JJCO Japanese Journal of Clinical Oncology

Japanese Journal of Clinical Oncology, 2019, 49(10) 965–971
doi: 10.1093/jjco/hyz084
Advance Access Publication Date: 12 June 2019
Original Article

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Outcome of maintenance systemic chemotherapy with drug-free interval for metastatic urothelial carcinoma

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Received 18 March 2019; Editorial Decision 15 May 2019; Accepted 21 May 2019

Abstract

Objective: Aiming to achieve long-term disease control, maintenance systemic chemotherapy (MSC) with a 1–3-month drug-free interval is continued in selected patients. We report our experience of MSC for metastatic urothelial carcinoma (UC).

Methods: Of 228 metastatic UC patients treated with systemic chemotherapy, 40 (17.5%, 40/228) had continuously undergone MSC. Data on the regimen, cycle number, and reason for the discontinuation of MSC were also collected. We analyzed OS from the initiation of MSC until death or the last follow-up, using the log-rank test to assess the significance of differences.

Results: The median number of cycles of chemotherapy was 6, and the responses were CR in 6, PR in 20, SD in 13, and PD in 1 before MSC. Gemcitabine plus CDDP or carboplatin was mainly performed as MSC (70%, 28/40). MSC was repeated quarterly in 30 (75%, 30/40), every two months in 8 (20%, 8/40), and with other intervals in 2 (5%, 2/40). Overall, a median of 3.5 cycles (range: 1–29) of MSC was performed. The reason for the discontinuation of MSC was PD in 24 (60%, 24/40), favorable disease control in 9 (22.5%, 9/40), and myelosuppression in 3 (7.5%, 3/40), and for other reasons in 2 (5%, 2/40). MSC was ongoing in 2 (5%, 2/40). The median OS was 27 months from the initiation of MSC. PS0 ($P = 0.0169$), the absence of lung metastasis ($P = 0.0387$), and resection of the primary site ($P = 0.0495$) were associated with long-term survival after MSC.

Conclusions: In selected patients, long-term systemic chemotherapy could be performed with a drug-free interval. Our maintenance strategy with cytotoxic drugs may become one of the treatment options for long-term disease control.

Key words: metastatic urothelial carcinoma, systemic chemotherapy, maintenance chemotherapy

Introduction

Platinum-based combination chemotherapy is the mainstay of treatment for metastatic urothelial carcinoma (UC), and the gemcitabine plus cisplatin regimen has been the most widely used as the first-line treatment. In general, UC is a chemo-sensitive tumor. Good initial response rates of around 50–70% have been reported. However, the majority of patients show disease relapse during the follow-up after the completion of first-line chemotherapy, and salvage regimens have

been tested, including combination regimens or single agents, worldwide (1–3). Although the recent development of immunotherapy with check-point inhibitors, such as atezolizumab (4), pembrolizumab (5), nivolumab (6), durvalumab (7), or avelumab (8), has changed the treatment paradigm for metastatic UC, optimizing the use of an effective regimen may be a key factor to improve outcomes.

Maintenance therapy for patients showing a good response or disease stabilization after systemic chemotherapy has been introduced for several tumors, such as non-small cell lung cancer (9). In our hospital and affiliated teaching hospitals, aiming at long-term disease control, systemic chemotherapy was continued with a 1–3-month drug-free interval for selected patients who achieved disease control. In the present study, we report our experience of this maintenance systemic chemotherapy (MSC) strategy for metastatic UC patients.

Materials and methods

The present retrospective study was approved by the institutional review board. A total of 228 metastatic UC patients treated with at least two cycles of systemic chemotherapy between 2000 and 2013 at Hokkaido University Hospital and 6 affiliated teaching hospitals were included. Data on the patient characteristics, details of treatments such as chemotherapy regimens or numbers of chemotherapy cycles performed, and

Table 1. Patient characteristics

	MSC cohort, $n = 40$	Non MSC cohort, $n = 188$	p-value
Age, year	median 63 (range, 42–80)	median 67.5 (range, 30–83)	0.044
Sex male / female			
Male	28 (70%)	146 (77.7%)	0.3111
Female	12 (30%)	42 (22.3%)	
ECOG performance status			0.0844
0	35 (87.5%)	132 (70.2%)	
1	2 (5%)	36 (19.1%)	
2	2 (5%)	7 (3.7%)	
3	0	2 (1.1%)	
Unknown	1 (2.5%)	11 (5.9%)	
Primary site			
Bladder	21 (52.5%)	90 (47.9%)	0.6108
Upper urinary tract	17 (42.5%)	81 (43.1%)	
Both	1 (2.5%)	14 (7.4%)	
Urethra/prostate	1 (2.5%)	3 (1.6%)	
Pathology of primary site			
Pure urothelial carcinoma	33 (82.5%)	142 (75.5%)	0.507
Others	4 (10%)	32 (17%)	
Unknown (cytology positive)	3 (7.5%)	14 (7.4%)	
Baseline laboratory data			
Hemoglobin, g/dL ($n = 224$)	median 12.25 (range, 9.2–15.2)	median 12.1 (range, 7.3–17.8)	0.859
Lactic dehydrogenase, IU/L ($n = 225$)	medain 178 (range, 124–996)	medain198 (range, 105–1154)	0.0608
CRP, mg/dL ($n = 223$)	median 0.38 (range, 0.02–9.43)	median 0.5 (range, 0.01–19.87)	0.67
Corrected calcium, mg/dL ($n = 209$)	median 9.4 (range, 4.4–10.8)	median 9.5 (range, 4.1–11.7)	0.5197
Estimated GFR (eGFR), mL/ min./ 1.73 m^2 ($n = 224$)	median 61.0 (range, 34.3–122.7)	median 56.2 (range, 21.2–130.1)	0.4093
eGFR ($n = 224$)			
Fit (≥60 mL/min./1.73 m^2)	22 (55%)	80 (42.6%)	0.1856
Cisplatin-unfit (<60 mL/min./1.73 m^2)	18 (45%)	104 (55.3%)	
Primary site at the initiation of chemotherapy			
Resected	27 (67.5%)	94 (50%)	0.0418
Not resected	13 (32.5%)	94 (50%)	
Metastatic site			
Lymph node	24 (60%)	127 (67.6%)	0.364
Lung	18 (30%)	68 (36.2%)	0.2994
Bone	11 (27.5%)	34 (18.1%)	0.1886
Liver	5 (12.5%)	15 (8.0%)	0.3793
Local recurrence	3 (7.5%)	16 (8.5%)	0.8316
Visceral metastasis (lung, liver, or bone)			
Yes	25 (62.5%)	94 (50%)	0.1485
No	15 (37.5%)	94 (50%)	
Single organ metastasis	20 (50%)	124 (66%)	0.061
Response after first-line chemotherapy			
CR	5 (12.5%)	23 (12.2%)	0.0002
PR	18 (45%)	55 (29.3%)	
SD	15 (37.5%)	39 (20.7%)	
PD	2 (5%)	66 (35.1%)	
Unknown	0	5 (2.7%)	

MSC = maintenance systemic chemotherapy.

overall survival outcomes were retrospectively collected. Based on this cohort, we previously published a paper evaluating prognostic factors in real-world clinical practice in Japan (10,11). Our general treatment strategy was reported in a previous study. Briefly, in the early study period, the MEC regimen (methotrexate, epirubicin, and cisplatin), which was accepted as an alternative to MVAC in Japan based on a prospective randomized study showing a similar response rate and incidence of adverse effects (12), was utilized as the first-line regimen. In the later period, the GC regimen (gemcitabine and cisplatin) was selected. In patients refractory to first-line chemotherapy, a salvage regimen such as a taxane-based combination regimen was considered. In patients with an impaired renal function, dose reduction was considered, as previously reported (13), or cisplatin was replaced with carboplatin. In selected patients with oligometastasis, which meant metastasis in a single organ with a small number of metastases (e.g. single pulmonary metastasis), a good performance status, and stabilization of disease, surgical consolidation was also considered. The objective response was evaluated by the treating physician according to the Response Evaluation Criteria in Solid Tumors, version 1.1, in most cases.

In selected patients showing disease control, systemic chemotherapy was intentionally continued while extending the interval of treatment, named 'maintenance systemic chemotherapy (MSC)', after discussion between patients and physicians. They were the main cohorts in the current study. The reasons for the discontinuation of MSC were newly collected for the present analysis.

Statistical methods

Patient characteristics between MSC and non-MSC cohorts were compared using the Mann–Whitney *U* test. Overall survival (OS) was estimated from the initiation of treatment for metastatic UC or the initiation of MSC until death or the last follow-up. The log-rank test was used to determine the significance of differences between survival estimates. The Cox proportional hazards model was also utilized to identify prognostic characteristics. The parameters analyzed were sex, age, ECOG-performance status (PS), primary site, histology 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, visceral metastasis [lung, liver, or bone]), and number of metastatic organs.

Because of the heterogeneity of patient backgrounds between MSC and non-MSC cohorts, propensity score matching was also utilized to adjust for the confounding factors in order to select patients for MSC. A logistic regression model, which included age (continuous), sex, ECOG PS, status of primary site (resected or not), metastatic sites (presence of lymph node, lung, bone, liver, local recurrence, or absence), number of metastatic organs (single or multiple), and baseline renal function (fit or unfit), was used to estimate each patient's probability of receiving MSC. Patients without MSC were matched on a one-to-one basis with patients with MSC based on nearest-neighbor matching. All calculations were performed using JMP version 12.2.0. A value of $P < 0.05$ was considered significant.

Results

Table 1 shows patient characteristics according to the receipt/non-receipt of MSC. The MSC group showed a younger age (median age, years: MSC 63, non-MSC 67.5, $P = 0.044$), more frequent resection of the primary site (MSC 67.5%, non-MSC 50%, $P = 0.0418$), and a better PS (PS0: MSC 87.5%, non-MSC 70.2%, $P = 0.0844$) at the time of initiating systemic chemotherapy. In terms of the response after first-line chemotherapy, the majority of patients in the MSC cohort showed at least stable disease, while 35.1% showed progressive disease in the non-MSC cohort.

Table 2. Summary of maintenance chemotherapy

MSC was started following	
First-line	30
Second-line	8
Third-line	2
Chemotherapy cycles performed before MSC	Median 6 (range, 2–15)
Response before induction of MSC	
CR	6
PR	19
SD	14
PD	1
Regimens used as MSC	
Gemcitabine plus CDDP or carboplatin	28
Methotrexate plus epirubicin plus CDDP or nedaplatin (CDDP analog)	8
Paclitaxel plus ifosphamide plus nedaplatin	3
Gemcitabine monotherapy	1
Interval of MSC	
Every 3 months	30
Every 2 months	8
2–4 months	2
Chemotherapy cycles performed as MSC	Median 3 (range, 1–29)
Reason for discontinuation of MSC	
PD	24
Disease stabilization	9
Myelosupression	3
Patient's wish	1
Death due to other cause	1
On MSC	2
Treatment after cessation of MSC	
BSC/follow up	19
Salvage chemotherapy	15
Participation in clinical trial	2
Radiation	1

Table 2 shows a summary of MSC. Thirty patients (75%, 30/40) underwent MSC following first-line chemotherapy, and 10 (25%, 10/40) patients following salvage chemotherapy. The median number of chemotherapy cycles was 6, and the responses were CR in 6 patients (15%, 6/40), PR in 19 patients (47.5%, 19/40), SD in 14 patients (35%, 14/40), and PD in 1 patient (2.5%, 1/40) before MSC introduction. Gemcitabine plus CDDP or carboplatin was mainly performed as MSC (70%, 28/40). MSC was repeated quarterly in 30 patients (75%, 30/40), every 2 months in 8 patients (20%, 8/40), and with other intervals in 2 patients (5%, 2/40). Overall, a median of 3 cycles (range: 1–29) of MSC were performed. The reason for the discontinuation of MSC was PD in 24 patients (60%, 24/40), favorable disease control in 9 patients (22.5%, 9/40), and myelosuppression in 3 patients (7.5%, 3/40), and for other reasons in 2 patients (5%, 2/40). MSC was ongoing in 2 patients (5%, 2/40). In 15 patients (37.5%, 15/40), salvage chemotherapy treatment was performed following MSC.

Figure 1 shows overall survival curves from the initiation of treatment for metastatic UC. Overall, the median OS was 39 months

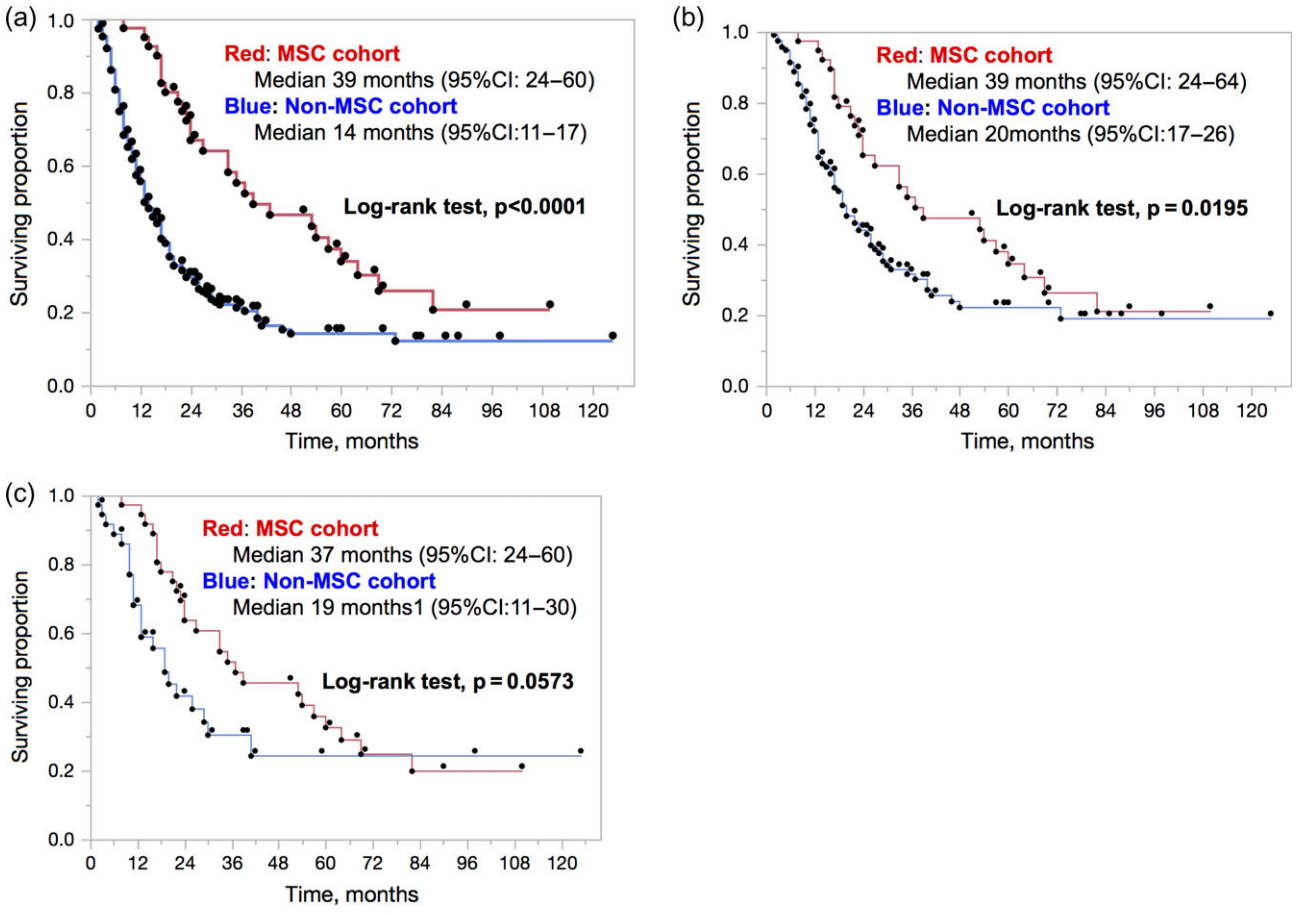

Figure 1. Overall survival curves from the initiation of treatment for metastatic UC. (a) The median OS was 39 months from the initiation of treatment for metastases in the MSC cohort, as compared with 14 months in the non-MSC cohort ($P < 0.0001$). (b) As for patients showing CR/PR/SD after first-line chemotherapy ($n = 155$), MSC was still associated with longer survival (median OS: MSC cohort; 39 months, non-MSC cohort; 20 months, $P = 0.0195$). (c) Median OS was 37 months in the MSC cohort and 19 months in the non-MSC cohort after propensity score matching ($P = 0.0573$).

from the initiation of treatment for metastases in the MSC cohort, as compared with 14 months in the non-MSC cohort (Figure 1a, $P < 0.0001$). As for the patients showing CR/PR/SD after first-line chemotherapy ($n = 155$), MSC was still associated with longer survival (median OS: MSC cohort; 39 months, non-MSC cohort; 20 months, $P = 0.0195$, Figure 1b). To further improve compatibility, propensity score matching was utilized in the patients showing CR/PR/SD after first-line chemotherapy. Table 3 shows patients characteristics after propensity score adjustments. The patient distributions were closely balanced between the two cohorts. Median OS was 37 months in the MSC cohort and 19 months in the non-MSC cohort after propensity score matching (Figure 1c, $P = 0.0573$).

Figure 2a shows an OS estimate from the initiation of MSC. The median OS was 27 months from the initiation of MSC. Regarding the survival impacts of baseline clinical characteristics, PS0 ($P = 0.0169$), the absence of lung metastasis ($P = 0.0387$), and resection of the primary site ($P = 0.0495$) were associated with long-term survival after the initiation of MSC (Table 4). None of these factors retained prognostic significance on multivariate analysis, although lung metastasis and the performance status showed marginal values (Table 5). Figure 2b shows the OS curves from the initiation of MSC divided by the timing of maintenance initiation. There was no significant difference in survival between the two cohorts (first-line vs. second /third –line, $P = 0.8041$).

Discussion

In order to maintain the response to chemotherapy and delay disease progression, we continued the systemic chemotherapy in selected patients mainly with at least stable disease after the first-line systemic chemotherapy, when the patients agreed with the present maintenance strategy of administrating the effective agents with drug holidays. Overall, the median OS was 39 months in the MSC cohort, as compared with 14 months in the non-MSC cohort (Figure 1a, $P < 0.0001$). After propensity score matching in the patients showing CR/PR/SD after first-line chemotherapy, the median OS was 37 months in the MSC cohort and 19 months in the non-MSC cohort (Figure 1c, $P = 0.0573$). Our observation reflected the treatment outcome of real-world clinical practice, not a clinical trial, and a well-controlled randomized study is necessary to determine the clinical benefit of the present maintenance strategy. However, our observation suggested that long-term systemic chemotherapy could be performed with a drug-free interval, and the maintenance of cytotoxic drugs could be one of the treatment options for long-term disease control. Gemcitabine plus CDDP or carboplatin was dominantly utilized in an MSC setting ($n = 28$), usually every 3 months (2-month drug holiday). Recently, we routinely replace CDDP with carboplatin to minimize the accumulation of renal toxicity when considering MSC.

Table 3. Characteristics after propensity score matching of the patients showing CR/PR/SD after first-line chemotherapy

	n = 36 with MSC	*n* = 36 without MSC	p-value
Age, year	median 64 (range, 42–80)	median 67.5 (range, 45–78)	0.4463
Sex male / female			
Male	26	23	0.4478
Female	10	13	
ECOG performance status			
0	32	29	0.4781
1	2	5	
2	2	2	
Primary site			
Bladder	19	17	0.5803
Upper urinary tract	15	17	
Both	1	0	
Urethra/prostate	1	2	
Pathology of primary site			
Pure urothelial carcinoma	29	32	0.5124
Others	4	3	
Unknown (cytology positive)	3	1	
Baseline laboratory data			
Hemoglobin, g/dL (*n* = 72)	median 12.4 (range, 9.2–15.2)	median 12.45 (range, 8.6–16.5)	0.4107
Lactic dehydrogenase, IU/L (*n* = 72)	medain 178 (range, 124–699)	medain 202 (range, 150–441)	0.0977
CRP, mg/dL (*n* = 71)	median 0.46 (range, 0.02–9.43)	median 0.43 (range, 0.01–7.18)	0.7423
Corrected calcium, mg/dL (*n* = 66)	median 9.45 (range, 4.4–10.8)	median 9.45 (range, 7.5–10.8)	0.9282
Estimated GFR (eGFR), ml/min./1.73 m^2 (*n* = 72)	median 60.4 (range, 34.3–85.7)	median 61.3 (range, 28.5–99.3)	0.9686
eGFR (*n* = 72)			
Fit (≥60 mL/min./1.73 m^2)	19	19	1
Cisplatin-unfit (<60 mL/min./1.73 m^2)	17	17	
Primary site at the initiation of chemotherapy			
Resected	23	26	0.4478
Not resected	13	10	
Metastatic site			
Lymph node	22	21	0.8101
Lung	16	18	0.6367
Bone	10	8	0.5859
Liver	4	4	1
Local recurrence	3	5	0.4511
Visceral metastasis (lung, liver, or bone)			
Yes	22	24	0.6235
No	14	12	
Single organ metastasis	17	16	0.813
Response after first-line chemotherapy			
CR	5	9	0.0875
PR	17	21	
SD	14	6	

A maintenance strategy is not a new concept for metastatic urothelial cancer treatment. Grivas et al. investigated the role of sunitinib maintenance in patients with advanced UC showing stable disease or a partial or complete response after 4 to 6 chemotherapy cycles. Participants were randomly assigned to sunitinib at a dose of 50 mg/day (4 weeks on and 2 weeks off) or placebo, and the primary endpoint was the 6-month progression rate. The study was prematurely closed due to poor accrual (sunitinib: *n* = 26, placebo: *n* = 28, predefined accrual goal: 42 participants per treatment arm), and maintenance sunitinib did not improve the 6-month progression rate (sunitinib: 71.7%, placebo: 64.3%) (14). Powles et al. also did not observe a clinical benefit of maintenance lapatinib (HER1 and HER2 tyrosine kinase inhibitor) in patients with HER-1 and HER-2 bladder cancer, who showed stable disease during 4 to 8 cycles of chemotherapy for advanced metastatic UC (15). In terms of chemotherapeutic agents, several previous studies suggested possible clinical activity. García-Donas et al. reported the outcomes of maintenance therapy with vinflunine (16). The 87 patients were included in their study after disease control with 4 to 6 cycles of a cisplatin and gemcitabine regimen and were randomly assigned to receive vinflunine every 3 weeks plus best supportive care, or best supportive care alone. The median progression-free survival of 6.5 months in the vinflunine group with an acceptable safety profile, which was significantly longer than the 4.2 months achieved in the best supportive care group (hazard ratio = 0.59, *P* = 0.031). Muto et al. reported their experiences of maintenance monotherapy with gemcitabine (17). A total of 33 patients underwent maintenance therapy after a mean of 2.7 courses of prior chemotherapy. Gemcitabine (1000 mg/m2) was administered on an outpatient basis every 4 weeks, and a median of 9 courses was administered. They observed that the median cancer-specific survival was 15 months after the induction of maintenance

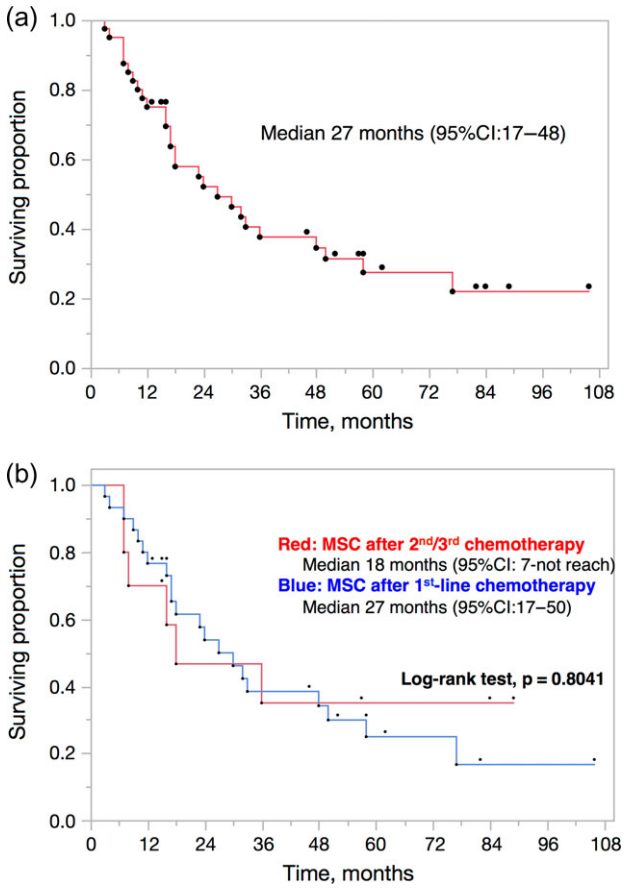

Figure 2. Overall survival curve from the initiation of MSC. (a) Overall, the median OS was 27 months from the initiation of MSC. (b) There was no significant difference in survival between the two cohorts (first-line vs. second /third -line).

chemotherapy. Also in other malignancies, maintenance treatment has been performed using a drug different from that in the induction regimen, for example, maintenance olaparib after platinum-based chemotherapy in advanced ovarian cancer patients (18), or single agents of the induction regimen such as pemetrexed after pemetrexed plus cisplatin in advanced non-squamous non-small-cell lung cancer patients (19). Because we continued the combination regimen with the aid of drug holidays, our strategy might represent relative dose reduction. Regarding immune checkpoint inhibitors, 'Testing the PD-1 Inhibitor Pembrolizumab as Maintenance Therapy After Initial Chemotherapy in Metastatic Bladder Cancer (NCT02500121)' is ongoing.

In the present cohort, PS0 (P = 0.0169), the absence of lung metastasis (P = 0.0387), and resection of the primary site (P = 0.0495) were associated with long-term survival after the initiation of MSC (Table 4). These factors might be associated with maintaining a good health status, including the absence of local symptoms and a good respiratory function during MSC treatment, enabling the continuation of long-term systemic chemotherapy. When dividing the outcomes by the timing of maintenance initiation (first-line or second/third -line), we did not find any ignificant difference in survival between the two cohorts. Although the present cohort was very small, our observations suggest that the maintenance strategy could be utilized in a salvage regimen if at least stable disease is observed during treatment.

Table 4. Univariate analysis of prognostic factors after the initiation of MSC

	n	Median survival time (95% CI)	P-value
Age, year			
≥67	16	24 (9-NR)	0.9749
<67	24	30 (17–58)	
Sex			
Male	28	24 (16–33)	0.0856
Female	12	NR (8-NR)	
ECOG performance status			
PS 0	35	32 (18–58)	0.0169
PS 1	4	12.5 (3-NR)	
Primary site			
Primary, bladder	21	32 (17–77)	0.3189
Others	19	23 (9–48)	
Pathology of primary site			
Pure urothelial carcinoma	33	30 (17–50)	0.707
Others	4	NR (7-NR)	
Baseline laboratory data			
Hemoglobin, <10 g/dL	3	NR (24-NR)	0.4775
≥10 g/d+	37	27 (16–48)	
LDH, ≥200 IU/L	13	50 (8-NR)	0.5546
<200 IU/L	27	24 (16–36)	
CRP, ≥1 mg/dL	12	NR (11-NR)	0.0532
<1 mg/dL	28	24 (16–36)	
Corrected Ca, ≥10 mg/dL	3	17 (7-NR)	0.9172
<10 mg/dL	35	27 (16–50)	
eGFR, fit (≥60 mL/min./1.73 m^2)	22	32 (17–58)	0.8792
Unfit (<60 mL/min./1.73 m^2)	18	23 (7-NR)	
Prior chemotherapy			
Yes	4	NR (23-NR)	0.0529
No	36	24 (16–36)	
Primary site at the initiation of chemotherapy			
Resected	27	33 (18–77)	0.0495
Not resected	13	17 (7–36)	
Metastatic site			
Lymph node, yes	24	27 (16–50)	0.8226
No	16	33 (10–77)	
Lung, yes	18	24 (17–33)	0.0427
No	22	48 (17-NR)	
Bone, yes	11	58 (11-NR)	0.3293
No	29	27 (16–36)	
Liver, yes	5	30 (7-NR)	0.7923
No	35	27 (17–50)	
Local, yes	3	10 (7-NR)	0.7371
No	37	30 (17–50)	
Visceral metastasis (lung, liver, or bone), yes	25	27 (17–50)	0.4053
No	15	32 (12-NR)	
Single-organ metastasis			
Yes	20	33 (18–58)	0.2633
No	20	17 (7–50)	

CI = confidence interval, NR = not reach

We recognize that our study was limited by its retrospective nature and small sample size. Assessment of the radiological response might not have been as strict as that in prospective clinical trials. We did not have data on adverse events or the quality of life during MSC treatment. We could not come to a conclusion regarding the appropriate indication for MSC chemotherapy, or its ideal duration. As described above, a future prospective study is needed to clarify the survival benefit of MSC. Nevertheless, we consider that several important findings were generated by the present study.

Table 5. Multivariate analysis of prognostic factors after the initiation of MSC

	No. of patients	Hazard ratio (95% CI)	p-value
ECOG performance status			
PS 0	35	1	0.0601
PS 1	4	4.476 (0.930–16.88)	
Primary site at the initiation of chemotherapy			
Resected	27	1	0.306
Not resected	13	1.571 (0.652–3.654)	
Lung metastasis			
No	22	1	0.0535
Yes	18	2.2357 (0.988–5.303)	

Conclusions

In the selected patients, long-term systemic chemotherapy could be performed with a 1–3-month drug-free interval. Our maintenance strategy with cytotoxic drugs may become one of the treatment options for long-term disease control.

Conflict of interest statement

None declared.

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