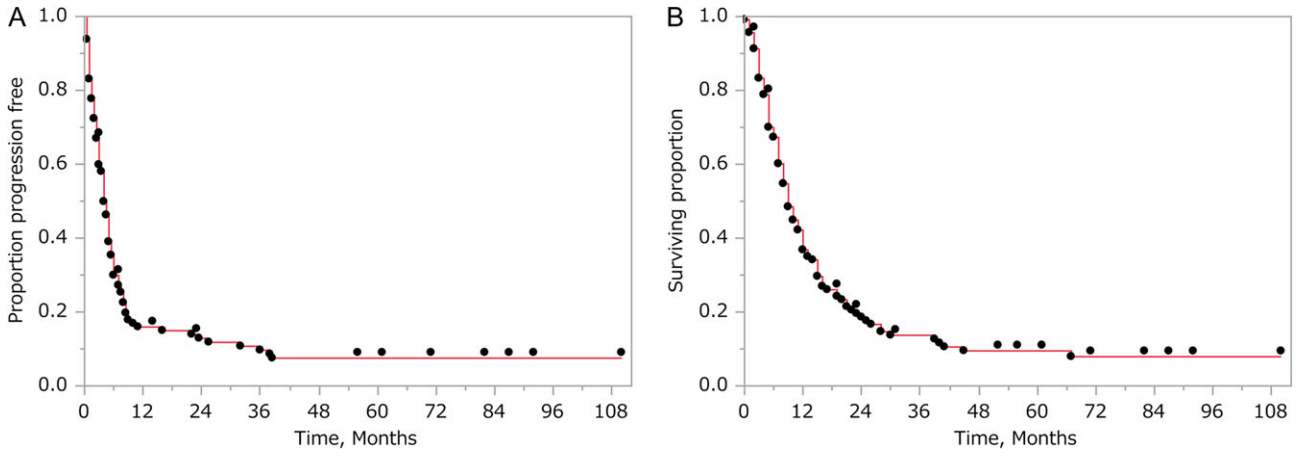

Figure 1. PFS (A) and OS (B) curve for patients treated with second-line chemotherapy. OS, overall survival; PFS, progression-free survival.

Table 2. Summary of responses to the second-line chemotherapy

Response	No. of patients (%)
CR	8 (7.0)
PR	24 (21.1)
SD	22 (19.3)
PD	54 (47.4)
NE	6 (5.3)

of prolonged OS. In terms of the survival impact of ECOG PS, our observations were in line with previous studies; using a pooled database built from several phase II or III clinical trials of second-line chemotherapy for metastatic UC, Bellumunt et al. and Sonpavde et al. observed that a PS score >0 was a significant prognostic factor affecting OS (5–7).

Several researchers have reported the survival impact of CRP in various cancers, including lower or upper UC after extirpative surgery (12–14). Saito et al. reported that baseline and nadir CRP levels and CRP kinetics status were significantly correlated with the prognosis of advanced or metastatic UC patients who had received gemcitabine, etoposide and cisplatin as second-line chemotherapy (14). Furthermore, Ishioka et al., in a total of 223 patients with advanced or metastatic UC, noted that CRP was a continuously significant prognostic factor for OS, and the predictive accuracy of a survival nomogram that they developed was improved by adding CRP, although around 40% of their cohort were treated solely by best supportive care (15). Our observation that a CRP level <1 mg/dl was an independent predictor of prolonged OS, further supported its importance in the treatment of metastatic UC patients.

Regarding the prognostic impact of the response to prior chemotherapy, we observed that a good response (CR and PR) to the first-line chemotherapy was associated with the survival outcomes after salvage treatments. Previously, Pond et al. reported in their pooled patients with advanced UC undergoing second-line chemotherapy, collected from six phase II trials, that the objective responses (PR and CR) to previous chemotherapy did not confer an independent prognostic effect with second-line therapy (16), in contrast to our observation. However, they reported that, when examining the response to prior chemotherapy as stable disease or better as compared with others, a borderline significant correlation ($P = 0.05$) with OS was detected. In the present cohort, we also observed that a relatively good response (CR, PR and SD) to the first-line chemotherapy was associated with the survival outcomes (data not shown). As shown in Table 1, a combination of PIN was the most frequently used regimen (57%, 65/114), because our group was conducting a phase II study of the PIN regimen for the early study period (1), which made the PIN regimen the most familiar option among our group. In another phase II study of PIN regimen, Kitamura et al. reported that patients with a CR or PR after the first-line chemotherapy showed a good response to PIN (2). Taken together with the possibility of cross-resistance to chemotherapeutic agents, for example, between cisplatin and a cisplatin-analog, we believe that a good response to previous chemotherapy could reflect good survival outcomes after second-line chemotherapy, although our observations need to be confirmed in a larger cohort.

Recently, immune checkpoint inhibitors (ICIs) such as programmed death-ligand 1 (PD-L1) and programmed cell death protein 1 (PD-1) checkpoints were developed as efficacious antitumor drugs for patients with advanced or metastatic UC, mainly in those whose disease has progressed after first-line platinum-containing chemotherapy (17–21). For example, atezolizumab, a PD-L1 inhibitor, led to an objective response rate of 15% and median OS time of 7.9 months in a multicenter phase II trial (17). Pembrolizumab, a PD-1 inhibitor, was correlated with a significantly longer OS time (10.3 vs. 7.4 months, respectively, hazard ratio for death = 0.73, $P = 0.002$) and a lower rate of adverse events than chemotherapy as a second-line therapy for platinum-refractory, advanced UC in an international phase III trial (18). Very recently, Szabados et al. reported a very interesting study evaluating the response to systemic chemotherapy after ICIs (22). They collected two cohorts undergoing sequential treatments for metastatic UC. Cohort A ($n = 14$) received ICIs initially followed by systemic chemotherapy after disease progression, and cohort B ($n = 14$) received salvage chemotherapy after the failure of first-line chemotherapy followed by ICIs. The best response rate to chemotherapy after ICIs was 64% for cohort A and 21% for cohort B, which were the same response rates to first-line or second-line chemotherapy previously reported in the pre-ICI era.

Although ICIs probably change the landscape in the treatment of advanced UC, we consider that salvage chemotherapy still remains an important treatment option. The prognostic factors and survival model we built in the present study might be applicable for patient stratification in the future. However, we do not have clear answers

Table 3. Univariate and multivariate analyses of the prognostic characteristics at the time of the second-line chemotherapy start point

	No. of patients	Median survival, months (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Age, year					
≥65	62	8 (6–11)	0.0769		
<65	52	10.5 (8–15)			
Sex male/female					
Male	85	9 (7–11)	0.1956		
Female	29	12 (6–23)			
Performance status					
≥1	44	5.5 (4–8)	<0.0001	2.460 (1.437–4.191)	0.0011
0	67	13 (9–19)		1	
Primary site					
Bladder only	49	10 (8–15)	0.4721		
Others	65	9 (6–12)			
Pathology of primary site					
Pure UC	83	10 (8–15)	0.1457		
Others	20	7 (4–14)			
Hb					
<10 g/dl	41	8 (5–9)	0.0145	1.038 (0.563–1.679)	0.8927
≥10 g/dl	73	12 (8–15)		1	
NLR					
≥3	55	7 (5–9)	0.0005	1.102 (0.539–1.529)	0.7134
<3	44	15 (11–21)		1	
Platelets					
<20 10^4/μl	35	12 (8–20)	0.0354	0.998 (0593–1.663)	0.995
≥20 10^4/μl	79	8 (6–11)		1	
LDH					
≥200	62	8.5 (7–11)	0.2027		
<200	52	11 (8–15)			
CRP					
≥1	39	5 (3–7)	<0.0001	2.631 (1.434–4.762)	0.002
<1	74	13 (11–16)		1	
Albumin					
≥4.0	43	15 (11–21)	0.0002	0.800 (0.465–1.394)	0.4264
<4.0	65	8 (5–9)		1	
eGFR					
Fit	29	10 (5–15)	0.7114		
Cisplatin-unfit	85	9 (7–12)			
Prior chemotherapy response					
SD or PD	55	7 (5–8)	0.0002	1.839 (1.132–2.973)	0.0141
PR or CR	58	12 (9–16)		1	
Time from prior chemotherapy					
≥3 Months	42	12 (8–17)	0.129		
<3 Months	72	8 (7–11)			
Visceral metastasis (lung, liver or bone)					
Yes	63	9 (7–12)	0.6245		
No	51	10 (7–14)			
Liver metastasis					
Yes	18	6.5 (3–8)	0.0444	1.479 (0.739–2.770)	0.2568
No	96	10 (9–12)		1	

Hb, hemoglobin; CI, confidence interval.

regarding whether patients with adverse characteristics should be treated by ICI first after the failure of first-line chemotherapy. We need to accumulate more experiences, especially cases treated by ICI.

Our analysis was limited by its retrospective nature and small sample size. We could not come to a conclusion regarding the appropriate chemotherapy regimen that should be used in a salvage setting due to the heterogeneity of our cohort, although the efficacy of combination chemotherapy comparing to that of single-agent use might be superior according to a recent review (23). Furthermore, as an important limitation, the dominant second-line chemotherapy regimen in the present study was PIN, which is not widely utilized outside of Japan. Assessment of the radiological response might not be as strict as that in prospective clinical studies. It is unknown whether the prognostic factors identified in this analysis are applicable in the new era of ICIs, and we need to accumulate experience and reassess that in the future. Nevertheless, we believe that several important findings were generated by the current analyses.

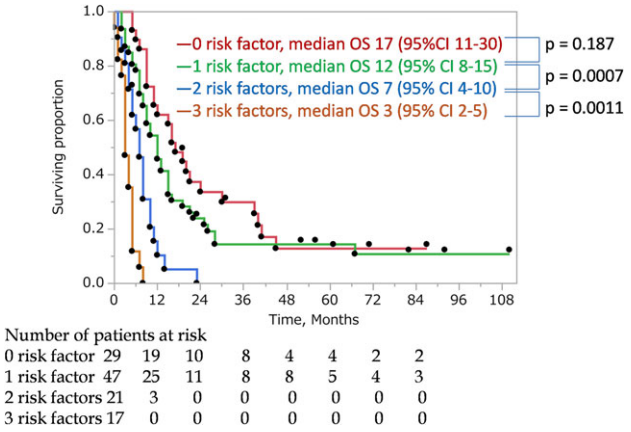

Figure 2. OS curve for patients treated with second-line chemotherapy divided by risk factor.

Conclusions

The ECOG PS at presentation, CRP level and response to prior chemotherapy were prognostic factors for metastatic UC patients undergoing second-line chemotherapy in real-world clinical practice. In the future, this information might provide additional clues to aid in the choice of salvage treatment, such as second-line chemotherapy or the use of ICIs after the failure of first-line chemotherapy.

Supplementary data

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

Funding

There were no financial supports for this study.

Conflict of interest statement

There are no competing financial interests related to this study.

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