First-Line Chemotherapy Response Is a Predictive Factor for Immune Checkpoint Inhibitors Treatment in Advanced Urothelial Carcinoma, a Real World Retrospective Study

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Research Article

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Abstract

Background: Immune checkpoint inhibitors (ICIs) have become important tools for the treatment of advanced urothelial carcinoma (aUC). However, the clinical strategy using ICIs and chemotherapy is still controversy. The aim of this study was to evaluate the association of clinical parameters in aUC patients with ICIs treatment.

Methods: We retrospectively analyzed aUC patients who received atezolizumab and pembrolizumab between January 2015 and October 2020. The associations between baseline demographics and clinical outcomes were evaluated.

Results: Of the 74 included patients, the median age was 67 years. Among them, 53 patients received atezolizumab and the other 21 received pembrolizumab. There were 50 patients receiving first line ICIs therapy and the other 24 received second line monotherapy. Fifty-two (83.87%, 52/62) received cisplatin among all chemotherapy patients. The median progression free survival was 10.94 months and the overall survival was 28.44 months. Poor chemotherapy response or no chemotherapy, liver metastases, Eastern Cooperative Oncology Group (ECOG) status and higher neutrophil/lymphocyte ratio (NLR) were associated with higher risk of diseases progression (HR=5.70, 95% CI 2.04-15.90, p=0.001, HR=6.08, 95% CI 1.79-20.57, p=0.004; HR=5.40, 95% CI 1.76-16.57, p=0.003; HR=6.08, 95% CI 2.56-14.44, p<0.001 and HR= 1.02, 95% CI 1.01-1.03, P=0.002 respectively). Liver metastases and WBC before ICI were associated with increased death risk (HR=11.95, 95%CI 3.22-44.34, p<0.001; HR=1.0001, 95% CI 1.00001-1.00002, p=0.036 respectively) while ICI response was associated with decreased death (HR=0.22, 95%CI 0.08-0.62, p=0.004). Chemotherapy responders were associated with better ICI treatment response (OR=6.52, 95%CI 1.45-29.24, p=0.014) while lymph node metastases and poor ECOG was associated with poor ICI response (OR=0.31, 95%CI 0.10-0.94, p=0.038; OR=0.32, 95%CI 0.11-0.95, p=0.040).

Conclusions: Our data showed predictive role of first-line chemotherapy response to ICIs treatment efficacy in aUC patients as well as other prognostic factors, such as ECOG status, serum white blood cell count or NLR and liver metastases.

Introduction

For decades, chemotherapy becomes the standard of treatment for advanced urothelial carcinoma (aUC). Recent progress of immune checkpoint inhibitors (ICI) in metastatic UC opened a new page in this field. Five programmed cell death protein 1 (PD-1) and programmed death ligand 1 (PD-L1) inhibitors, pembrolizumab, nivolumab, atezolizumab, durvalumab and avelumab showed benefits on overall survival among post-chemo metastatic UC patients and received accelerated approval by the US Food and Drug Administration (FDA) in 2016.[1–5] However, recent evidence of phase 3 trials, DANUBE and IMvigor 211 did not reach the primary end point; thus durvalumab and atezolizumab were voluntarily withdrawn the indications in chemotherapy pre-treated bladder cancer.[3,6] In addition, results of the front line setting using ICI combination with chemotherapy in phase 3 IMvigor 130 and Keynote 361 did not

show overall survival benefits which lead to a treatment dilemma in advanced UC.[7,8] By far, the first line treatment of metastatic UC with ICI is still controversy. Herein, we evaluated metastatic UC patients underwent ICI treatment and looked for the associations between clinical characteristics and outcomes.

Materials And Methods

Patients

This retrospective study was conducted through chart review. All methods were carried out in accordance with relevant guidelines and regulation and were approved by the institute review board of Taichung Veterans General Hospital, number CE19386B. The informed consents of all patients were waived by the institute review board of Taichung Veterans General Hospital as well. Metastatic UC patients who received atezolizumab or pembrolizumab with measurable radiographic outcomes between January 2015 and October 2020 were included.

Study assessment

The study end points were progression free survival after ICI treatment, overall survival after treatment start of metastatic diseases and ICI treatment response. Baseline patient characteristics including continuous variables, age, chemotherapy and ICI treatment cycles and duration, blood sample analysis before ICI, such as white blood cell (WBC) count, hemoglobin, neutrophil/lymphocyte ratio (NLR), platelets, lactate dehydrogenase (LDH) and albumin were recorded. The timing of blood samples collected were two weeks before ICI given. Other categorical parameters such as gender, primary tumor site, smoking, diabetes mellitus, chronic kidney disease (CKD), end stage renal disease (ESRD), metastatic sites, Eastern Cooperative Oncology Group (ECOG) status, survival status, treatment model, ICI response, chemotherapy duration, and ICI duration were recorded as well. CKD was defined as estimated glomerular filtration rate less than 60 mL/minutes but not exceed ESRD. ESRD was defined as patients who received regular dialysis therapy. Metastatic sites were recorded according to radiographic findings by each sites among each case. Chemotherapy response and ICI response were recorded according to the Response Evaluation Criteria in Solid Tumor (RECIST) 1.1. The periods of radiographic evaluation were depended on the clinical demands between 4 weeks and 6 months among each cases. However, in the ICI and chemotherapy combination treatment patients, it is difficult to separate the treatment effect between both. Therefore, the treatment effect would be recorded both for chemotherapy, as well as for ICI. The chemotherapy duration or ICI duration were defined as the period between the date of starting treatment and the radiographic progression date or the last dose date.

Statistical analysis

The differences between continuous values were analyzed by Mann-Whitney U and Fisher's exact test t test for continuous variables. Chi-square test was used for categorical variables. The progression free

survival (PFS) and overall survival (OS) curves were plotted by the Kaplan–Meier method. Univariate and multivariate Cox hazard proportional regression was used to estimate the hazard ratio (HR) and 95% confidence interval (CI) for association between variables and PFS, OS and ICI treatment response. The ICI treatment response was defined as complete response or partial response. All the statistical analyses were performed using SAS software version 9.2 (SAS Institute, Inc., Cary, NC, USA).

Results

Total 85 patients receive atezolizumab and pembrolizumab for the treatment of metastatic UC in our database during the study period. Three patients included in a clinical trial that was not completed and the other eight patients without follow-up radiographic studies were excluded. Finally, 74 patients were included in this analysis. Among them, 53 patients received atezolizumab and the other 21 received pembrolizumab. Thirty-eight patients received ICI combined chemotherapy as the first line therapy, while 12 patients had ICI as first line monotherapy and the other 24 used chemotherapy followed by ICI. The baseline characteristics and patient demographics were listed in table 1. The median age was 67 years (ranged 40 to 92) and male predominant (62.16%, 46/74). Poor general performance paitents accounted for only 13.51% (10/74) while ECOG 0 patients were 43.24% (32/74). Thirty-nine patients (52.7%) had upper urinary tract tumor and only 1 patient had concomitant upper and lower tract tumors. Less than a quarter of patients had history of cigarette smoking and the prevalence of diabetes and CKD were less than one third. Lymph nodes were the most common sites of metastases (56.76%, 42/74) while ten percent (8/74) of patients had liver metastases. The median results of blood tests before ICI given were as followed, WBC count 7845/cumm, hemoglobin 11.4 g/dL, NLR 5.9, platelet count 262.5k, LDH 195 U/L, and albumin 3.9 g/dL. Sixty-two patients received chemotherapy as first line therapy and 83.87% (52/62) of them took cisplatin. Twenty-nine patients (46.77%, 29/62) reached complete response (CR) or partial response (PR) after chemotherapy while forty-two patients (56.76%, 42/74) had CR/PR after ICI treatment. The median treatment cycles of chemotherapy and ICI were 4 and 6 respectively. The median chemotherapy and ICI duration of treatment were 7.79 and 7.24 months respectively while the median follow-up duration was 12.7 months.

Figure 1 showed the median progression free survival after ICI treatment was 10.94 months and the median overall survival since systemic treatment was 28.44 months.

In the Cox hazard proportional regression model, no chemotherapy response (PR and SD) or no chemotherapy, liver metastases, ECOG status and higher NLR were associated with higher risk of diseases progression (HR=5.70, 95% CI 2.04-15.90, p=0.001, HR=6.08, 95% CI 1.79-20.57, p=0.004; HR=5.40, 95% CI 1.76-16.57, p=0.003; HR=6.08, 95% CI 2.56-14.44, p<0.001 and HR= 1.02, 95% CI 1.01-1.03, P=0.002 respectively, Table 2). Liver metastases and WBC before ICI were associated with increased death risk (HR=11.95, 95%CI 3.22-44.34, p<0.001; HR=1.0001, 95% CI 1.00001-1.00002, p=0.036 respectively) while ICI response and was associated with decreased death (HR=0.22, 95%CI 0.08-0.62, p=0.004, Table 3). Chemotherapy response was associated with better ICI treatment response (OR=6.52, 95%CI 1.45-29.24, p=0.014) while lymph node metastases and poor ECOG status was associated with

poor ICI response (OR=0.31, 95%CI 0.10-0.94, p=0.038; OR=0.32, 95%CI 0.11-0.95, p=0.040 respectively, Table 4).

Discussion

Our study demonstrated a prognostic and predictive value of first-line chemotherapy response to clinical outcomes in aUC patients which corresponded to the findings in JAVELIN bladder 100.[9] No first-line chemotherapy response or no chemotherapy were associated with poor PFS (HR = 5.70, p = 0.001, and HR = 6.08, p = 0.004 respectively). Despite of PFS, we also found chemotherapy response CR/PR/SD can predict the ICI treatment response (OR = 6.52, p = 0.014). This phenomenon corresponded to the rationale that chemotherapy induction in UC can deplete immunosuppressant cells, increasing T-cell infiltration into tumors, increasing antigen presentation and increasing PD-L1 expression.[10,11] Although we can't find the association between chemotherapy response and OS, ICI treatment responders showed a 78% risk reduction in death and implicated the importance of the ICI response. In addition, without external validation of our database, the estimated PFS and OS in our study (10.94 and 28.44 months respectively) showed a comparative outcome with the JAVELIN study (3.7 and 21.4 months respectively).[9] We suggested the comparable clinical outcome in our study was the result of large proportion lymph node metastatic only (41.89%, 31/74) and high cisplatin utility rate (83.87%, 52/62) which also lead to a chemotherapy response rate 46.77% (29/62). The baseline demographics in our series showed a unique UC characteristic in Taiwan. Upper tract UC accounted for the largest proportion (54%, 40/74) and female patients were predominant among this part which lead to an increase of the female gender percentage (37.84%).[12,13] These characteristics were different from other reported series while urinary bladder UC and male gender were extremely larger.

In the chemotherapy era, Bajorin et al. determined Karnofsky performance status less than 80 and visceral metastases were two independent factors for survival; Bellmunt et al. identified ECOG status more than 0, hemoglobin level less than 10, and presence of liver metastases as poor prognostic factors to OS.[14,15] In ICI era, Khaki et al. reported a database analysis on prognostic model of first-line ICI therapy and found ECOG ≧ 2, albumin < 3.5 g/dL, NLR > 5 and liver metastasis were associated with worse OS.[16] Ruiz-Bañobre et al. declared another prognostic model using ECOG, liver metastases, peritoneal metastases, albumin level and proton pump inhibitor use in a mixed first-line and second-line ICI treatment setting.[17] Sonpavde et al. collected phase I/II clinical trial database and found ECOG-PS (1 vs 0, HR = 1.80), liver metastasis (HR = 1.55), platelet count (HR = 2.22), NLR (HR = 1.94) and LDH (HR = 1.60) were fiver prognostic factors for overall survival.[18] Our data showed similar clinical biomarkers such as liver metastasis, ECOG status 1 or 2, and high NLR which were associated with higher risk of disease progression as well as liver metastasis, poor ICI response and WBC before ICI to increased death risk. Despite the performance status related clinical markers such as ECOG, hemoglobin level and albumin were considered on the OS because of the short survival nature in metastatic UC, Yu et al. revealed the pathophysiology of liver metastases in patients and preclinical models.[19] They found that liver metastases diminished peripheral T cells as well as the diversity and function which may cause

increased NLR and reduce the response of ICI treatment. Interestingly, we also found lymph node metastases was associated with poor ICI response. The true reason may not be clarified because of lacking other histology evidence. Currently, PD-L1 stain and new generation sequencing for the genomic profiling are considered as predictive biomarkers for ICI treatment and were approved by USFDA for specific indications.[20–22] However, genomic exams and clinical outcomes varied from a trial to another as well as the high costs of examinations. Therefore, clinical parameters, such as our results, can provide an alternative aspect on the predictive role using chemotherapy response as an indicator of ICI treatment effect.

Limitations of this study include small patient population, the retrospective nature, lack of external validation, and confounding of chemotherapy response and ICI response in the first-line combination group. Thirty eight patients (51.35%, 38/74) received combination chemotherapy and ICI as first-line therapy; however, instead of clarifying the individual drug response, we can only record the combination results as the surrogate. In addition, we did not obtain tissue PD-LI data and can't provide the

In conclusion, our real world experience revealed the first-line chemotherapy response as well as clinical factors including ECOG status, liver metastases, NLR, WBC before ICI could act as prognostic or predictive markers to the ICI related clinical outcomes. Utility of these clinical biomarkers can help in regimen decision and avoid fruitless treatments.

Declarations

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Disclosure

The authors have declared no conflicts of interest.

References

1. Bellmunt, J. *et al.* Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma. *N Engl J Med.* **376**, 1015–1026 https://doi.org/10.1056/NEJMoa1613683 (2017).
2. Sharma, P. *et al.* Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicentre, single-arm, phase 2 trial. *Lancet Oncol.* **18**, 312–322 https://doi.org/10.1016/s1470-2045(17)30065-7 (2017).
3. Powles, T. *et al.* Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): a multicentre, open-label, phase 3 randomised controlled trial. *Lancet.* **391**, 748–757 https://doi.org/10.1016/s0140-6736(17)33297-x (2018).

4. Powles, T. *et al.* Efficacy and Safety of Durvalumab in Locally Advanced or Metastatic Urothelial Carcinoma: Updated Results From a Phase 1/2 Open-label Study. *JAMA Oncol.* **3**, e172411 https://doi.org/10.1001/jamaoncol.2017.2411 (2017).
5. Patel, M. R. *et al.* Avelumab in metastatic urothelial carcinoma after platinum failure (JAVELIN Solid Tumor): pooled results from two expansion cohorts of an open-label, phase 1 trial. *Lancet Oncol.* **19**, 51–64 https://doi.org/10.1016/s1470-2045(17)30900-2 (2018).
6. Powles, T. B. *et al.* J. Bellmunt. in ESMO(2020).
7. Galsky, M. D. *et al.* Atezolizumab with or without chemotherapy in metastatic urothelial cancer (IMvigor130): a multicentre, randomised, placebo-controlled phase 3 trial. *Lancet.* **395**, 1547–1557 https://doi.org/10.1016/s0140-6736(20)30230-0 (2020).
8. Alva, A. *et al.* B.H., and T.B. in ESMO(2020).
9. Powles, T. *et al.* Avelumab Maintenance Therapy for Advanced or Metastatic Urothelial Carcinoma. *N Engl J Med.* **383**, 1218–1230 https://doi.org/10.1056/NEJMoa2002788 (2020).
10. Tsai, T. F. *et al.* Cisplatin contributes to programmed death-ligand 1 expression in bladder cancer through ERK1/2-AP-1 signaling pathway. *Biosci Rep.* **39**, https://doi.org/10.1042/bsr20190362 (2019).
11. McDaniel, A. S. *et al.* Expression of PDL1 (B7-H1) Before and After Neoadjuvant Chemotherapy in Urothelial Carcinoma. *Eur Urol Focus.* **1**, 265–268 https://doi.org/10.1016/j.euf.2015.03.004 (2016).
12. Chen, C. S. *et al.* Association between lymphovascular invasion and oncological outcome in node-negative upper tract urothelial carcinoma with different stage. *Urol Oncol.* **39**, 132 (2021).
13. Hsieh, M. C. *et al.* The comparison of oncologic outcomes between metastatic upper tract urothelial carcinoma and urothelial carcinoma of the bladder after cisplatin-based chemotherapy. *Urol Oncol.* **33**, 495499 (2015).
14. Bajorin, D. F. *et al.* Long-term survival in metastatic transitional-cell carcinoma and prognostic factors predicting outcome of therapy. *J Clin Oncol.* **17**, 3173–3181 https://doi.org/10.1200/jco.1999.17.10.3173 (1999).
15. Bellmunt, J. *et al.* Prognostic factors in patients with advanced transitional cell carcinoma of the urothelial tract experiencing treatment failure with platinum-containing regimens. *J Clin Oncol.* **28**, 1850–1855 https://doi.org/10.1200/jco.2009.25.4599 (2010).
16. Khaki, A. R. *et al.* A New Prognostic Model in Patients with Advanced Urothelial Carcinoma Treated with First-line Immune Checkpoint Inhibitors. *Eur Urol Oncol.* https://doi.org/10.1016/j.euo.2020.12.006 (2021).
17. Ruiz-Bañobre, J. *et al.* Rethinking prognostic factors in locally advanced or metastatic urothelial carcinoma in the immune checkpoint blockade era: a multicenter retrospective study. *ESMO Open.* **6**, 100090 https://doi.org/10.1016/j.esmoop.2021.100090 (2021).
18. Sonpavde, G. *et al.* Five-Factor Prognostic Model for Survival of Post-Platinum Patients with Metastatic Urothelial Carcinoma Receiving PD-L1 Inhibitors. *J Urol.* **204**, 1173–1179 https://doi.org/10.1097/ju.0000000000001199 (2020).

19. Yu, J. *et al.* Liver metastasis restrains immunotherapy efficacy via macrophage-mediated T cell elimination. *Nat Med.* **27**, 152–164 https://doi.org/10.1038/s41591-020-1131-x (2021).
20. Powles, T. & Morrison, L. Biomarker challenges for immune checkpoint inhibitors in urothelial carcinoma. *Nat Rev Urol.* **15**, 585–587 https://doi.org/10.1038/s41585-018-0056-3 (2018).
21. Twomey, J. D. & Zhang, B. Cancer Immunotherapy Update: FDA-Approved Checkpoint Inhibitors and Companion Diagnostics. *Aaps j.* **23**, 39 https://doi.org/10.1208/s12248-021-00574-0 (2021).
22. Doroshow, D. B. *et al.* PD-L1 as a biomarker of response to immune-checkpoint inhibitors. *Nat Rev Clin Oncol.* https://doi.org/10.1038/s41571-021-00473-5 (2021).

Tables

Due to technical limitations, table 1-4 is only available as a download in the Supplemental Files section.

Figures

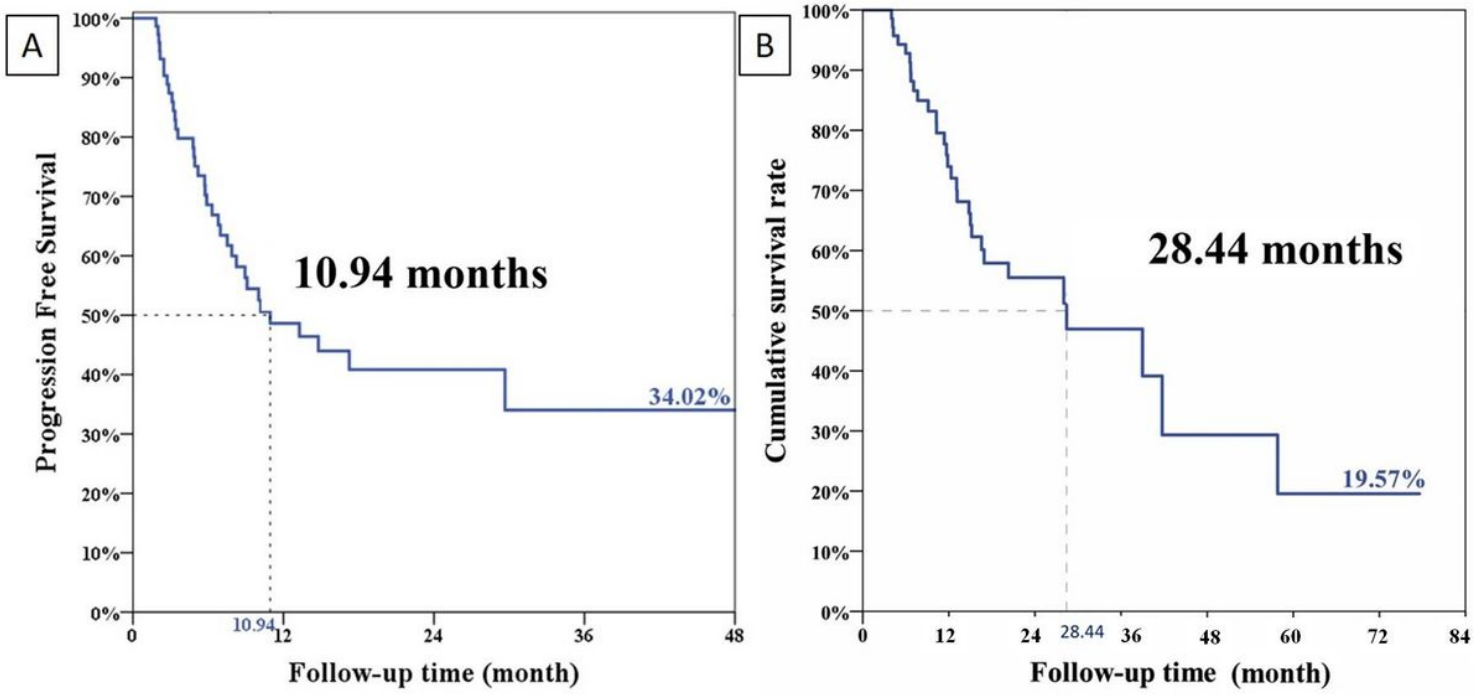

Figure 1

Survival analyses (A) Progression free survival (B) Overall survival for advanced urothelial carcinoma patients who received immune checkpoint inhibitors

Supplementary Files

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- Table14.pdf