Repeat Treatment of Patients With Advanced Urothelial Carcinoma With Immune Checkpoint Inhibitors Following Prior Progression on a Checkpoint Inhibitor Regimen: A Case Series

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Abstract

Introduction: Immune checkpoint inhibitors (ICIs) have become one of the mainstays of systemic therapy for advanced urothelial carcinoma (aUC). Increasingly ICIs are also being utilized earlier in the course of UC treatment. Limited data are available regarding ICI treatment efficacy in aUC patients who have progressed on prior ICI regimens. This case series aims to address this knowledge gap. Patients and Methods: We identified all aUC patients treated with ICI or combination following prior progression on another ICI regimen at two academic institutions. Patient demographic, clinicopathologic and treatment data were retrospectively collected from chart review at each site. Best response to ICI treatment was defined by investigator at each site. Results: Among 7 patients with aUC who received ICI treatment following prior progression on a different ICI regimen, radiographic response to the second ICI regimen was observed in only 1 patient (14%) treated with combination of pembrolizumab/entrectinumab vedotin. Conclusion: Efficacy of ICI treatment in patients who previously progressed on another ICI regimen appears limited. These observations should be validated in larger cohorts, as it is anticipated that this clinical scenario will become more common in the future.

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Keywords: Bladder cancer, Immunotherapy, Urothelial cancer, Repeat treatment, Anti-PD-1 or Anti-PD-L1 agents

Introduction
In recent years immune checkpoint inhibitors (ICI) have become the standard of care for patients with locally advanced or metastatic urothelial carcinoma (UC), as from 2016 to 2017 five different ICIs received FDA approval in the platinum-refractory setting: atezolizumab, pembrolizumab, nivolumab, avelumab and durvalumab.1–4 Only pembrolizumab was supported by data from a phase III randomized trial showing an overall survival (OS) advantage over chemotherapy.5 The FDA labels of atezolizumab and durvalumab were voluntarily withdrawn in 2021 following negative phase III studies.6 For treatment-naïve aUC patients who are cisplatin-ineligible and have high PD-L1 expression, both atezolizumab and pembrolizumab are FDA approved for frontline treatment based on data from single-arm phase II studies.7,8 These approvals were upheld at ODAC meetings in 2021 (Table 1).

Increasingly ICIs are being investigated and utilized earlier in the treatment course of UC. In 2020, Pembrolizumab received approval for treatment of non-muscle invasive bladder cancer (NMIBC) refractory to prior Bacille Calmette-Guérin (BCG) treatment.9 In the neoadjuvant space, pembrolizumab and atezolizumab have shown promising activity prior to radical cystectomy based on initial results of the PURE-01 and ABACUS trials.10,11 A number of other ICI and ICI/chemotherapy combinations are also under investigation in this space.12 CheckMate-274 adjuvant study demonstrated a disease-free survival advantage with nivolumab relative to placebo in patients with high-risk disease at the time of cystectomy, leading to the FDA approval of nivolumab for this indication.13 In the metastatic setting, the results of the Javelin Bladder-100 study reported in 2020 were practice changing, showing a significant survival advantage with switch maintenance avelumab in patients benefiting from frontline platinum-based chemotherapy.14 Ongoing trials are investigating combination treatments with immunotherapy agents for treatment-naïve patients with metastatic disease, including combinations with pembrolizumab/entrectinumab vedotin or with sacituzumab govitecan.15–17

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Table 1 Immune Checkpoint Inhibitors Approved for Urothelial Carcinoma

| Treatment Setting | NMIBC(BCG-Refractory) | Adjuvant (post-Radical Cystectomy) | Frontline Metastatic | Post-Platinum Switch Maintenance | Platinum-Refractory |
|-------------------|------------------------|-----------------------------------|---------------------|----------------------------------|---------------------|
| Immune checkpoint inhibitors approved by the FDA | Pembrolizumab | Nivolumab | Pembrolizumab | Avelumab | Pembrolizumab |
|                   |                        |                                   |                     | Nivolumab | Avelumab |

Abbreviation: NMIBC = non-muscle invasive bladder cancer.

Figure 1 Example of a patient responding to subsequent immune checkpoint inhibitor (ICI) regimen after prior progression on an ICI treatment. Scans from patient case #2. Patient progressed on initial switch maintenance treatment with avelumab, but subsequently had good response to combination of pembrolizumab and enfortumab vedotin, with marked improvement in liver lesions.

Based on these recent trends, increasing numbers of aUC patients will likely be recommended to receive ICI or ICI combinations following prior treatment with similar regimens. The data for this approach in aUC is currently very limited, although other studies have reported outcomes of sequential immunotherapy treatment in RCC or in phase I trials across solid malignancies. In this case report we present a multi-institutional experience of patients with aUC treated with more than one ICI regimen, and discuss the efficacy of this approach (Table 2, Figure 1).

Case Reports

This case report includes 7 patients with aUC who were treated with two different ICI lines throughout their treatment course. ICI regimens included either anti-PD-1 or anti-PD-L1 agents, sometimes given in combination with other drugs.

Case 1

A 75 year old man initially diagnosed with muscle-invasive bladder cancer (MIBC) in early 2019 was enrolled in a clinical trial of neoadjuvant atezolizumab since he was cisplatin-ineligible. He completed three cycles of atezolizumab from March 2019 to May 2019 followed by a radical cystectomy in May 2019. On treatment he experienced weight loss which was potentially attributed to atezolizumab. Pathology from radical cystectomy revealed advanced disease (pT4aN2) and thus limited response to neoadjuvant atezolizumab. Surveillance scans in July 2019 revealed a new lung lesion which was then biopsy-confirmed as aUC.

Scans at time of progression on avelumab

Later scans following pembrolizumab/EV
## Table 2  Case Series Patient Characteristics

| Patient | Demographics and Histology | PD-L1 Expression | First Immunotherapy Treatment (Time Between First and End of Last Cycle) | Treatment Setting | Best Response | Duration Between ICI Treatments (Days) | Second Immunotherapy Treatment and Dose | Treatment Setting | Best Response | Last Follow Up After second line ICI |
|---------|---------------------------|------------------|-------------------------------------------------|------------------|--------------|---------------------------------------|----------------------------------------|------------------|--------------|---------------------------------|
| 1       | 75 yo man; urothelial carcinoma | Low              | Atezolizumab (63 d) 1200 mg IV every 3 wk | Neoadjuvant      | No Downstaging (pT4aN2) | 157            | Pembrolizumab (64 d) 200 mg IV every 3 wk | Second line metastatic | PD | 20 mo alive on subsequent treatment |
| 2       | 59 yo woman; urothelial carcinoma with micropapillary features | Low              | Avelumab (78 d) 10 mg/kg IV every 2 wk | Post-platinum switch maintenance | PD | 40 | Pembrolizumab (ongoing for 180 d) 2 mg/kg IV every 3 wk | Third line metastatic | PR | Second line IO + EV treatment ongoing for 6 mo |
| 3       | 73 yo man; squamous cell carcinoma | Unknown          | Durvalumab/Tremelimumab (63 d) 1500 mg IV and 75 mg IV every 4 wk | Third line metastatic | PD | 244 | Pembrolizumab (127 d) 200 mg IV every 3 wk | Fifth line metastatic | PD | Pursued subsequent therapy 5 mo later and passed away 11 mo later |
| 4       | 49 yo man; urothelial carcinoma | High             | Atezolizumab (63 d) 1200 mg IV every 3 wk | First line metastatic | PD | ~150 | Ipilimumab and Nivolumab (42 d) 1 mg/kg IV and 3 mg/kg IV every 3 wk | Third line metastatic | PD | Patient admitted to hospice 2 wk later |
| 5       | 58 yo woman; urothelial carcinoma | Unknown          | Pembrolizumab (43 d) 2 mg/kg IV every 3 wk | Second line metastatic | PD | 111 | Atezolizumab (41 d) 1200 mg IV every 3 wk | Fifth line metastatic | PD | Patient passed away 5 wk later |
| 6       | 92 yo man; urothelial carcinoma | Unknown          | Pembrolizumab (477 d) 2 mg/kg IV every 3 wk | First line metastatic | PR | 4 | Atezolizumab (43 d) 1200 mg IV every 3 wk | Second line metastatic | PD | Patient pursued subsequent treatment and passed away 6 wk later |
| 7       | 67 yo man; urothelial carcinoma | Unknown          | Pembrolizumab (213 d) 200 mg IV every 3 wk | First line metastatic | SD | 103 | Nivolumab (175 d) 480 mg IV every 3 wk | Third line metastatic | PD | Progressed on subsequent therapy 3 mo later |

Abbreviations: IO = ImmunoPET; EV = enfortumab vedotin; ICI = immune checkpoint inhibitor; PD = disease progression; PR = partial response.

*Pembrolizumab was added to the treatment plan after completion of one cycle of Enfortumab Vedotin (1.25 mg/kg 3 wk on / 1 wk off) monotherapy.

*Patient was treated with pembrolizumab twice (second-line and fourth-line treatment for metastatic disease).

*High PD-L1 expression is CPS > 10, low expression is CPS < 10.
He started carboplatin/gemcitabine chemotherapy but had disease progression (PD) after three cycles with multiple new lung metastases. He was then started on pembrolizumab in October 2019 which he tolerated well, but following four cycles of treatment had unequivocal progression on scans in January 2020. Shortly afterwards, he started enfortumab vedotin (EV) and had a partial response (PR) which persists over 18 months into treatment.

**Case 2**

A 59 year old woman was initially diagnosed with metastatic micropapillary UC in spring of 2020. She started cisplatin/gemcitabine chemotherapy in May 2020 and completed six cycles with a PR on September 2020 scans. She was then started on avelumab switch-maintenance therapy in October 2020. In December 2020, after five cycles of treatment, restaging scans showed progression with new osseous metastases and she completed palliative XRT. In January 2021 she was started on EV and completed one cycle before pembrolizumab was added to the treatment plan. A PR was observed following two cycles of EV/pembrolizumab combination treatment in March 2021. This response was confirmed on scans in May 2021 and she remains on this regimen as of August 2021.

**Case 3**

A 73 year old man diagnosed with a mixed urethral squamous cell and UC in 2017 was started on TIP chemotherapy in July 2017. He completed four cycles with a PR in October 2017. He was subsequently started on olaparib in November 2017 due to the presence of somatic BRCA2 deletion but had PD in March 2019. In April 2019, he was enrolled on an immunotherapy trial of durvalumab with tremelimumab but had PD after two cycles. He was switched to cisplatin/gemcitabine in June 2019 and had a PR after three cycles and again after six cycles. He was then started on EV in February 2020, and after completing one cycle of monotherapy, pembrolizumab was added to treatment plan. While on treatment, he developed a rash which was potentially attributed to EV rather than pembrolizumab. After three cycles of combination therapy, scans revealed PD in May 2020. Patient was subsequently treated on a clinical trial and then again with olaparib before passing away in May 2021.

**Case 4**

A 49 year old man was diagnosed with MIBC and started on cisplatin/gemcitabine in October 2019. After completing three cycles, restaging scans in December 2019 showed increasing lymphadenopathy. In early 2020, he was started on atezolizumab, but after completing three cycles, had PD in March 2020. He then started EV in April 2020, but in June 2020, scans again indicated PD. He had palliative XRT and was then started on ipilimumab and nivolumab in July 2020. After two cycles of treatment, there was clinical and radiographic progression in August 2020 and patient decided to pursue hospice.

**Case 5**

A 58 year old woman initially diagnosed with upper tract UC in 2012, was treated with carboplatin/gemcitabine in January 2016 for metastatic disease but had PD following one cycle of treatment. She was then started on pembrolizumab in February 2016, however had to discontinue treatment after two cycles due to progression on scans in March 2016. She then started ddMVAC and completed four cycles with a PR on scans in April 2016. She then restarted pembrolizumab in May 2016, but after two cycles which she tolerated well, was switched to atezolizumab which had recently received FDA approval and was thought to be better tolerated than pembrolizumab. After two cycles of atezolizumab, her scans in August 2016 indicated PD, and she decided to pursue hospice.

**Case 6**

A 92 year old man was diagnosed with aUC, started on pembrolizumab in October 2016 which was associated with pruritis as an immune-related adverse event (irAE). His restaging scans in December 2016 revealed PR, and he continued on treatment for 22 cycles until PD was observed on December 2018 scans. In February 2018 he was started on atezolizumab. Restaging scans in April 2018, following two cycles of treatment which he tolerated well, showed ongoing progression leading to treatment discontinuation. He was subsequently started on everolimus in April 2018 but passed away in May 2018.

**Case 7**

A 67 year old man was diagnosed with upper tract UC in 2016 and completed 4 cycles of neoadjuvant cisplatin/gemcitabine prior to nephroureterectomy in January 2017 showing PT2N4d disease. Surveillance scans in November 2017 indicated metastatic recurrence in lungs, and he was started on pembrolizumab. He had a skin rash attributed to pembrolizumab as an irAE while on treatment. Scans in January 2018 revealed stable disease, but progression was later noted on restaging scans in June 2018. He was subsequently started on ddMVAC, and after three cycles had a PR on scans in August 2018. Due to a rising creatinine he was switched to nivolumab in September 2018, and soon after developed eczema potentially attributed to the treatment. On November 2018 restaging scans, he had PD with new lesions in his sacrum, which were treated with XRT in December 2018. Patient continued receiving nivolumab until progression was confirmed on February 2019 scans. He was subsequently started on a clinical trial, but progressed again and entered hospice in May 2019.

**Discussion**

The cases presented here highlight the challenge of treating patients with aUC with ICI or ICI combinations, following earlier progression on a different ICI regimen. Among the seven cases described, 1 patient had a response (PR) to initial line of ICI treatment (another patient had SD). This is fairly representative, as ORR of 15% to 20% can be expected in the platinum-refractory setting.1,5 With additional immunotherapy treatment following prior progression on ICI, only 1 patient had a response (PR), with rest having progressive disease. The patient with a response had previously progressed on avelumab maintenance after having a response to platinum-based chemotherapy. It should also be noted that this patient responded to treatment with EV/pembrolizumab,
thus relative contribution of pembrolizumab to this response is not clear. Although this does suggest a potential approach of using combination regimens of ICIs and other targeted agents following prior disease progression on ICI treatment, another patient similarly treated with pembrolizumab/EV following prior progression on durvalumab/tremelimumab, did not respond to EV/pembrolizumab combination.

Given recent approvals of ICIs for NMIBC, as adjuvant therapy after cystectomy in high-risk patients, and in the metastatic post-platinum switch-maintenance settings, clinical scenarios like these will become more common as more patients with aUC will be treated with ICIs earlier in their disease course. Furthermore, there is promising data of ICIs combinations with targeted agents for frontline treatment of aUC, including combinations of ICIs with enfortumab vedotin, sacituzumab govitecan, and with FGFR inhibitors. This will potentially lead to many more metastatic patients receiving these regimens in the frontline setting in the future. Some of these patients will likely have durable responses that persist for months to years, will then move on to other non-ICI treatment regimens and may eventually be in a position to consider ICI treatment again, potentially years after prior ICI exposure. Such patients may well be rechallenged with ICI monotherapy or combinations and may derive benefit from this treatment. Moving forward, the experience with ICI treatments administered after disease progression on a prior ICI, should be investigated in larger multi-institutional cohorts and also prospectively. This will help better define the efficacy of this approach and identify patients more likely to respond to ICI treatments after prior progression on a similar regimen. Multiple important questions remain, including whether ICI mechanism of action, as either an anti-PD-1 or an anti-PD-L1 agent, should impact the sequence of repeat ICI treatment; and whether other ICIs such as anti-CTLA4 agents and others currently in development, can be successfully utilized for patients refractory to anti-PD-1/PD-L1 therapy.

Drawing significant conclusions from a case series has its limitations, particularly in such a heterogeneous cohort. Patients included here received treatments in different settings, received other treatments between lines of ICI therapy and some also had variant histologies. Case series are also inherently susceptible to selection bias and other confounders. For most of these patients, status of putative biomarkers including PD-L1, TMB and alterations potentially predictive of IO response in aUC were also unknown. The incidence of irAEs with ICI treatment as described in this series was also not clearly associated with specific treatment outcomes. Nevertheless, this case series represents an important initial hypothesis-generating effort that future studies can build on.

Conclusion

This case series is an initial report describing ICI treatment following prior progression on a different ICI regimen in patients with aUC. The efficacy of this approach appears to be limited, with no patients responding to a pure ICI switch, and only 1 patient responding to a second line ICI/EV combination regimen after previously having disease progression on ICI monotherapy. Whether there is a role for combination ICI-antibody-drug conjugate or other immunotherapeutic approaches after progression on a PD-1/PD-L1 agent is an active area of investigation. Larger studies are needed to further define the efficacy of this approach.

Clinical Practice Points

- ICIs form the backbone of therapy for patients with aUC and will be used more frequently and earlier in the disease course in the coming years.
- Treatment efficacy with ICIs following prior progression on a different ICI regimen appears limited in patients with aUC.
- Subsequent treatment with ICI following prior progression on ICI may be more effective in certain clinical contexts, such as by combining ICIs with targeted agents.

Disclaimers

The views expressed in this article reflect the view of the authors and do not reflect the official views of the affiliated institutions. This study has not been presented elsewhere.

Disclosure

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