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Acute Kidney Injury after CAR-T Cell Therapy: Low Incidence and Rapid Recovery

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Abstract

Chimeric antigen receptor (CAR) T cell therapy using engineered cytotoxic T cells has shown promising responses in various hematological malignancies. Cytokine release syndrome (CRS) and immune effector cell associated neurological syndrome (ICANS) are recognized toxicities of CAR-T, while kidney injury remains less recognized. The objective of this study was to identify the incidence of acute kidney injury (AKI) post CAR-T cell therapy, potential risk factors, and kidney function recovery. We performed a retrospective review of 46 adult patients with Non-Hodgkin lymphoma treated with CAR-T therapy from February 2018 to February 2019 at our institution. Serum creatinine values prior to CAR-T therapy through day 100 were used to assess AKI, as defined by the Kidney Disease Improving Global Outcomes (KDIGO) criteria: grade 1 (1.5 - < 2-fold), grade 2 (2 - < 3-fold), and grade 3 (≥ 3-fold) baseline. CRS and ICANS were graded using the consensus criteria by the American Society of Transplantation and Cellular

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Conflict-of-interest disclosure

Dr. Perales reports honoraria from Abbvie, Bellicum, Celgene, Bristol-Myers Squibb, Incyte, Merck, Novartis, Nektar Therapeutics, Omeros, and Takeda. He serves on DSMBs for Cidara Therapeutics, Servier and Medigene, and the scientific advisory boards of MolMed and NexImmune. He has received research support for clinical trials from Incyte, Kite/Gilead and Miltenyi Biotec. He serves in a volunteer capacity as a member of the Board of Directors of American Society for Transplantation and Cellular Therapy (ASTCT) and Be The Match (National Marrow Donor Program, NMDP), as well as on the CIBMTR Cellular Immunotherapy Data Resource (CIDR) Committee.

Dr Jaimes is Chief Medical Officer, shareholder and co-founder of Goldilocks Therapeutics, Inc.

Dr. Jain is a consultant for Takeda Oncology.

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Therapy. The overall incidence of CRS was 78.3% (95% CI 66–90.5%) of which 13% (95% CI 3.3–22.8%) developed grade 3–4 CRS, while overall incidence of ICANS was lower at 45.7% (95% CI 3.1–60.3%). The cumulative incidence of any grade AKI by day 100 was 30% (95%CI 16.9–43.9%) with grade 1 AKI incidence at 21.7% (95%CI 9.7–33.8%) and grade 2–3 AKI incidence at 8.7% (95%CI: 0.4–17%). None of the patients developed severe AKI requiring renal replacement therapy. Patients with prior autologous or allogeneic stem cell transplantation, those requiring intensive care unit level care and with grade 3–4 CRS had a higher incidence of AKI. Most patients recovered with kidney function returning to baseline within 30 days. We conclude that with early recognition and management of CAR-T complications, the incidence of AKI is low, the severity of injury is mild, and most patients recover kidney function within 30 days.

Keywords

Chimeric Antigen Receptor T Cell Therapy; acute kidney impairment; toxicity

Introduction

Chimeric antigen receptor (CAR) T cell therapy has shown promising responses in various hematological malignancies and is set to lead the way for the era of adoptive T cell therapy in these type of malignancies[1–9]. CARs are genetically engineered surface receptors consisting of an extracellular antigen-binding domain that recognizes a specific tumor antigen, intracellular T cell signaling domains i.e. CD3zeta, and co-stimulatory molecules such as CD28 and 4–1BB[10]. When incorporated on autologous T cells, CARs redirect the specificity and function of T cells, that are hence able to recognize specific tumor antigens independent of human leucocyte antigen or major histocompatibility complex[11].

While high responses have generated enthusiasm, more continues to be learnt about the potential toxicities and effects on organ function[12–16]. This is especially the case since utilization has grown since the FDA approval of axicabtagene ciloleucel for B cell lymphomas and tisagenlecleucel for B cell acute lymphoblastic leukemia and B cell lymphomas in 2017. Cytokine release syndrome (CRS) and immune effector cell associated neurological syndrome (ICANS) have been recognized and well-described in response to CAR-T cell therapy[8, 17–21]. While the mechanisms are complex and not completely understood, they are thought to be mainly mediated by pro-inflammatory cytokines such as interleukin (IL)-6, IL-1 derived from host monocytes and macrophages and effector cytokines such as interferon-γ and granulocyte macrophage colony stimulating factor derived from CAR-T cells[22–24]. CRS leads to endothelial injury causing capillary leak, while pericyte injury has been implicated in the development of ICANS[20, 22].

As the landscape of utilization of CAR-T cell therapy evolves, it will be imperative to understand their effects on various organ systems to allow for informed and safe clinical practices[25]. In this study we investigated the incidence, risk factors and recovery of acute kidney injury (AKI) in patients receiving axicabtagene ciloleucel or tisagenlecleucel CAR-T cell therapy for Non-Hodgkin’s lymphoma (NHL).

Materials and Methods

Patient demographics and study definitions

We studied adult patients treated with FDA approved CAR-T cell therapies between February 2018 and February 2019 for relapsed/ refractory NHL at our institution. Patients were treated with either axicabtagene ciloleucel (Yescarta®, Kite-Gilead) or tisagenlecleucel (Kymriah ®, Novartis). All data collection and analysis were performed with approval by the Institutional Review Board at Memorial Sloan Kettering Cancer Center.

Serum creatinine values from 7 days prior to CAR-T therapy through day 100 following the therapy were collected and used to assess for the presence of acute kidney injury (AKI). Baseline creatinine and glomerular filtration rate (GFR) based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula were obtained within 7 days prior to CAR-T cell therapy[26]. AKI was defined by serum creatinine using the Kidney Disease: Improving Global Outcomes (KDIGO) criteria: grade 1 (1.5 - < 2-fold), grade 2 (2 - < 3-fold), and grade 3 (≥ 3-fold) baseline [27]. Of note, decrease in urine output is also part of KDIGO grading but was not used in this study due to its retrospective nature.

Baseline patient demographic data including age, gender, ethnicity, and co-morbidities such as hypertension and diabetes were retrospectively collected from the MSKCC clinical database with additional chart review as required. Indication for CAR-T cell therapy, prior lines of therapy, history of autologous or allogeneic hematopoietic cell transplantation (HCT), and type of lymphodepletion regimen were also collected. Post CAR-T cell events investigated included admission to the intensive care unit (ICU) and administration of nephrotoxic agents such as vancomycin, ibuprofen, acyclovir, trimethoprim/ sulfamethoxazole (TMP-SMX) and intravenous (IV) contrast. Clinical notes were reviewed for tumor lysis syndrome diagnosis and/or administration of rasburicase at time of kidney injury. Toxicity data was obtained for CRS and ICANS with grade of severity of each based on consensus guidelines by ASTCT[17, 28]. Pertinent laboratory values including peak C-reactive protein (CRP), ferritin, IL-6 and IL-10 were collected. Treatment for toxicities with either tocilizumab, dexamethasone, or other agents was also recorded. For patients that developed AKI, all creatinine values for the 30 days that followed were recorded to evaluate kidney recovery. In depth chart review was performed for patients that developed AKI including evaluation of urine studies, renal ultrasound, and renal consultation if present. Patients were censored at last follow up or at time of death.

Statistical analysis

Patient baseline characteristics, laboratory values and accompanying toxicities were summarized in the median (the range) or the percent by AKI present and absent. The overall cumulative incidences were calculated for CRS and ICANS based on the cumulative incidence function. Competing events did not apply to CRS and ICANS in this cohort considering the earliest death occurred 3 weeks post CAR-T therapy. Day 100 cumulative incidence of AKI post CAR-T therapy was estimated with death as a competing event. Progression of disease and relapse were not considered competing events. The number of

AKI events was small and limited our ability to perform a stable association analysis on the risk of AKI.

Results

Patient Baseline Characteristics

A total of 46 patients were included in the analysis with a median age at CAR-T therapy of 63 years (range 19 – 86 years) (Table 1). Most patients were male (33/46, 72%) and of Caucasian ethnicity (38/46, 83%). The majority of patients had diffuse large B cell (DLBCL) subtype (44/46, 96 %) while the remaining two patients had unclassifiable B cell NHL subtype. Patients received a median of 4 lines of treatment (range 2–10) prior to CAR-T cell therapy. Some of the patients underwent HCT including autologous HCT (9/46, 20%), allogeneic HCT (3/46, 7%), or both autologous and allogeneic HCT (1/46, 2%) prior to CAR-T therapy[29]. Lymphodepletion regimen consisted of cyclophosphamide/fludarabine in most patients (43/46, 93%) while a few received bendamustine (3/46, 7%). Most patients received axicabtagene ciloleucel (34/46, 74%) and the remainder received tisagenlecleucel (12/46, 26%).

Baseline co-morbidities relevant to kidney dysfunction, included hypertension (13/46, 28%) and diabetes mellitus (1/46, 2%). No patient had a history of renal transplant or was on dialysis prior to CAR-T therapy. The median baseline creatinine prior to the start of lymphodepletion was 0.8 (range 0.5 – 2) mg/dL, and median GFR was 88 [(range 36–160) mL/min/1.73m^2]. Four patients had stage 3 CKD at baseline with a starting GFR ≤ 60mL/min/1.73m^2 thought to be related to prior chemotherapy. Fourteen patients had urinalysis prior to CAR-T therapy and five patients had proteinuria estimated to be >30 mg/dL. Median overall follow up was 8.3 (range 2.8 – 16.8) months.

CRS, ICANs, and AKI Outcomes of CAR-T Therapy

The overall incidence of CRS was 78.3% (95% CI 66–90.5%) as shown in Figure 1 including 13% (95% CI 3.3–22.8%) with grade 3–4 CRS. The overall incidence of ICANS was 45.7% (95% CI 3.1–60.3%), including 23.9% (95% CI 11.5–36.4%) grade 3–4 ICANS. Fourteen patients had any grade AKI during the first 100 days after CAR-T therapy. Median day onset for any grade AKI was 48 (range 6 to 100) days. Median creatinine at AKI onset was 1.1mg/dl (range 0.9–2.1mg/dl). Cumulative incidence of any grade AKI was 30% (95%CI 16.9–43.9%) with grade 1 AKI incidence at 21.7% (95%CI 9.7–33.8%) and grade 2–3 AKI incidence at 8.7% (95%CI: 0.4–17%) (Figure 1). Six patients developed AKI after progression of their primary hematologic disease.

Pre and post CAR-T therapy AKI Risk Factors

Baseline characteristics of all patients, including those who developed AKI after relapse or progression of disease, are described in Table 1. The AKI and no-AKI groups were similar in age and gender. The no-AKI group had more patients with hypertension (34% vs. 14%) and diabetes (3% vs. 0%). Patients with AKI did not have underlying cardiomyopathy at time of CAR-T infusion. Both groups underwent a similar median of 4 prior lines of chemotherapy and cyclophosphamide/fludarabine as the conditioning regimen. The AKI

group had a larger percentage of patients with prior HCT (43% vs. 22%), p value for statistical significance not reported as the number of events was too low. The median time between prior HCT and CART therapy was 22.8 months (range 4–63 months). The baseline serum albumin was similar in both groups with a median of 3.6 mg/dl (range 2–4.5 mg/dl). The median baseline creatinine was similar in both groups 0.8 mg/dl (range 0.6–1.5 mg/dl) in the AKI and 0.9 mg/dl (range 0.5–2 mg/dl) in the no-AKI group.

Most patients received axicabtagene ciloleucel (74%) and the remainder received tisagenlecleucel (26%) CAR construct. Thirty-five percent (12/34) of patients that received axicabtagene ciloleucel had AKI compared to 17% (2/12) that had tisagenlecleucel therapy. Lymphodepletion regimen with cyclophosphamide/fludarabine was used in the majority of patients that developed AKI (13/14, 93%). There were no differences in the median ferritin and peak IL-6 levels between the groups. More patients in the AKI group were admitted to the ICU as compared to the no-AKI group 36 % vs. 22 %, respectively. Nephrotoxic medication exposures prior to AKI included acyclovir (10/14, 71%), vancomycin (11/14, 79%), ibuprofen (1/14, 7%), and TMP-SMX (2/14, 14%). Intravenous contrast was administered in 50% of patients that developed AKI with a median of 14 days (range 3–19) prior to AKI onset. Patients were not being managed for TLS and were not on rasburicase at the time of AKI.

In the AKI group, a similar percentage of patients had CRS (71%) and ICANS (43%) vs. the no-AKI group (81% and 47%), respectively. There was however a larger percentage of grade 3–4 CRS in the AKI group (29%) vs. the no-AKI group (6%). More patients received tocilizumab for CRS treatment in the AKI group 29% vs no-AKI group 25%. More patients also received dexamethasone in the AKI 43% versus the no-AKI group 25%.

Kidney recovery

Creatinine trend 30 days following AKI onset for each patient is plotted in Figure 2. Of the 14 patients that developed AKI, three patients died within three weeks (range 15 to 28 days) of AKI onset due to progression of underlying disease. The remaining eleven patients were alive at 30 days and 91% (10/11) had return of their kidney function to baseline. The remaining patient had a serum creatinine that stayed 1.5x higher than baseline by the end of follow up.

Discussion

The new era of genetically modified T cells to treat malignant diseases is changing therapeutics in oncology but can lead to unexpected toxicities. Although the more common toxicities have been identified as CRS and ICANS, other adverse effects such as kidney injury are not well defined. This study investigated the incidence of AKI in 46 patients undergoing CAR-T cell therapy for NHL at our institution. We found that the cumulative incidence of any grade kidney injury was 30% and that the incidence of severe AKI was very low. The low incidence of AKI limited our ability to perform comparative analysis between the AKI and no-AKI group. Despite the small size of this study, it is encouraging to note that the overall incidence of AKI was low and none of the patients sustained severe kidney injury requiring renal replacement therapy following CAR-T therapy.

We identified that prior history of autologous or allogeneic HCT, ICU admission and grade 3–4 CRS may be risk factors for AKI despite the inability to report statistical significance due to the low number of events. Patients undergoing HCT may have indolent kidney injury sustained from prior conditioning regimens, endothelial injury or post HCT complications including infections or thrombotic microangiopathy [30–32]. Baseline assessment of estimated GFR using creatinine may not necessarily identify this subgroup of high-risk patients and more accurate estimation of GFR may be considered[33]. As an example, the lower range of creatinine at AKI onset was 0.9mg/dl for some patients, where the baseline creatinine was 0.6mg/dl (grade 1 kidney injury with a 1.5x increase from baseline). Careful attention should be noted since patients with low muscle mass may have low pre therapy creatinine where early kidney injury can be missed. There was also a higher incidence of AKI in patients admitted to the ICU likely related to critical illness and reduced renal perfusion[34].

CRS has been reported in 57% to 93% of patients undergoing CAR-T therapy, and varies based on the primary hematologic disease and type of CAR-T construct[35]. In our study, the overall incidence of CRS was 78.3% (95% CI 66–90.5%) and grade 3–4 CRS incidence was 13% (95% CI 3.3–22.8%). CRS post CAR-T therapy is a potential risk factor for AKI given the hypotension and vasodilatory shock reducing kidney perfusion[36] though this relationship has not been demonstrated to date. The ensuing cytokine cascade increases vascular permeability, third spacing and worsening hypotension. Additionally, circulating cytokines can cause direct cardiac toxicity which can diminish cardiac output[37] and result in cardiorenal syndrome[36, 38]. ICANS on the other hand is thought to cause more local toxic encephalopathy[17] where presence of a systemic component would likely meet criteria for CRS.

In our study, we found that the occurrence of overall CRS and ICANS was similar between the AKI and no-AKI groups, although there was a higher percentage of grade 3–4 CRS in the AKI group. Inflammatory markers including IL-6, IL-10 and ferritin levels were similar in both the AKI and no-AKI groups. Further, for CRS, the majority of events were grade 1–2 rather than grade 3–4. Given the higher percentage of AKI in grade 3–4 CRS, it is possible that early recognition and appropriate management of CRS prevents progression to a more severe grade and consequential ischemia and kidney injury. Time to treatment of CRS in the AKI versus no-AKI group was not different in this small cohort however with median of 5 days (range 2–8 days) and median of 4.5 days (range 1–9 days), respectfully. Lastly, it is also possible that axicabtagene ciloleucel may indirectly increase risk of AKI through CRS related mechanisms, given the recent findings of this construct associated with higher toxicity, [39] though larger studies are needed to study this more definitively.

In addition to highlighting the low incidence of AKI following CAR-T therapy, another important finding from our study is that kidney function in most patients returned to baseline within 30 days of AKI. As mentioned in results, 3 patients died within 3 weeks of AKI onset. In-depth chart review suggests pre-renal injury in 10/11 remaining patients where injury was short lived as opposed to severe acute tubular toxicity that would take longer time to recover. The patient whose kidney function remained 1.5x higher than baseline had a background of urinary obstruction and was being seen by urology for ureteral stent exchange. Intra-renal causes due to nephrotoxic medications may have further contributed

given over 70 % of patients were on vancomycin at the time of kidney injury. This antibiotic was given for broad spectrum coverage due to hypotension in the setting of CRS. Vancomycin trough levels were therapeutic <20 mcg/ml for all patients except one where level was 26mcg/ml at time of AKI. Acyclovir was another common medication received prior to AKI, which is renally dosed and given for antiviral prophylaxis in patients receiving CAR-T therapy at our center. Intravenous contrast is a less likely cause of AKI in this cohort given a median of 14 days administration prior to AKI when contrast induced nephropathy typically occurs within 48 hours[40]. Careful review of over the counter medications and limited use of potential nephrotoxic medications when possible is recommended even prior to CAR-T therapy.

Tumor lysis syndrome is another risk of CAR-T[36, 41] and although this was not the cause of AKI in our cohort, markers of tumor lysis should be monitored. Glomerular injury can be suspected when urine protein to creatinine ratio is >3 g/g of creatinine[27]. Our cohort did not have significant proteinuria at baseline with only 5 patients found to have low levels proteinuria on their urinalysis, which was not further quantified. Two of these patients developed AKI with their proteinuria unchanged at the time of kidney injury. Baseline urinalysis is important to obtain in order to distinguish pre-existing and therefore unrelated proteinuria from other comorbidities such as diabetes. We therefore recommend obtaining a baseline urinalysis prior to CAR-T therapy to help with differential diagnosis if patients develop AKI.

A post renal cause of AKI or obstruction can be evaluated with a renal ultrasound. Given that our cohort improved with intravenous fluids, the majority of patients did not have a renal ultrasound. Three patients underwent renal ultrasound where one had a prior history of a ureteral stent. Hydronephrosis and obstruction in the remaining two was not found. Five of 14 patients were seen by nephrology and in 4 of 5 cases an electrolyte abnormality, specifically hyponatremia, was the primary reason for consultation. Electrolyte issues have also been shown to be adverse effects of CAR-T therapy[42] and although not the focus of this manuscript, require close attention.

Our study is limited by its small sample size, retrospective nature and low number of AKI events which precludes further hazard risk analysis to identify other modifiable risk factors. As the experience in CAR-T cells grows for various malignancies, larger studies are needed to risk stratify patients for specific organ toxicities including kidney injury. Despite the limitations, this study is novel in describing the effects of CAR-T therapy on kidney function. In our study, we were able to conclude that thus far, incidence of kidney injury is low, grade/severity of kidney injury is low grade, and renal function recovery is likely within the first 30 days after development.

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Highlights

Incidence of acute kidney injury following CAR-T therapy is low.

Prior SCT, admission to ICU, and grade 3–4 CRS post CAR-T may increase risk of AKI.

If acute kidney injury occurs post CAR-T, most patients recover kidney function.

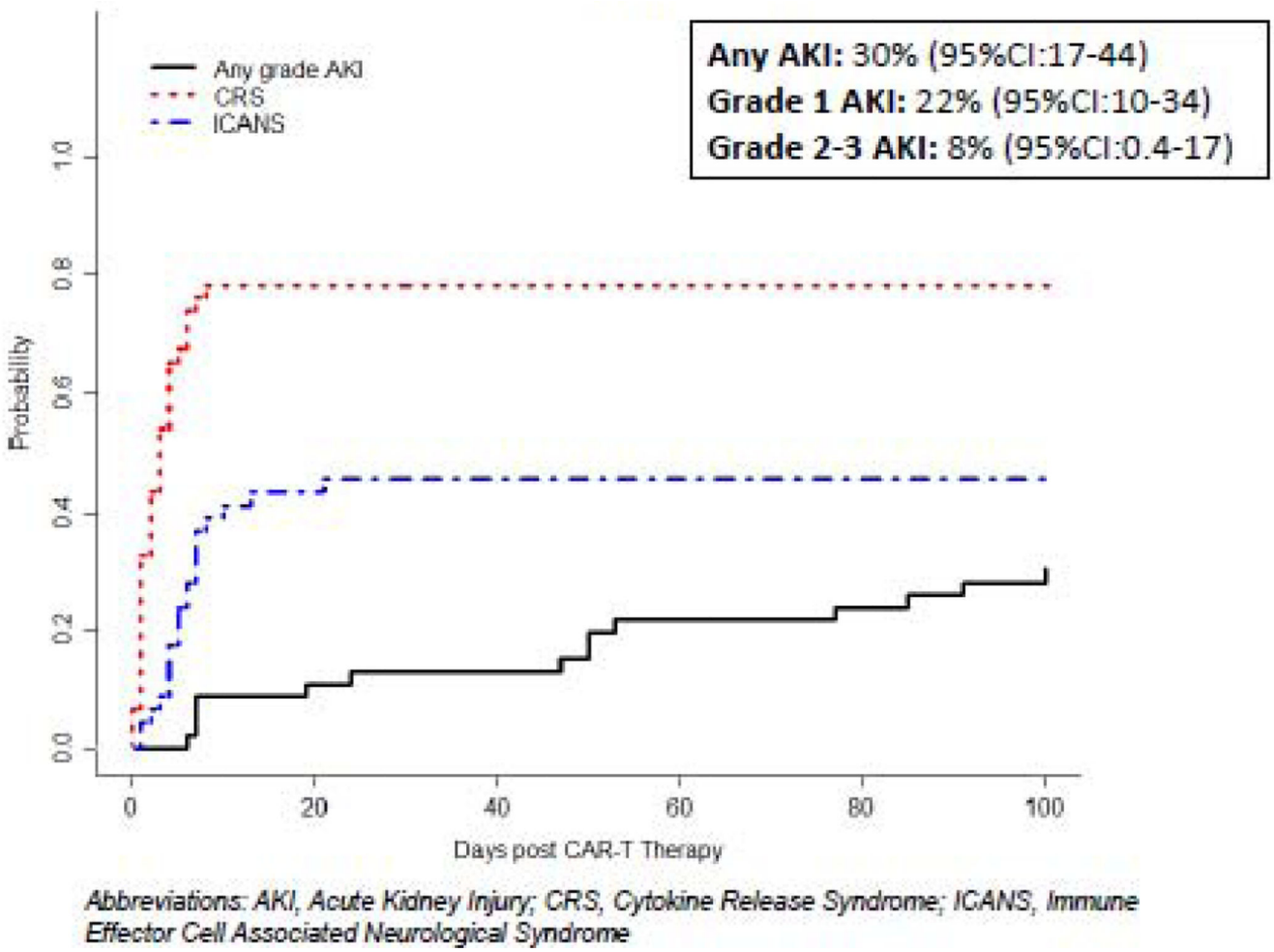

Figure 1: Cumulative Incidence of AKI, CRS, and ICANS in CAR-T recipients in the first 100 days.

Cumulative incidence curve showing AKI, CRS and ICANS post CAR-T therapy. Incidence of CRS 78.3% (95% CI 66–90.5%), of which 13% (95% CI 3.3–22.8%) was grade 3–4 CRS. Incidence of ICANS was 45.7% (95% CI 3.1–60.3%), including 23.9% (95% CI 11.5–36.4%) with grade 3–4 ICANS. Cumulative incidence of any grade AKI was 30% (95%CI 16.9–43.9%) with grade 1 AKI incidence at 21.7% (95%CI 9.7–33.8%) and grade 2–3 AKI incidence at 8.7% (95%CI: 0.4–17%) during the first 100 days post CAR-T therapy.

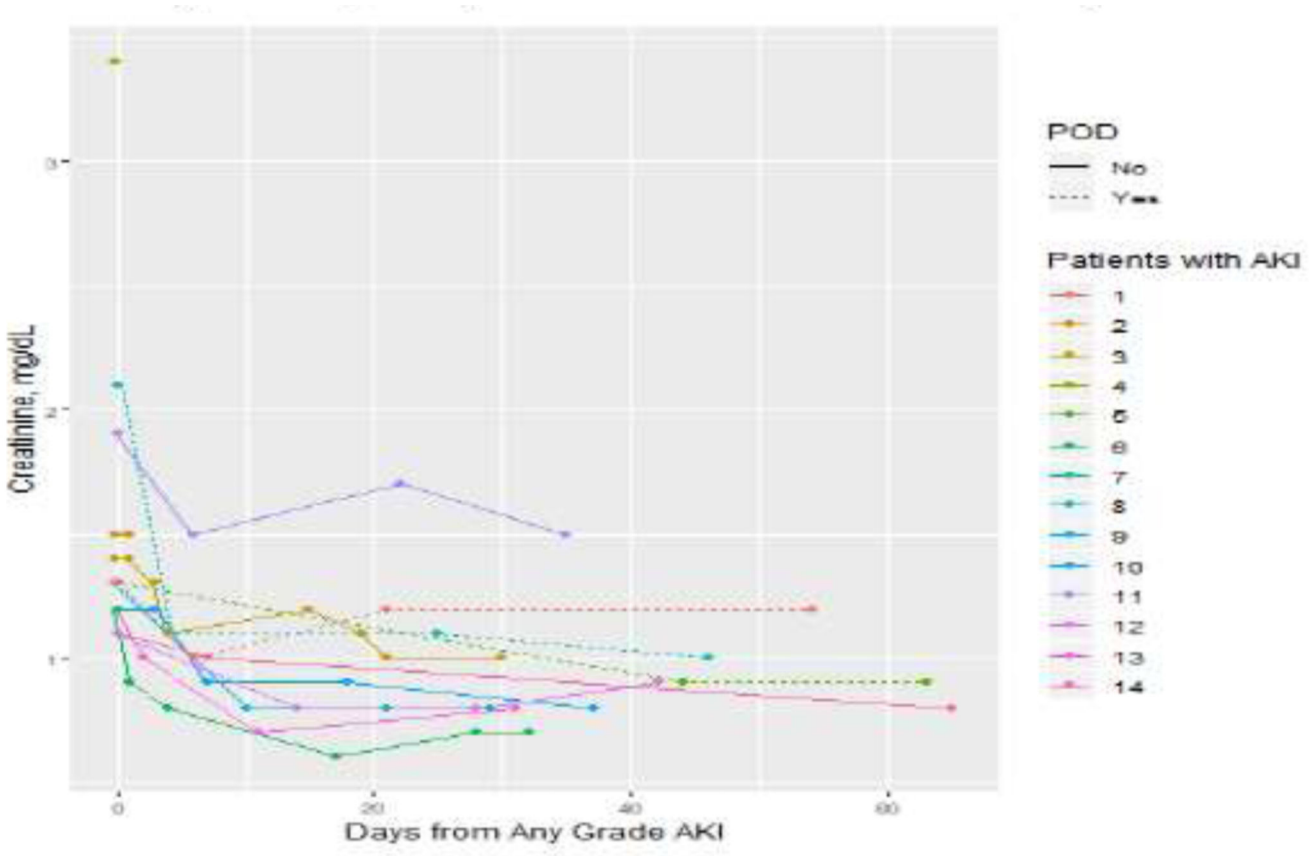

Figure 2: Kidney Recovery 30 days and onward after AKI in CAR-T recipients

Of the 14 patients that developed AKI, three patients died within three weeks of AKI due to progression of underlying disease. The remaining eleven patients were alive at 30 days and 91 % (10/11) had return of their kidney function to baseline. One patient's creatinine remained 1.5x higher than baseline.

Table 1:

Pre and Post CAR-T Therapy Patient Characteristics (N= 46)

	Total (N=46)	AKI (N=14)	No AKI (N=32)
PRE CAR-T			
Age, years (median, range)	63 (19–86)	63 (38–71)	62 (20–86)
Male Gender (N, %)	33 (72%)	12 (86%)	21 (66%)
Hypertension (N, %)	13 (28%)	2 (14%)	11 (34%)
Diabetes (N, %)	1 (2%)	0	1 (3%)
Diagnosis (N, %) **DLBCL**	44 (96%)	13 (93%)	31 (97%)
Prior Lines of Chemotherapy (median, range)	4 (2–10)	4 (2–10)	4(2–9)
Lymphodepletion regimen (N, %)			
Cyclophosphamide/Fludarabine	43 (93%)	13 (93%)	30 (94%)
Bendamustine	3 (7%)	1 (7%)	2 (6%)
Prior HCT (N, %)			
autoHCT	9 (20%)	4 (29%)	5 (16%)
alloHCT	3 (7%)	2 (14%)	1 (3%)
autoHCT and alloHCT	1 (2%)	0	(3%)
Baseline Albumin g/dL			
(median, range)	3.6 (2–4.5)	3.6 (2–4.5)	3.6 (1.9–4.3)
Baseline Creatinine mg/dL (median, range)	0.8 (0.5–2)	0.8 (0.6–1.5)	0.9 (0.5–2)
Baseline GFR mL/min/1.73m^2 (median, range)	88 (36–160)	94 (49–160)	88 (36–144)
POST CAR-T			
CAR construct (N, %)			
Axicabtagene ciloleucel	34 (74%)	12 (86%)	22 (69%)
Tisagenlecleucel	12 (26%)	2 (14%)	10 (31%)
Peak CRP mg/dL (median, range)	12 (0.3–36)	10 (0.4–35)	12 (0.3–36)
Peak Ferritin ng/ml (median, range)	788 (56–11443)	1665 (77–7918)	699 (56–11443)
Peak IL-6 pg/ml (median, range)	179 (7–23752)	204 (14–23752)	174 (7–15827)
Peak IL-10 pg/ml (median, range)	52 (9–2253)	59 (19–961)	50 (9–2253)
ICU admission (N, %)	12 (26%)	5 (36%)	7 (22%)
CRS total (N, %)	37 (80%)	10 (71%)	26 (81%)
Grade 1–2	31 (67%)	6 (43%)	24 (75%)
Grade 3–4	6 (13%)	4 (29%)	2 (6%)
ICANS (N, %)	21 (46%)	6 (43%)	15 (47%)
Grade 1–2	10 (22%)	3 (21%)	7 (22%)
Grade 3–4	11 (24%)	3 (21%)	8 (25%)
Tocilizumab (N, %)	12 (26%)	4 (29%)	8 (25%)
Dexamethasone (N, %)	14 (30%)	6 (43 %)	8 (25%)
Relapse or POD (N, %)	23 (50%)	*9/14 (64%)	14 (44%)

Abbreviations: CRS, Cytokine Release Syndrome; CRP, C-Reactive Protein; DLBCL, Diffuse Large B Cell Lymphoma; GFR, Glomerular Filtration Rate; ICU, Intensive Care Unit; ICANS, Immune Effector Cell Associated Neurological Syndrome; IL-6, Interleukin 6; IL-10, Interleukin 10; POD, Progression of Disease.

* Nine is the total number of patients with relapse or POD that had AKI. Three of these patients developed AKI before date of relapse/POD and six patients developed AKI after.