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Research article

A Single-Institution Study of Renal Outcomes in Patients Receiving Checkpoint Inhibitors

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Abstract

Background: Checkpoint inhibitors (CPI) are becoming more widely used in a number of solid and hematologic malignancies. The reported incidence of renal toxicities has varied and the effect of other co-morbidities or concomitant medications on the risk of AKI is not clear. In our single-institution study; we monitored the renal function in patients receiving CPI treatment to determine the incidence of AKI and examine the probable nephrotoxic effects of many clinical and treatment-related factors. Methods: An IRB-approved retrospective analysis was performed using patients seen at Moffitt Cancer Center between 1/1/2015 and 1/1/2016 who were receiving CPI therapy (ipilimumab, nivolumab, pembrolizumab or any combination). Selected patients had a minimum of 3 months of follow-up including laboratory analysis of renal function. If available, basic metabolic panel, serum magnesium, phosphorus and urine studies were also collected at baseline, 3, 6, 9 and 12 months. The primary endpoint was AKI, defined as increase in serum creatinine by > 0.3 mg/dL or ≥ 50% from baseline. Results: A total of 206 patients were selected with 3-12 months of follow-up. There were 19 patients (9%) who had AKI. The incidence of AKI among patients receiving nivolumab, pembrolizumab, ipiliumab or concurrent ipililimumab/nivolumab was 3.8%, 9.8%, 7.3% and 9.5%, respectively (not statistically significant). There was no significant difference in the incidence of HTN or DM between groups, nor was there a difference in CKD stages, baseline creatinine, or baseline blood pressure. Concomitant antihistamine use was higher in the AKI group (42% vs 15%, p = 0.003). This was also true for diuretics (37% vs 17%, p = 0.03). In the AKI group, 10 patients discontinued CPI therapy due to disease status (progression vs surveillance). Four patients had AKI associated with immune-related toxicities, one with CPI-related acute interstitial nephritis (AIN). Conclusions: In our cohort, CPI therapy was well-tolerated from the standpoint of renal function. Of the 19 patients who experienced AKI, only 4 patients (1.9%) had AKI associated with autoimmune-related CPI toxicity with one report of AIN. While our data do not suggest co-morbidities such as HTN, DM or CKD have any correlation with incidence of AKI, concomitant use of other potentially nephrotoxic medications may be associated with increased risk of AKI.

Introduction

Immunotherapy is an emerging field for a number of both solid and hematologic malignancies. Checkpoint inhibitors are antibodies against cell surface receptors (e.g., CTLA-4 and PD-1) present on various immune cells (e.g., activated T cells) that function by inhibiting immune cell activation, allowing tumor cells to avoid immune surveillance. Checkpoint inhibitors act by blocking these interactions, thereby allowing the immune system to "activate" against tumor cells [1, 2]. These drugs have shown clinical benefits of tumor regression and stabilization in various solid tumors [2-6] and there is growing evidence of efficacy in certain hematologic malignancies [7]. Ipilimumab is a monoclonal antibody that targets CTLA-4, which is an inhibitory receptor present on T cells. Nivolumab and pembrolizumab are monoclonal antibodies directed against PD-1, which is an inhibitory receptor found on activated T cells, B cells, natural killer T cells, monocytes, and dendritic cells [2, 8, 9].

There are a number of toxicities from these drugs secondary to immune activation. These include dermatitis, pneumonitis, hepatitis and gastritis/colitis (e.g. [10, 11]). The potential for renal toxicity from checkpoint inhibitors has been well reported but the overall incidence is quite variable, ranging from 2.2% to 29% [2, 12-14]. Generally, patients with CPI-induced direct renal toxicity have biopsy findings consistent with acute interstitial nephritis (AIN, [2, 12]) which is usually responsive to steroid treatment [12], although there have been reports of other etiologies associated with CPI-related renal toxicity (e.g.,

[15]). AIN itself is rare, and many of the studies reporting incidence of AKI in CPI treated patients lack renal biopsies confirming AIN [2, 12]. Furthermore, there are various other potential causes of AKI in cancer patients (e.g., pre-renal, ATN, infection, non-CPI drug toxicity). It is also unclear the relationship between co-morbidities associated with renal insufficiency (e.g., HTN, DM) and the incidence of AKI in CPI-treated patients. Here, we present a single-institution study of renal outcomes in patients receiving CPI therapy over treatment period up to 1 year with additional analyses including co-morbidities, concomitant use of other renally toxic medications and changes in blood pressure during treatment.

Methods

This case series involved an IRB-approved (protocol #19081) retrospective chart review of patients seen at Moffitt Cancer Center from 01/01/2015 to 01/01/2016 with either solid or hematologic malignancies receiving a checkpoint inhibitor (ipilimumab, nivolumab, pembroluzimab or any combination). Patients selected had baseline blood pressure and electrolyte panels. Additionally, serum creatinine levels were collected at 3,6,9 and 12 months when available with a minimum of 3 months of follow-up. When available, follow-up data for blood pressure, basic metabolic panel, serum magnesium, serum phosphorus and urine studies was collected at 3,6,9 and 12 months. Additional clinical data regarding primary cancer diagnosis, staging, co-morbidities and concomitant nephrotoxic medications was also collected for each patient. The primary endpoint was acute kidney injury (AKI), defined as increase in serum creatinine by > 0.3 mg/dL within 48 hours or a 50% increase in serum creatinine (SCr) from reference value (based on KDIGO criteria, [16]). Secondary endpoints were de novo electrolyte abnormalities and variations in blood pressure. Comparisons made between the AKI and non-AKI groups were done using non-parametric analyses for continuous and categorical variables using SPSS™ 24.

Results

A total 206 patients were selected with a minimum of 3 months of follow-up. The clinical characteristics of the patient population are described in Table 1. The median age was 69 with a majority being male (65%). Regarding the primary malignancy, most patients had melanoma (81%) or NSCLC (12%) and the majority of patients had stage IV disease (79%). Regarding baseline renal function, most patients were classified as CKD 0-1 (78%) with the remaining patients classified as either CKD 2-4 or unclassified. There were no patients with end stage renal disease (ESRD) at baseline.

The 18 patients (9%) missing data for CKD classification all had normal creatinine values at baseline. Most patients received single-agent therapy, including sequential therapy. More patients received pembrolizumab than ipilimumab or nivolumab (54%, 37% and 35%, respectively). The median number of doses received was 8, ranging from 1 to > 26 (i.e., continued therapy after the 12 month follow-up interval).

Based on the KDIGO criteria, there were 19 patients (9%) who had AKI during the one year follow-up: 16 patients had stage 1 AKI (i.e., peak serum Cr < 2 x baseline), 1 with stage 2 AKI (peak serum Cr 2-3 x baseline) and 2 with stage 3 AKI (peak serum Cr > 3 x baseline). None of the patients in the AKI group required dialysis. Most patients in the AKI group had melanoma (14 with stage 4 disease, 2 with stage 3 disease). There were 2 patients with stage 4 RCC and 1 patient with stage 4 SCLC. Five patients had prior CPI therapy with disease progression and were receiving a subsequent line of CPI therapy when data was collected for this study. Comparisons between the AKI and non-AKI groups are shown in Table 2. The median age was higher in the AKI group (73 vs 68) which approached significance (p = 0.057). There was no significant

Table 1. Characteristics of study population

Age	
Median (range)	69 (25 – >89)
Gender	n (%)
Male	133 (65)
Female	73 (35)
Ethnicity	
Caucasion	157 (76)
African American	5 (2)
Hispanic/latino	4 (2)
Asian	1 (< 1)
unknown	39 (19)
CKD stage	
0-1	160 (78)
2	13 (6)
3	11 (5)
4	4 (2)
unknown	18 (9)
Co-morbidities	
HTN	102 (50)
DM	29 (14)
HTN + DM	22 (11)
Tumor pathology	
Melanoma (skin/soft tissue)	166 (81)
NSCLC	24 (12)
Renal cell carcinoma	5 (2)
Hodgkins Lymphoma	5 (2)
Other	6 (3)
Tumor Stage at initiation of CPI	
2	6 (3)
3	13 (6)
4	163 (79)
unknown	24 (12)
Single agent Ipilimumab	27 (13)
Single agent Nivolumab	46 (22)
Single agent Pembrolizumab	84 (41)
Sequential single agent CPI	28 (14)
Combined IPI + NIVO	21 (10)
Total doses of CPI received	
Median (range)	8 (1 - >26)
Additional concurrent systemic therapy	10 (5)

Table 2. Clinical characteristics within subgroups with or without AKI. * $p < 0.05$

	No AKI (n = 187)	AKI (n = 19)	P value
Age			
Median (range)	68 (25 - >89)	73 (49 – 87)	0.057
BMI			
Median (range)	27.8 (8.8 – 58.9)	27.4 (17.5 – 51.4)	0.719
CKD stage	**n (%)**	**n (%)**	
0-1	145 (78)	15 (79)	0.291
2	12 (6)	1 (5)	
3	9 (5)	2 (11)	
4	4 (2)	0	
Unknown	17 (9)	1 (5)	
Co-morbidities			
HTN	91 (49)	11 (58)	0.214
DM	28 (15)	1 (5)	0.248
HTN + DM	21 (11)	1 (5)	0.425
Nephrotoxic meds			
Antihistamines	28 (15)	8 (42)	0.003*
Diuretics	31 (17)	7 (37)	0.03*
Blood pressure (mmHg)	mean ± SD	mean ± SD	
Max Systolic BP	142 ± 19	146 ± 17	0.170
Min Systolic BP	119 ± 15	117 ± 13	0.802
Max Diastolic BP	83 ± 9	80 ± 9	0.206
Min Diastolic BP	71 ± 9	65 ± 10	0.022*

difference in the incidence of HTN, DM or CKD between groups. There was a lower incidence of DM in the AKI group compared to the non-AKI group (5% vs 15%, respectively) although this was not significant ($p = 0.248$). There was no difference in baseline blood pressure or serum electrolyte panels between groups. There was no difference in the maximum recorded systolic or diastolic BP; however, the AKI group did have a lower minimum DBP (65 ± 10 vs 71 ± 9 mmHg, respectively, $p = 0.022$). Six patients in the AKI group had significant increases in systolic blood pressure (> 20 mmHg from baseline SBP) during treatment, with most occurring at the time of or preceding the AKI (data not shown), two of whom had improvement in SBP associated with AKI resolution.

Regarding concomitant medications with nephrotoxic potential, patient's home medication lists were considered (i.e., not inpatient medications or pre-medications given with antineoplastic therapy). There was a significantly higher incidence of concomitant diuretic use in the AKI group (37% vs 17%, $p = 0.03$). There was also a higher incidence of antihistamine use in the AKI group (42% vs 15%, $p = 0.003$).

Table 3 illustrates incidence of AKI based on specific CPI therapy received. This table shows total number of cases receiving the specified therapy. There were 34 patients that received multiple agents in sequence during the follow-up period. AKI events shown in Table 3 are attributed to the current therapy being given during the AKI. The lowest incidence of AKI was noted during nivolumab therapy (3.8%) although this was not statistically significant compared to the other treatments (Table 3).

Table 3. Incidence of AKI for specific checkpoint inhibitor therapies.

CPI therapy	No. Patients	No. with AKI	P value (vs nivo)
Ipilimumab	55	4 (7.3%)	0.443
Nivolumab	52	4 (3.8%)	n/a
Pembrolizumab	112	11 (9.8%)	0.189
Concurrent ipi + nivo	21	2 (9.5%)	0.338

Summaries of the AKI events and changes in CPI therapy are shown in Table 4. Of the 19 patients in the AKI group, 9 had resolution of the AKI, 3 had persistently increased serum creatinine and 7 had AKI at the end of follow-up. Median time to AKI was 9 months (range 3-12 months). In the group of patients with resolution of AKI, 3 patients had autoimmune toxicities associated with the AKI (1 with presumed AIN) and were treated with steroids. The patient with presumed AIN (receiving pembrolizumab) had stage 2 AKI with pyuria and negative urine eosinophils with no evidence of UTI. Pembrolizumab was discontinued and AKI resolved after a course of steroids. One patient stopped therapy due to disease progression and 5 patients continued therapy without interruption or steroid treatment. Of these 5 patients, one had AKI associated with UTI that resolved with antibiotics. One patient had received 4 cycles of ipilimumab for unresectable stage IIIB melanoma, which resulted in tumor debulking followed by resection and CR (AKI occurred after surgery). One patient received 7 cycles of neoadjuvant pembrolizumab followed by resection of an oligometastatic melanoma and CR. This patient had elevated systolic blood pressure initially (SBP 150s-160s

for first 3 months) and AKI occurred at month 3. AKI resolution was associated with improvement in SBP. One patient with metastatic melanoma developed AKI while on pembrolizumab (had colitis with ipilimumab without AKI) which resolved without interruption in pembrolizumab and they eventually switched to surveillance after attaining a partial response to pembrolizumab.

Of the 3 patients who had persistently elevated serum creatinine without resolution of AKI, 1 patient discontinued therapy due to disease progression and 2 patients continued therapy, 1 of whom had underlying CKD 3 and was thought to have progression of known renal disease unrelated to therapy. There were 7 patients who had AKI at the end of the follow-up period. Of these patients, 6 stopped therapy due to disease progression (2 with stage 3 AKI). As shown in Table 4, only 1 patient had CPI therapy discontinued due to direct renal toxicity (presumed AIN). The remaining therapeutic changes were due to changes in disease status or other autoimmune toxicities.

Urinalyses and urine microscopy were available for 7 patients in the AKI group. Proteinuria (qualitative by urinalysis) was present in 2 patients, one with known CKD and proteinuria at baseline and the other with rapidly progressive disease associated with stage 3 AKI who transitioned to hospice care. Both patients with documented pyuria on urine microscopy were mentioned previously (UTI and AIN). The average baseline sodium, potassium and bicarbonate levels were not different between the AKI and non-AKI groups. There were also no significant changes in serum electrolyte levels associated with the AKI group (data not shown).

Table 4. Summary of AKI events (top) & therapeutic changes (bottom)

AKI Total	19
AKI resolved	9
Disease progression	1
Colitis s/p steroids	1
Transaminitis/pancreatitis s/p steroids	1
Autoimmune nephritis s/p steroids	1
Continued therapy (1 treated for UTI)	5
AKI persistent	3
Disease progression	1
Continued therapy	2
AKI at end of follow-up, status unknown	7
Disease progression	6
Pneumonitis s/p steroids	1
Continuous therapy without interruption	2
Discontinuation of all CPI therapy – Total events	14
Disease progression	7
Response (PR/CR) – switched to surveillance	3
Autoimmune nephritis	1
Pneumonitis	1
Pancreatitis/transaminitis	1
Colitis/transaminitis	1
CPI interruption without discontinuation	2
Pneumonitis, transaminitis	3
Change in CPI therapy	
Disease progression & colitis	1
Disease progression	1
Colitis	1

Discussion

As CPI therapy becomes more widely used, the autoimmune toxicities are becoming more prevalent. The incidence of renal toxicity is rare in clinical trials using CPI therapy (e.g., [5, 17-19]); however, subsequent retrospective studies have found higher incidence of AKI [2, 12-14]. In our study, the incidence of AKI was 9.2%, which was primarily stage 1 (7.8% stage 1, 1.4% stage 2-3). This is higher than the pooled analysis done by Cortazar et al, which showed an overall incidence of 2.2% [12]; however, this study pooled results from multiple centers via various publications. Our data represents a single center data set using the same laboratory and reference values. A study of 99 patients with available serum creatinine data reported stage 1 AKI in 29% of patients receiving ipilimumab and 24.5% of patients receiving anti-PD-1 therapy [13]. In our study, we observed a lower overall incidence of AKI than this study, but we did confirm a similar AKI incidence between anti-CTLA4 and anti-PD-1 therapies (7.3% vs 7.9%, respectively). Cortazar et al. also observed similar incidence of AKI among those receiving either anti-CTLA4 therapy or anti-PD-1 therapy [12]. Interestingly, we did not see a significantly higher incidence of AKI among patients receiving concurrent ipilimumab and nivolumab, as has been previously shown [12, 18]; however, our study may be limited by the small number of patients receiving the combination therapy (n = 21).

There was no specific CPI therapy shown to have a significantly higher incidence of AKI compared to others. The highest and lowest incidence of AKI was noted in the pembrolizumab and ipilimumab-treated groups, respectively, although this difference was not significant (9.8% vs 3.8%, p = 0.189). It should be noted that most of the cases of AKI during pembrolizumab therapy were related to either disease progression or other autoimmune toxicities with only one case of direct renal toxicity secondary to presumed AIN. Reports of AKI incidence in clinical trials using pembrolizumab has been relatively low [5, 19-20]. Given that many of our patients had worsening renal function at time of disease progression, they would have been taken off study in a clinical trial which may explain the higher incidence observed in our population.

Only 1 patient receiving pembrolizumab had AKI that was presumed to be related to CPI-induced renal toxicity. This patient was diagnosed with AIN based on the presence of pyuria without evidence of UTI. This patient had no other signs or symptoms of immune-mediated adverse events. Their SBP was elevated from baseline at the time AIN was diagnosed and both renal function and SBP improved after treatment with steroids. CPI-induced AIN has been documented in a number of other studies and most cases show partial or complete resolution with steroid treatment [12, 15, 21, 22]. Many of these cases are associated with ipilimumab therapy; however, there have been several reported cases of biopsy-proven AIN patients receiving pembrolizumab [12, 23]. While AIN should always be considered in patients with AKI while on CPI therapy, it is a rare event. Various medications (e.g., proton pump inhibitors, antibiotics, NSAIDs) can cause AIN [24]. Our patient was receiving both PPI and NSAID therapy before data collection. While renal function had been stable on these medications, it is possible that this patient had developed a tolerance until CPI

therapy was initiated which triggered an immune response. Caution is advised when prescribing CPI therapy to patients who are already taking medications associated with AIN.

There were 4 other AKI events associated with other CPI-related autoimmune toxicities, 3 of which resolved with steroids and change/discontinuation of CPI therapy. Other autoimmune toxicities, especially colitis and pancreatitis, can cause changes in fluid balance (ie, dehydration or systemic vasolidation) causing decreased renal perfusion, which is a more likely cause of AKI in patients receiving CPI therapy than direct CPI-induced renal toxicity. Interestingly, the use of diuretics and antihistamines were significantly higher in the AKI group. This further illustrates that AKI events in patients receiving CPI therapy may often be related to other factors, including other potentially nephrotoxic medications.

Both hypertension and DM are associated with increased risk of developing CKD (e.g., [25, 26]). In our study, we evaluated the prevalence of these co-morbidities in our study population and found no differences between the AKI and non-AKI groups. The incidence of AKI in the population with a history of HTN was 10.8% vs 7.7% in patients without HTN ($p = 0.444$). Overall, we did not observe any significant correlation between a history of HTN and/or DM and incidence of AKI. We also did not observe any differences in incidence/severity of CKD between groups. Many of these patients are already on medications to control their disease which can prevent worsening renal function (e.g., antihypertensives and glycemic control) as well as avoiding other potentially nephrotoxic medications. The increased attention given to these patients may explain why these comorbidities did not appear to increase incidence of AKI in our population. However, we did observe significant SBP elevation in several patients within the AKI population which preceded the AKI in some cases. Blood pressure management is important in preserving renal function and needs to be addressed in patients receiving CPI therapy.

Our study has several limitations. First, the majority of patients had metastatic melanoma. Given the increased use of CPI therapy in other malignancies, it is important to evaluate toxicities in each treatment setting. However, previous phase 3 clinical trial results have shown similar incidence of AKI (~1-3%) in both metastatic melanoma and NSCLC treated with single-agent CPI therapy [17, 18]. It should be noted that of the 5 RCC patients in our study, 2 were in the AKI group (both had disease progression at time of AKI). There was a relatively small population of cases receiving concurrent ipilimumab/nivolumab as well, and we did not confirm prior studies showing increased incidence of AKI in this population. Our data also lacks complete urine studies for many of the patients in the AKI group and there was no renal biopsy performed on the patient with presumed AIN. The lack of urine studies is likely because most patients had mild, stage 1 AKI; furthermore, most of the patients in the AKI group had treatment discontinued due to disease progression rather than concern for renal toxicity.

CPI therapy is overall very well tolerated, especially when compared to conventional cytotoxic chemotherapy. The reported incidence of renal insufficiency in patients receiving CPI therapy is highly variable among both clinical trials and retrospective studies. This variability may be explained by differences in laboratory analyses; however, it is also very likely related to the various etiologies of AKI in cancer patients. Patients on clinical trial may be monitored more closely and could potentially receive more supportive care (ie, IV fluids) based on smaller changes in renal function to prevent adverse events. It is important to note we did not observe higher prevalence of HTN, DM or CKD in the AKI group. While CPI therapy can cause renal toxicity, they are still well tolerated even in patients at increased risk for renal dysfunction. Overall, our results suggest that adverse renal events in patients receiving CPI therapy are most likely to be secondary to other etiologies and unrelated to direct CPI-induced renal toxicity. In cases of AKI associated with direct renal toxicity or other autoimmune toxicity, CPI interruption/discontinuation and steroid treatment can be effective. In general, renal biopsies should be considered in patients who have an AKI while on CPI therapy unless there is another likely etiology.

Declarations Ethics Approval and Consent to Participate

This study was performed using retrospective data for patients seen at Moffitt Cancer Center. This protocol was approved by Moffitt Scientific Review Committee (SRC) and the USF IRB. Protocol #MCC 19081.

Consent for Publication

Not applicable

Competing Interests

There are no financial disclosures or competing interests for this study.

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Authors' Contributions

D Kerr – study design, IRB approval, dataset processing/-compilation & analysis, manuscript preparation. S Mushtaq – study design, IRB approval, data collection, manuscript preparation. S Mirza - study design, IRB approval, data collection, manuscript preparation. S Shah – data collection. H Hassanein – data collection.K Shirley – data collection. J-H Lee – data collection. R Lopez – data collection. B Shah – supervising faculty. C Bassil – supervising faculty, study design, IRB approval, manuscript editing.

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