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Metastatic Urothelial Tumor Progression Following First Line Chemotherapy: Prognostic Factors and Importance of Second Line Chemotherapy

Mohammad S. Ma'koseh♦, Rami A. Al-wardat, Murad Y. Salam, Samer H. Salah

Department of Medical Oncology, King Hussein Cancer Center, Amman, Jordan

Abstract

Background: Limited data exists to support the benefit from second-line chemotherapy in patients with metastatic urothelial carcinoma. Factors that predict survival following progression after first-line platinum-based regimens in patients treated outside clinical trials are not clear. This study intends to evaluate different prognostic factors and the impact of second-line chemotherapy on survival.

Methods: We retrospectively reviewed patients with metastatic urothelial carcinoma who experienced disease progression following first-line platinum-based regimens for metastases. These patients received treatment and follow up visits at a single institution. The effect of demographic, disease characteristics, and second-line therapy on overall survival was examined through univariate and multivariate cox-regression analyses.

Results: There were 64 patients included. A total of 27 (42%) patients did not receive second-line chemotherapy because of poor Eastern Cooperative Oncology Group performance status, 20 (31%) received combination chemotherapy (platinum-based in 17), and 17 (27%) received a single agent chemotherapy. The median overall survival from the date of documented progression after first-line therapy was 5.0 months. In multivariate analysis, a correlation existed between poor overall survival and performance status of ≥1 (HR: 5.74, 95% CI: 1.4- 45.57, *P*=0.036), no second-line chemotherapy (HR: 2.72, 95% CI: 1.39-5.31, *P*=0.003), and ≥2 metastatic sites (HR: 5.19, 95% CI: 1.74-15.44, *P*<0.001).

Conclusion: A significant proportion of patients with metastatic urothelial carcinoma were not eligible for second-line chemotherapy because of poor performance status. Use of second-line chemotherapy, Eastern Cooperative Oncology Group performance status, and number of metastatic sites were important determinants of survival.

Keywords: Urothelial neoplasms, Prognosis, Chemotherapy, Performance status, Metastatic sites

♦Corresponding Author:
Mohammad S. Ma'koseh, MD
King Hussein Cancer Center,
Queen Rania Al-Abdulla Street,
Amman 11941, Jordan
Tel: +96266300460, ext: 1652.
Email: maakoseh727@yahoo.com

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Introduction

Bladder cancer is the fourth most common cancer in American men and ninth most common malignancy in American women.[1] Approximately 20%-40% of patients either present with more advanced disease or progress following treatment for superficial or muscle invasive disease.[2]

There is no consensus about standard second-line chemotherapy for patients with metastatic urothelial carcinoma (UC) who develop progressive disease following first-line platinum-based chemotherapy.[3,4] In addition, there is a paucity of data regarding the effect of chemotherapy on overall survival (OS) in this setting.Vinflunine, a novel vinca alkaloid,is the only agent that has been evaluated in a randomized controlled trial that enrolled 370 patients randomized to either vinflunine or best supportive care. Over-all response rate to vinflunine was 9%, and there was a small (6.9 vs. 4.6 months) OS benefit over best supportive care demonstrated on the treated population. However, this survival benefit was not statistically significant in the intention-to treat analysis.[5] This negative result in the intention to treat analysis has resulted in the absence of consensus for adopting vinflunine as a standard second-line option.

Many phase 2 studies assessed the efficacies of different chemotherapy regimens for UC in a second-line setting.[6-10] However, the single-arm design, heterogeneity in inclusion criteria, and the study population in these studies limited our ability to determine the best second-line chemotherapy regimen for those who progress beyond standard first-line platinum-based regimens.[11]

Studies identified prognostic factors for survival in patients who received second-line chemotherapy. Poor performance status, low hemoglobin, and liver metastases were identified as independent poor prognostic factors in a phase 3 vinflunine randomized trial.[12] A recent meta-analysis conducted in patients treated with different second-line chemotherapeutic agents determined that poor performance status, low hemoglobin, and metastatic patterns other than lymph node only metastases were independent prognostic factors for OS.[13]

We have retrospectively reviewed patients with metastatic UC who progressed following standard first-line platinum-based regimens and received treatment outside the context of clinical trials. We intend to seek a better understanding of the outcomes of this population when treated in a real world setting regardless of whether patients have received second-line chemotherapy. This group of patients are likely to include those with worse Eastern Cooperative Oncology Group performance status (ECOG PS) compared to the highly selected clinical trial populations.

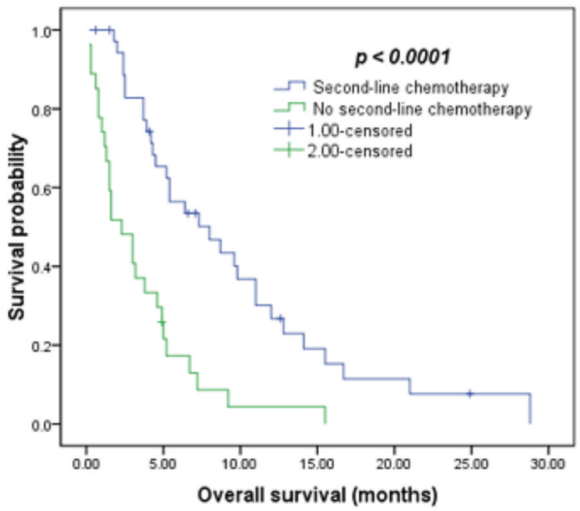

Figure 1. Overall survival (OS) estimation according to second-line chemotherapy administration.

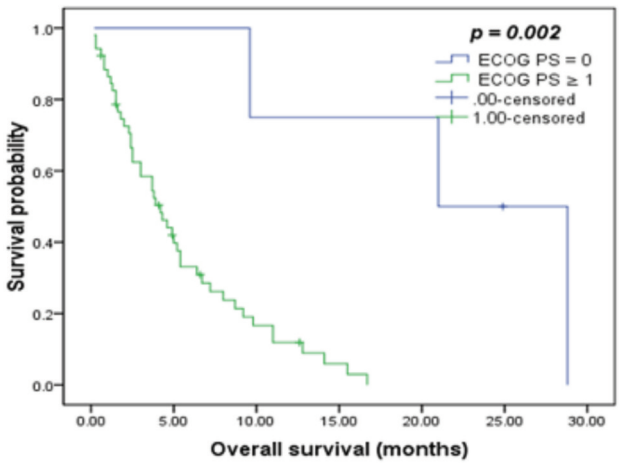

Figure 2. Overall survival (OS) estimation according to Eastern Cooperative Oncology Group performance status (ECOG PS).

Materials and Methods

We retrospectively analyzed medical records of patients with a pathologic diagnosis of UC, who had documented radiological progression following standard first-line platinum-based chemotherapy, and received treatment and follow-up visits at King Hussein Cancer Center in Jordan. Adjuvant or neoadjuvant chemotherapy was not considered first-line treatment.

The following data were retrieved from patients' charts and electronic medical records; age, ECOG PS, smoking status, weight loss (defined as significant if ≥10% from baseline in ≤6 months), and sites of metastases. In addition, different laboratory variables (hemoglobin, white blood cell count, neutrophil count, platelet count, creatinine clearance, alkaline phosphatase, lactate dehydrogenase, serum albumin, and corrected calcium) were documented for all patients.

Definitions and statistical considerations

We defined OS as the time from starting second-line chemotherapy until last follow-up or death. Progression-free survival (PFS) was defined as time from the initiation of second-line chemotherapy until the first documentation of disease progression (DP), last follow-up, or death.

The effect of demographics, disease characteristics, laboratory parameters, and the use of second-line chemotherapy on OS was examined through univariate analysis.

Survival curves were plotted by the Kaplan-Meier method and compared by the log-rank test. All *P*-values of <0.05 were considered statistically significant. Finally, we performed a multivariate analysis utilizing the backward stepwise Cox-regression model to identify the independent prognostic factors. All statistical analyses were

Table 1. Characteristics of patients with metastatic urothelial carcinoma (UC) at time of progression after first-line platinum-based regimens.

Variables	Number (%)
Gender	
Male	60 (94)
Female	4 (6)
ECOG PS*	
0	5 (8)
1	32 (50)
≥2	27 (42)
Smoking	
Current	27 (42)
Ex-smoker or never smoked	37 (58)
Weight loss (>10% over last 6 months)	12 (19)
Number of metastatic sites	
1	14 (22)
≥2	49 (77)
Unknown	1 (1)
Perioperative chemotherapy	
Yes	13 (20)
No	51(80)
Response to first-line chemotherapy	
Yes	28 (44)
No	35(65)
Hemoglobin	
≥10 g/dl	36 (56)
<10 g/dl	28 (44)
White blood cells	
<12000	54(86)
>12000	9(14)
Platelets	
<500,000	56(90)
≥500,000	6(10)
Alkaline phosphatase	
<500 units/L	59(95)
≥500 units/L	3(5)
Creatinine clearance	
≥60ml/min	41(68)
<60ml/min	19(32)
Serum albumin	
≥3.5 g/dl	28(45)
<3.5g/dl	34(55)

*ECOG PS: Eastern Cooperative Oncology Group performance status.

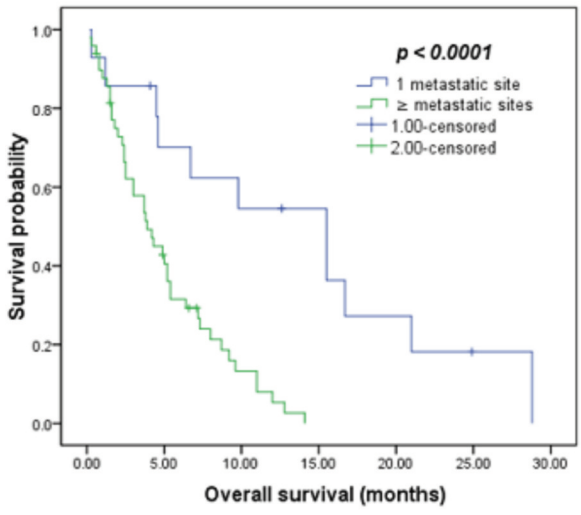

Figure 3. Overall survival (OS) estimation according to number of metastatic sites.

Table 2. Results of univariate analysis for factors that influenced overall survival (OS).

Variable	Median OS (months)	*P*-value
Male	4.9	0.45
Female	1.5	
Age <60 years	4.9	0.32
Age ≥60 years	4.6	
Perioperative chemotherapy	4.9	0.88
No perioperative chemotherapy	4.6	
Response to first-line		
Yes	4.5	0.85
No	5.0	
Smoking status		
Current smoker	3.9	0.33
Quit smoking	4.5	0.26
No smoking	5.4	
Weight loss		
Yes	2.4	0.015
No	5.2	
ECOG PS*		
0	21.0	0.002
≥1	4.2	
Second-line chemotherapy	8.0	
No second-line chemotherapy	2.3	<0.0001
Number of metastatic sites		
1	15.5	<0.0001
≥2	3.9	
Serum hemoglobin		
< 10 g/dl	3.9	0.042
≥ 10 g/dl	5.4	
Lymph node only metastases	15.5	
Other metastases	4.3	0.005
Liver metastases	4.3	
No liver metastases	5.2	0.097
WBC <12000	5.2	
WBC≥12000	1.5	0.001
Platelets<500	4.9	
Platelets ≥500	5.2	0.68
Alkaline phosphatase <500units/L	5.0	
Alkaline phosphatase ≥500units/L	3.7	0.66
Creatinine clearance <60 ml/min	4.6	
Creatinine clearance ≥60 ml/min	5.2	0.69
Serum albumin <3.5g/dl	3.0	
Serum albumin ≥3.5g/dl	8.0	<0.0001

*ECOG PS: Eastern Cooperative Oncology Group performance status

performed using SPSS, version 17 (SPSS Inc., Chicago, IL).

Results

Patients' characteristics

This study included 64 patients with a median age of 62 (range: 26-78) years. A total of 27(42%) patients initially presented with localized disease and received local treatment (20 underwent radical cystectomy and 7 received concurrent chemo-radiotherapy), whereas 37 (58%) presented with de-novo metastatic disease.There were 13(20%) patients who received perioperative chemotherapy (7 received neoadjuvant chemotherapy, 6 received adjuvant chemotherapy). Table 1 lists the patients' characteristics.

Table 3. Results of multivariate analysis for factors that affected overall survival (OS).

Variable	HR (95% CI)	*P*-value
Weight loss	1.41 (0.69–2.85)	0.36
ECOG PS* ≥1	5.74 (1.4–45.57)	0.036
Best supportive care only	2.72 (1.39–5.31)	0.003
≥2 metastatic sites	5.19 (1.74–15.44)	<0.0001
Hb <10 g/dl	1.75 (0.93–3.30)	0.087
Metastasis other than lymph node only	1.67 (0.33–8.34)	0.54
WBC >12000	1.13 (0.35–3.70)	0.84
Albumin <3.5g/dl	1.29 (0.53–3.17)	0.57

*ECOG PS: Eastern Cooperative Oncology Group Performance Status.

Treatment

A total of 37 (58%) patients received second-line chemotherapy whereas 27 (42%) received best supportive care only, mainly because of poor performance status.

Of patients who received second-line chemotherapy, 26 (70%) received combination chemotherapy and 11 (30%) had single agent chemotherapy. Platinum-based regimens were given to 23 (62%), whereas taxane-based chemotherapy was given to 27 (73%).

Survival outcomes

The entire cohort had a median OS of 5.0 months.Univariate analysis identified ECOG PS ≥1 or ≥2 metastatic sites, significant weight loss, metastatic spread other than "lymph node only", WBC counts >12000, serum albumin <3.5 g/dl, serum hemoglobin <10g/dl, and treatment with only best supportive care as predictors of inferior OS (Table 2).

On multivariate analysis, an ECOG PS of ≥1, no second-line chemotherapy, and ≥2 metastatic sites emerged as independent predictors for inferior OS, whereas serum hemoglobin approached significance (Table 3).

The median PFS for patients who received second-line chemotherapy was 3.1 months. Response to second-line chemotherapy was assessable for 30 patients - 11 (37%) had partial response, 8 (26%) had stable disease, and a further 11 (37%) had DP. Interestingly, response to second-line chemotherapy correlated with superior OS; median OS was 11.0 months compared to 5.2 months for non-responders (*P*=0.044). Median OS was superior for patients who were free from progression at 6 months after initiation of second-line chemotherapy (12.0 months) compared to patients with DP within 6 months of its initiation (5.2 months, *P*=0.022), and with combination chemotherapy (9.6 months) compared to single agent chemotherapy (4.3 months, *P*=0.044). Figures 1-3 show the impact of independent factors on OS outcomes.

Discussion

Patients with metastatic UC that progress after standard first-line platinum-based chemotherapy have poor prognoses. Second-line single agents show marginal activity with overall response rates of 10% to 20% and a median PFS of only 3 to 4 months.[6-10] Scant evidence exists that second-line systemic treatment may substantially improve OS.[11,14]

Our study showed a short median OS time (5 months) from the date of documented progression after first-line regimens, which appeared shorter than previously reported from second-line trials. Our less selected study population, which included patients with worse ECOG PS, and those considered unfit for second-line chemotherapy were the main reasons for the shorter OS observed in our series compared to other studies. However, the median OS for patients who received second-line chemotherapy in the current study (8 months) was almost comparable to what has been reported.[11,13]

The majority of second-line chemotherapy trials have been designed as single arm studies. As such, they do not provide data about the percentage

of patients eligible to receive second-line chemotherapy in real life. Our data have shown that a significant number of patients did not receive second-line chemotherapy for worsening performance status at the time of progression. Other factors that may hinder delivery of second-line chemotherapy include impaired renal function, advanced age, and the presence of multi-morbidity. This data may suggest the need to investigate maintenance regimens following the first-line chemotherapy, and to incorporate palliative care earlier as a means to improve survival. Both approaches have been proven to offer survival advantages in patients with other cancers such as advanced lung cancer.[15]

We evaluated various prognostic factors associated with poor OS, among which, poor PS, ≥2 metastatic sites, and best supportive care only had an association with worse OS.We did not observe an association with liver metastases and hemoglobin, as suggested by Bellmunt et al.[12]

We evaluated the impact of smoking on outcome. Patients who continued to smoke had worse OS (3.9 months) compared to non-smokers (5.4 months) but the difference was not statistically significant.

Our data suggested survival benefit with second-line chemotherapy compared to best supportive care only and with combination regimens versus single agents. Although administration of second-line chemotherapy remained an independent factor in multivariate analysis, this data should be interpreted with extreme caution as confounders not accounted for in this study might bias the results, given the small number of our series.

Recently, the programmed death-1 legend (PD-L1) monoclonal antibody atezolizumab received accelerated approval for treatment of patients whose disease has worsened during or following platinum-containing chemotherapy.[16] Approval was based on a phase 2 trial that demonstrated significant activity and well-tolerability.[17] More recent data demonstrated significant activity with the anti-PD-L1 avelumab (MSB0010718C) in 44 patients with metastatic UC with a median of 2 prior therapies (range: 1 to ≥4), with an overall response rate of 16%, stable disease in 42%, and a 70% PFS rate at 12 weeks.[18]

In conclusion, patients with progressive bladder cancer may benefit from second-line chemotherapy. Further studies are needed to help in selection the best treatment approach. Patients should be encouraged to participate in clinical trials.

Conflict of Interest

No conflict of interest is declared.

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