

Advanced Bladder Cancer Rechallenged With an Immune Checkpoint Inhibitor: A Case Report



Taha Bat, Dennis A. Buck, Rachel Nathan, Jordan Cinquino, Marcus Sikorski, Angie Elefante, Laurie Herbst, Norbert Sule, Andrew Fabiano, and Saby George

Immune checkpoint inhibitors (ICIs), nivolumab, pembrolizumab, atezolizumab, durvalumab, and avelumab, are currently approved for locally advanced and metastatic urothelial cancer. Unfortunately, adverse events associated with these medications are not entirely uncommon. Of those patients suffering from adverse events associated with ICI therapy, approximately 20% experience an immune-related adverse event (irAE).¹ High-grade irAE, as defined by CTCAE, have led to countless discontinuations of ICI therapies. However, it's notable that there have been multiple studies and case reports published examining patients with advanced melanoma and NSCLC who developed an irAE after treatment with ICI and have shown that after subsequent rechallenge with ICI these patients had reduced severity or absence of adverse events in addition to a favorable disease response.^{2,3} In an analysis of the 4-year outcomes of Keynote-006, it was found that of the 8 melanoma patients rechallenged with pembrolizumab, none experienced grade 3 or greater treatment related adverse events.⁴ These results suggest that there is likely an acceptable safety profile to warrant further investigation of the side effects and antitumor activity associated with ICI rechallenge in alternate patient populations, such as those with advanced or metastatic bladder cancer.

CASE PRESENTATION

The patient is an 86-year-old woman who presented with low back pain and hematuria. Urine cytology identified malignant cells consistent with high-grade urothelial carcinoma. Computed tomography (CT) imaging was then performed for further evaluation of malignancy which revealed four noncalcified pulmonary nodules, a lumbar spine lesion, as well as mediastinal and para-aortic lymphadenopathy. Subsequent positron emitted tomography-

CT scan showed fluorodeoxyglucose (FDG) uptake in the left renal mass (standardized uptake values (SUV) 10.2), hypermetabolic uptake in the L4 vertebral body (SUV 7.4), para-aortic nodes (SUV 10.8), and posterior mediastinum (SUV 12.4). Left kidney biopsy showed poorly differentiated carcinoma positive for cytokeratin 7 and 20, CGX2 and negative for PAX8, which was likely urothelial in origin given the patient's symptoms, abnormal urine cytology, and renal mass. Spinal levels from L3 to L5 were treated with 3000 cGy delivered in 10 fractions of 300 cGy on the linear accelerator utilizing an 18 MV photon beam prescribed to a depth of 7 cm. She then received 6 cycles of gemcitabine plus cisplatin which she tolerated well with partial response.

After 1 year of close surveillance the patient presented with recurrence of low back pain radiating to the right leg. Repeat CT imaging demonstrated progressive disease with an increase in the size of the left adrenal gland with density greater than an adenoma and stable sclerotic densities in L4 vertebral body. Positron emitted tomography-CT scan confirmed disease progression with hypermetabolic uptake in the left adrenal (SUV 4.3) as well as increased uptake in the L4 vertebral body (SUV 4.7). She received stereotactic body radiation therapy to the L4 vertebral body with 1400 cGy delivered in 7 fractions of 200 cGy each on a linear accelerator utilizing an 18 MV photon beam via single posterior field prescribed to a depth of 7 cm. She was then treated with 6 cycles of carboplatin and paclitaxel as second line therapy.

Nine months after completion of second line chemotherapy the patient presented once more with recurrent radicular symptoms and was found to have radiographic evidence of left renal mass and left adrenal nodule growth suggestive of disease progression (Figs. 1A and 2A). It was at this time that she presented to our institution for a second opinion. Soon after, she was started on pembrolizumab as third line chemotherapy. She maintained a partial response on this ICI, but developed a grade 3 pruritic rash following cycle 26 of pembrolizumab. Therapy was suspended and the patient was started on prednisone 60 mg daily. After 4 weeks, the patient's rash improved to grade 1

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From the Roswell Park Comprehensive Cancer Center, Buffalo, NY
Address correspondence to: Jordan Cinquino, D.O., 139 Altair Drive, Getzville, NY 14068. E-mail: jordanci@buffalo.edu

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Figure 1. (A) Left adrenal nodule prior to initial pembrolizumab therapy (37 × 25 mm). (B) Left adrenal nodule before pembrolizumab rechallenge (2.2 mm). (C) Left adrenal nodule after pembrolizumab rechallenge (1.2 mm). (Color version available online.)

and prednisone taper was completed. At that time the patient was clinically asymptomatic and chose to forgo further treatment in favor of active surveillance. During this surveillance period she had clinical and imaging follow-up every 3 months.

After 18 months of close observation she presented with new hematuria in the setting of a progressively enlarging left renal mass and left adrenal nodule seen on surveillance CT scans (Figs. 1B and 2B). Pembrolizumab was restarted at the original dose given every 3 weeks. After 3 cycles of pembrolizumab, restaging CT imaging showed partial response with near resolution of left adrenal nodule and decrease in size of left renal mass (Figs. 1C and 2C). She has received approximately 13 cycles of pembrolizumab and has been tolerating the therapy well without any further irAE or manifestation of disease progression at this time.

DISCUSSION BY SABY GEORGE, M.D

After development of high-grade adverse events while on cytotoxic chemotherapy or immunotherapy the primary approach is to discontinue treatment due to safety concerns. The unfortunate reality is that in patient populations with metastatic disease, as the case presented above, effective and safe therapies are typically in limited supply so discontinuation of an effective treatment further complicates future interventions. However, there has been some evidence to support disease response and safety when rechallenging with PD-1 inhibitors in patients with advanced melanoma.⁵⁻⁹ In studies which evaluated retreatment of melanoma patients who developed high-grade irAE on ipilimumab therapy an overall response

rate was found to vary from 11.8% to 23.0% and disease control rate from 48.4 to 60.5%.^{6,7} A similar study also examined the efficacy of single agent nivolumab retreatment after initial high-grade irAE on ipilimumab and nivolumab combination therapy in metastatic melanoma patients and revealed an overall response rate of 70.0% and disease control rate of 88.8%.⁸ What these findings suggest is that there is a significant amount of disease control in those retreated with PD-1 inhibitors.

These same studies also examined recurrence of irAE related to retreatment with CTLA-4 and PD-1 inhibitors in patients with melanoma.⁵⁻⁸ Approximately 51.4% (144/280) experienced an irAE of any severity yet only 12.8% (36/280) of the total patient population had a grade 3 or 4 irAE requiring discontinuation of ICI therapy.^{3,5-8} Similar results were found in a meta-analysis focused on irAE after primary treatment with ICIs showing that approximately 48% (1323/2752) of patients treated with CTLA-4 and PD-1 inhibitors experienced an irAE of any severity, and 13.4% (606/4,514) experienced grade 3 or higher irAE.¹⁰ The similarity in occurrence of irAE in those with primary treatment and retreatment support the conclusion that it is reasonably safe to further study antitumor activity and adverse effects in retreatment of those with previous irAE. A retrospective analysis was performed in the melanoma population treated with combination CTLA-4/anti-PD-1 therapy with the purpose of examining variables that may correlate with recurrence of an irAE in those with previous irAE warranting discontinuation of therapy.⁶ Some of the variables examined were length and type of immunosuppressive therapy, severity of initial irAE, ongoing steroid therapy or ongoing symptoms at rechallenge, and interval of time between discontinuation



Figure 2. (A) Left renal mass prior to initial pembrolizumab therapy (39 × 26 mm). (B) Left renal mass before pembrolizumab rechallenge (30 × 41 mm). (C) Left renal mass after pembrolizumab rechallenge (15 mm).

of initial therapy and rechallenge. While the power of the study was somewhat limited by its size ($n = 80$) there seemed to be a weak yet statistically significant positive correlation between irAE recurrence (of distinct or similar variety), shorter time interval between discontinuation and rechallenge, and the presence of steroids at rechallenge. Those who remained on steroid therapy at the time of rechallenge demonstrated higher recurrence rates compared to those who were no longer on therapy (55% recurrence vs. 31% recurrence, $P = .03$). In those who experienced recurrence of irAE the time interval between discontinuation of therapy and rechallenge was shorter (median of 56 days vs. 62 days in those without recurrence, $P = .03$). However, no correlation was found between irAE recurrence and severity of initial toxicity or duration/type of immunosuppression. Notably, the patient in the above case experienced both variables associated with reduced rate of recurrence, an extended time interval between initial discontinuation and rechallenge (approximately 18 months) and completed a steroid taper prior to rechallenge. Examination of this case further supports Pollack's findings and suggests that by extending the time interval between discontinuation and retreatment and allowing for completion of an appropriate steroid taper over approximately 2 months (as in this case study) risk of irAE recurrence can be reduced.

To our knowledge, we are the first to report a case where a patient with metastatic urothelial carcinoma demonstrated disease control and no evidence of irAE in rechallenge with ICI therapy. Similar reports and studies have been done in melanoma and NSCLC populations but not in the urothelial carcinoma population. This case demonstrates that there likely is utility in rechallenging other cancer populations with ICIs and suggests that further examination of factors that may correlate with recurrence of an irAE and/or favorable disease response in retreated populations may be warranted. Unfortunately, there is still limited published data to validate efficacy and safety associated with ICI rechallenging in those with a history of irAE. Without this evidence, this type of therapy should be reserved for those populations where the potential benefits seem to outweigh the risks.

In this case it's interesting to note that the patient experienced sustained disease control during pembrolizumab therapy but also for 18 months after discontinuation of therapy. We hypothesize that the initial exposure to pembrolizumab therapy may have led to clonal expansion of CD-8 T-cell machinery which was responsible for both disease control and irAE. We suspect that this T-cell response and memory triggered by initial pembrolizumab exposure persisted even after discontinuation of ICI leading to sustained disease control without further drug exposure. As the disease began to progress, the patient was again treated with pembrolizumab and subsequently achieved tumor reduction. The efficacy of rechallenge led us to hypothesize that the cancer did not develop

resistance to ICI therapy, despite evidence of progression. The mechanism of disease progression may have been T-cell exhaustion and thus, the reproducibility of antitumor response upon rechallenge. Recently presented clinical data from the Checkmate-214 trial in renal cancer patients is consistent with this phenomenon of long term disease control in patients who had to discontinue therapy due to high-grade irAE.¹¹ This trial also found lengthy time to retreatment and treatment-free intervals in this subset of patients who developed initial irAE. In summary, this case report encourages us to study the phenomenon of tumor control that occurs after development of irAE and particularly the mechanism of tumor progression at the end of treatment-free interval.

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