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Immunotherapy and Kidney Toxicities: Managing Immune-Related Adverse Events in Systemic Cancer Treatment

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Introduction

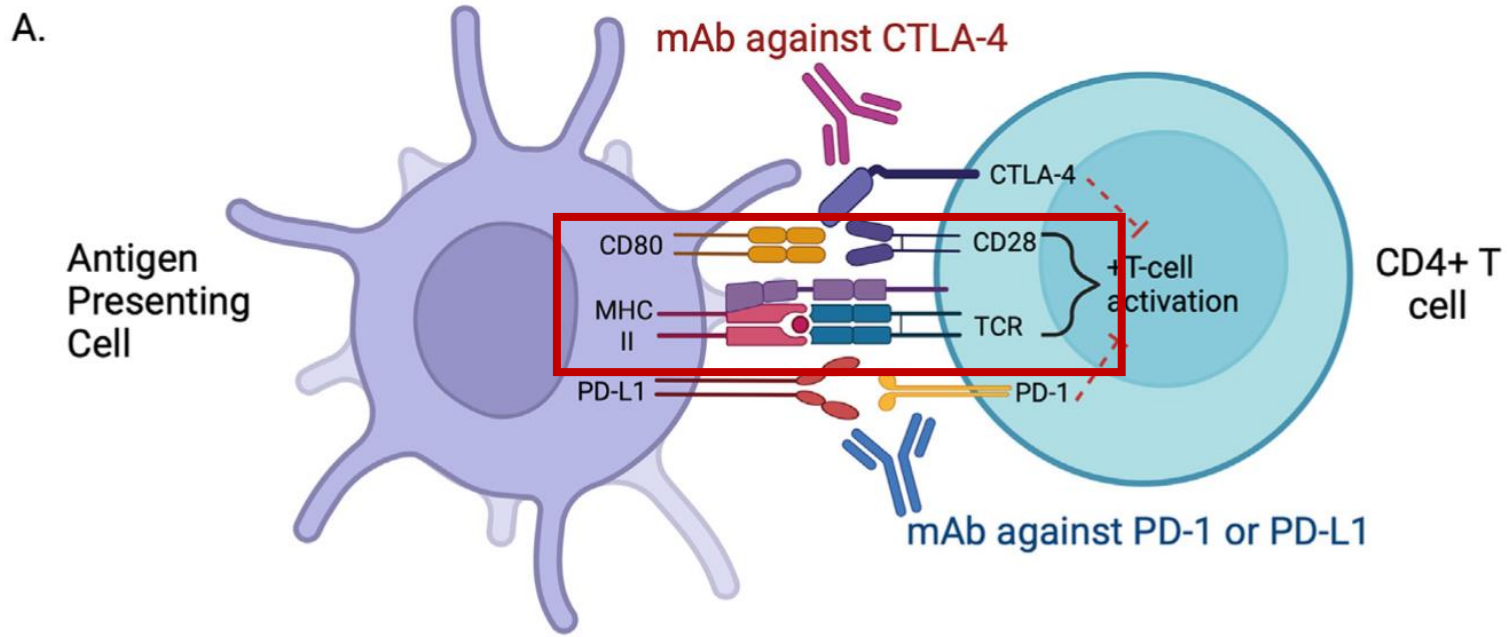
- In recent years, great breakthroughs have been made in tumor immunotherapy, which have significantly improved the survival rate of cancer patients.
- However, in clinical practice, traditional chemotherapy and radiotherapy remain the mainstay of treatment for most cancer types.
- To date, there have been various types of immunotherapy drugs, including tumor vaccines, cellular immunotherapy, immunomodulatory drugs targeting T cells, and immune checkpoint inhibitors (ICIs).

Cancer Immunotherapies

Table 1. List of approved cancer immunotherapies and their indications.

Immunotherapy	Class	Commercial Name	Indications
CAR T cells	Anti-CD19	Tisagenlecleucel (Kymriah®)	Acute lymphoblastic leukemia Diffuse large B cell lymphoma
		Axicabtagene ciloleucel (Yescarta®)	
		Lisocabtagene maraleucel (Breyanzi®)	
	Anti-BCMA	Idecabtagene vicleucel (Abecma®)	Multiple myeloma
Immune checkpoint inhibitors	Anti-PD1	Nivolumab (Opdivo®) Pembrolizumab (Keytruda®) Cemiplimab (Libtayo®)	Squamous head and neck cancer, lung cancer, melanoma, renal cell carcinoma, urothelial cancer, Hodgkin lymphoma and others.
	Anti-PDL1	Atezolizumab (Tecentriq®) Avelumab (Bavencio®) Durvalumab (Imfinzi®)	
	Anti-CTLA4	Ipilimumab (Yervoy®)	Melanoma, renal cell carcinoma
Bispecific antibodies	Anti-CD3/Anti-CD19	Blinatumomab (Blincynto®)	Acute lymphoblastic leukemia
	Anti-CD3/Anti-CD20	Mosunetuzumab (Lunsumio®)	Follicular lymphoma
BCG therapy	-	BCG (TheraCys® and TICE®)	Non-muscle invasive bladder cancer

T cells are normally activated by 2 signals



1. Antigen presenting cell displaying an antigen in the context of a self-MHC molecule to a T cell with receptor specificity for that antigen.
2. Binding of a costimulatory molecule (eg, CD28) on the T cell to its cognate ligand on the antigen presenting cell (eg, CD80/CD86).
3. Negative regulatory checkpoints such as CTLA-4 or PD-1 on the T cell interfere with co-stimulation or bind to PD-L1, respectively, to inactivate T cells.
4. Monoclonal antibodies against PD-1 and CTLA-4 prevent T-cell anergy against tumor cell antigen by preventing the inactivation of T cells.

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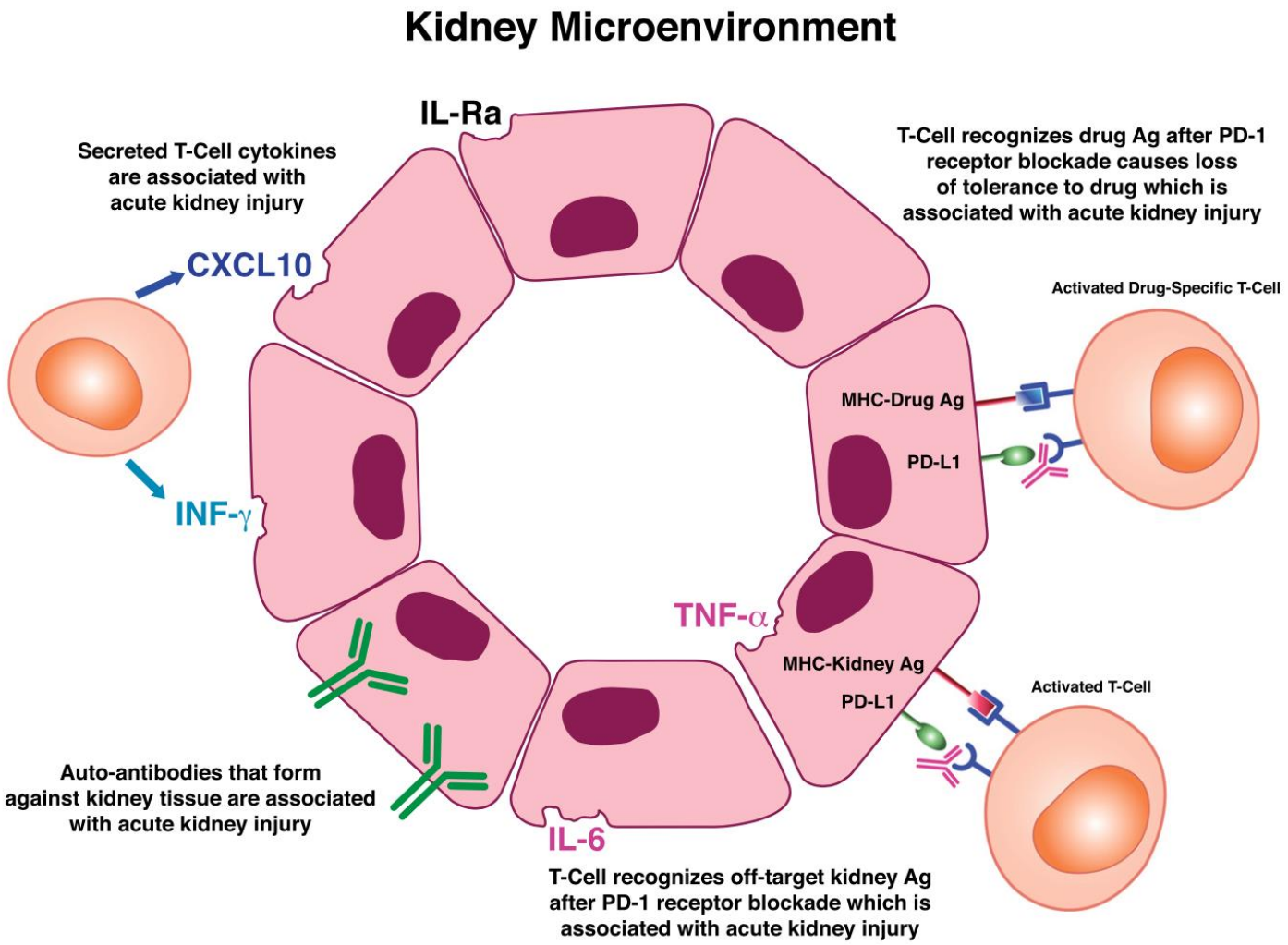
Immune-related adverse events (IrAEs)

- An irAE is defined as an inflammatory side effect attributed to a nonspecific increase in immune response with the use of CPIs.
- Authors have reported irAEs in almost every system in the body, with the most common involving the gastrointestinal tract (liver and colon), skin, endocrine system, and lungs, whereas hematological, neurological, cardiac, and renal irAEs are much less frequent.
- Although the kidneys are less involved, nephrotoxicity occurs in up to 2% to 5%, with a higher risk with combination ICIs. While initial studies noted a small incidence of AKI (2–3%), recent data suggest a higher incidence rate closer to 13–29% with ICI.

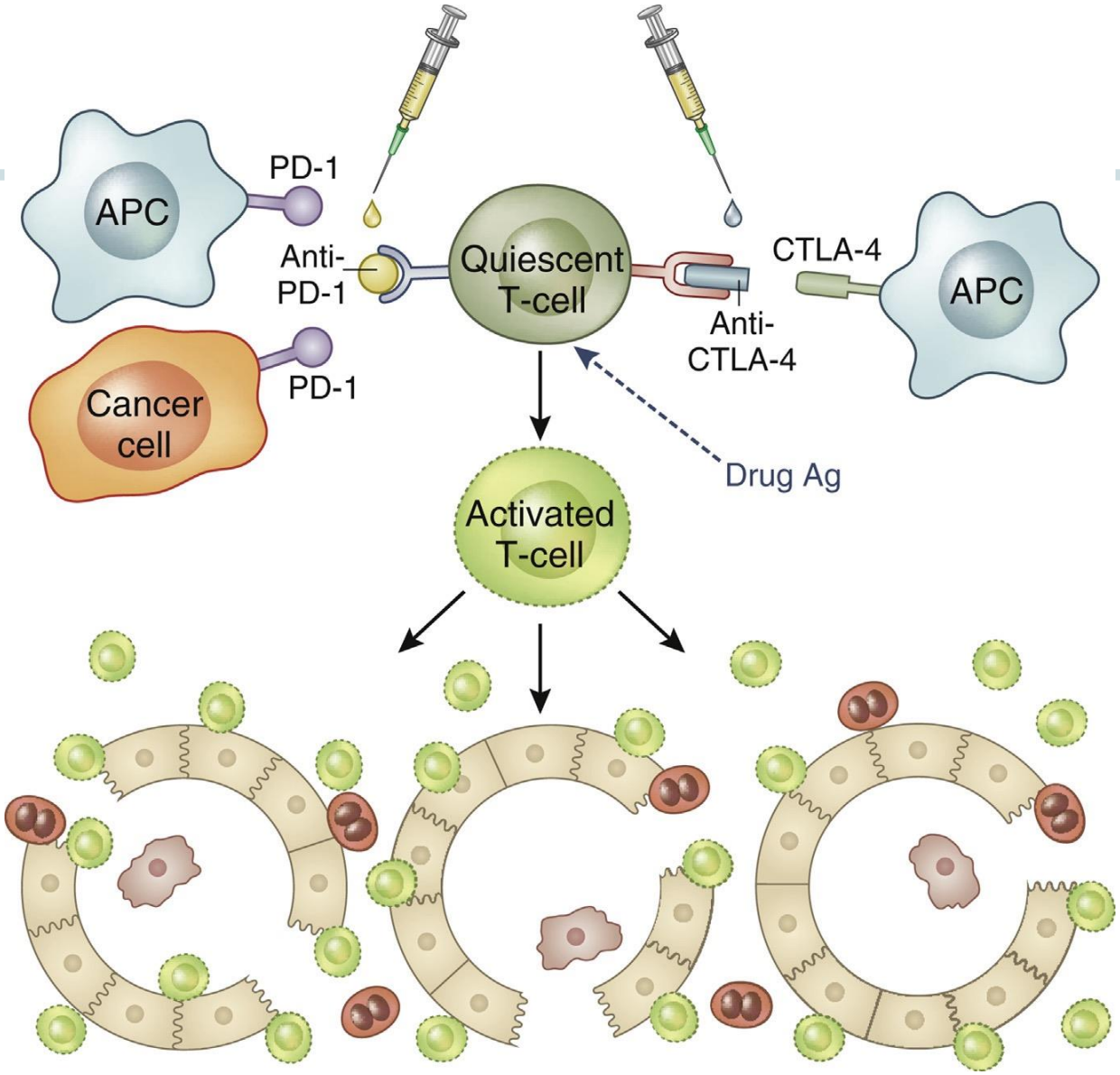
Proposed mechanisms of irAEs



- Autoreactive T cells
- Checkpoint receptors expressed on nontumor tissue
- Cross-presentation of antigens
- Loss of tolerance leading to reactivation of latent antibodies
- T-reg depletion
- Cytokines (Proinflammatory cytokines such as IL-17)
- Autoantibody formation
- A genetic predisposition for irAE development
- Environmental factors

Pathology of ICI-Related AKI

- Acute interstitial nephritis (AIN) is the most common reported histological manifestation of ICIs, although acute tubular injury has also been associated with ICI-induced AKI.
- Interstitial infiltrates are predominantly lymphocytes with the presence of varying degrees of plasma cells and eosinophils.
- Some cases of ICI-associated AIN also have granulomas.



A potential complication of this immune activation is the development of autoimmunity and reactivation of memory T-cells previously primed by exogenous drug exposure.

This can result in infiltration of the kidneys with inflammatory cells and development of acute tubulointerstitial nephritis (ATIN).

Kidney International (2016)

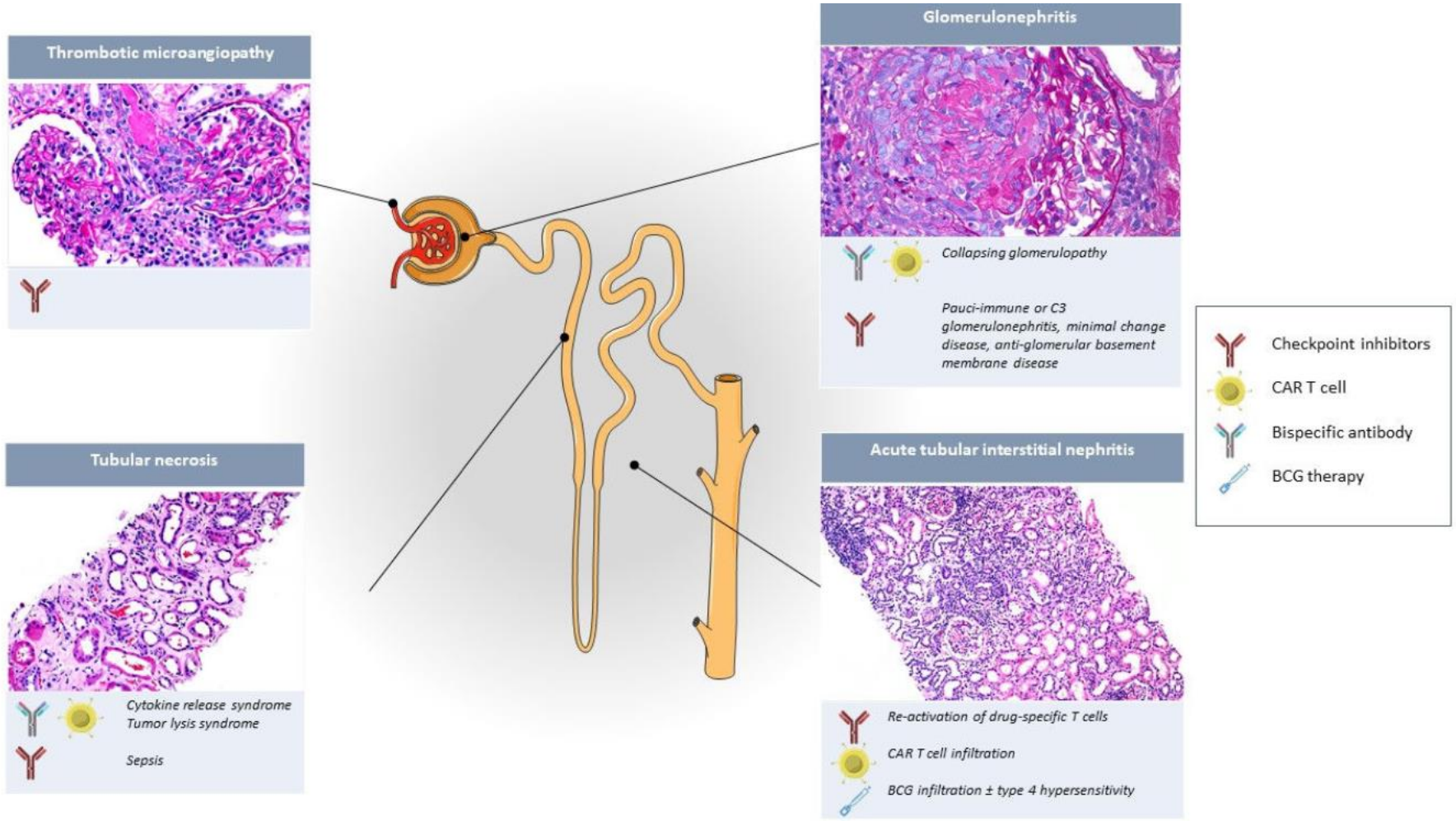


Figure 1. Acute kidney injury causes in cancer immunotherapy recipients and their site of injury in the nephron. We are grateful to Arkana Laboratories (Little Rock, AR, USA) for authorization to use renal pathology images.

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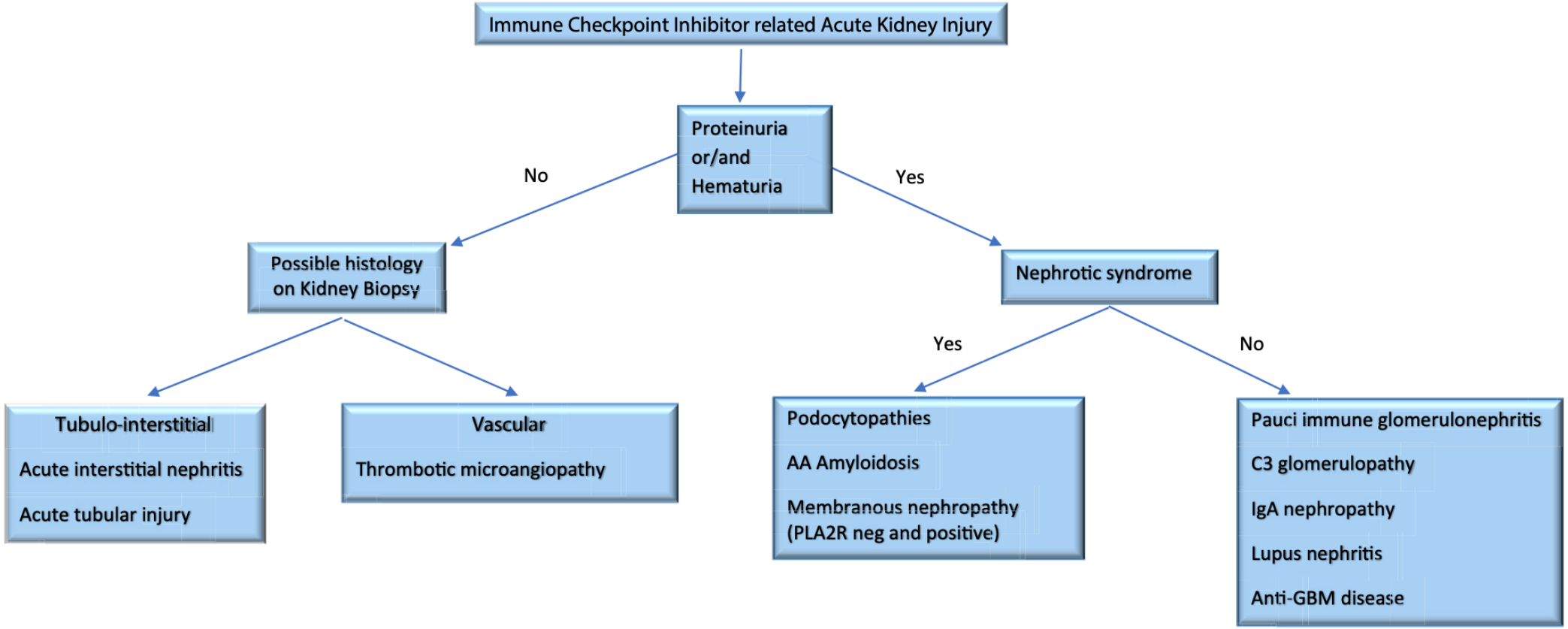

Figure 1. Various histological features seen in patients with immune checkpoint inhibitor–related acute kidney injury.

Adv Chronic Kidney Dis. 2021

Table 2. Acute kidney injury associated with approved cancer immunotherapy.

Immunotherapy	AKI Incidence	AKI Mechanisms	Treatment
CAR T cells	18.6%	Cytokine release syndrome	Anti-IL-6 (siltuximab), IL-6R (tocilizumab) and corticosteroids
		CAR T cell infiltration	-
		Tumor lysis syndrome	IV fluids, allopurinol, rasburicase
Immune checkpoint inhibitors	1–5%	Acute tubular interstitial nephritis	Corticosteroids ± Second-line immunosuppressants
		Acute tubular injury	
		Glomerulonephritis/Minimal change disease	
Bispecific antibodies	1%	Cytokine release syndrome	Anti-IL-6 (siltuximab), IL-6R (tocilizumab) and corticosteroids
		Tumor lysis syndrome	IV fluids, allopurinol, rasburicase
BCG therapy	2–3%	Acute interstitial nephritis ± granuloma	Anti-tuberculous tritherapy + corticosteroids

AKI: acute kidney injury, CAR: chimeric antigen receptor.

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› Kidney Int Rep. 2020 Oct 16;6(1):66-77. doi: 10.1016/j.ekir.2020.10.002. eCollection 2021 Jan.

A Systematic Review of Immune Checkpoint Inhibitor–Associated Glomerular Disease

Abhijat Kitchlu [1], Kenar D Jhaveri [2 3], Shikha Wadhwani [4], Priya Deshpande [5], Ziv Harel [6], Teruko Kishibe [7], Kammi Henriksen [8], Rimda Wanchoo [2 3]

Conclusion: Multiple forms of ICI-associated glomerular disease have been described. Pauci-immune GN, podocytopathies, and C3GN are the most frequently reported lesions. ICI-associated glomerular disease may be associated with poor kidney and mortality outcomes. Oncologists and nephrologists must be aware of glomerular pathologies associated with ICIs and consider obtaining a kidney biopsy specimen when features atypical for AIN are present.

Table 2. Risk Factors for Immune Checkpoint Inhibitor–Related Acute Kidney Injury

Patient-Specific Risk Factors	Therapy-Specific Risk Factors
Low baseline eGFR	Combination CTLA-4 and PD-1/PDL-1 blockade
Other organ irAE	Concurrent use of PPI, NSAIDs, or antibiotics
Hypertension	
Liver disease	

Table 2. Renal effects of cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antagonists and the programmed death-1 (PD-1) inhibitors

Agents	CTLA-4 antagonists (ipilimumab)	PD-1 inhibitors (nivolumab and pembrolizumab)
Mechanistic differences	1. Limits T-cell response early in the immune response in lymphoid tissues 2. Expressed by T cells 3. CTLA-4 ligands expressed by antigen-presenting cells	1. Limits T-cell response later in the immune response, primarily in peripheral tissues 2. Expressed by T cells and other immune cells 3. PD-1 ligands expressed by antigen-presenting cells and other immune cells and can be inducibly expressed in non-immune cells including tumor cells
Cancer	Metastatic melanoma**, lung cancer*, renal cell cancer*, prostate cancer*, cervical cancer*, colorectal cancer*, pancreatic cancer*, ovarian cancer*, urothelial cancer*	Metastatic melanoma**, non small cell lung cancer **, gastric cancer*, head and neck cancer*, urothelial cancer*, colorectal cancer*, gliobastoma*, pancreatic cancer*, hematologic malignancies*
Onset of AIN	AIN appears 6–12 weeks after initiation of therapy, with longest duration being 26 weeks. Late onset associated with more severe AKI requiring renal replacement therapy	AIN appears 3–12 months after initiation of therapy
Glomerular findings	Podocytopathy (membranous nephropathy and minimal change disease) and thrombotic microangiopathy reported	No cases of podocytopathy reported
Gender	No gender preferences	No gender preferences
Electrolyte disorders	Hyponatremia cases related to hypophysitis (secondary adrenal insufficiency)	Hyponatremia is rare
Transplant	In renal transplant patients, 2 cases reported no rejection when given as a solo agent	When given– patients had rejection especially following use with CTLA-4 inhibitors (4 cases reported), likely due to loss of tolerance

Am J Nephrol 2017

Diagnosis of ICI-Related AKI

- The cause of AKI in patients with cancer is often difficult to determine.
- For example, patients receiving ICIs are also exposed to other nephrotoxic chemotherapies such as cisplatin, or bevacizumab.
- In addition, they also struggle with hemodynamic insults such as hypotension, volume depletion, and infections.
- Differentiating AKI that is due to an ICI-related irAE or another cause of AKI can be a diagnostic challenge.

Diagnosis of ICI-Related AKI

- Overdiagnosis of irAEs has undesirable consequences such as inappropriate withholding or interruption of cancer therapy and increased risk for the complications of corticosteroid exposure.
- Tissue diagnosis with kidney biopsy is ideal in differentiating an AIN or other renal irAE from other causes of AKI.

Diagnosis and management of ICI-Related AKI

- The National Comprehensive Cancer Network (NCCN) does not recommend kidney biopsy unless Grade 2-3 or higher AKI develops, and the American Society of Oncology (ASCO) recommends proceeding with corticosteroids without kidney biopsy.
- There are select situations such as a solitary kidney, need for ongoing anticoagulation, or patient refusal where kidney biopsy cannot be performed safely.

Diagnosis and management of ICI-Related AKI

- Patients with non-kidney irAEs and AKI may not initially require kidney biopsy as corticosteroid therapy is indicated for their non-kidney irAE.
- Outside of these, kidney biopsy would be quite helpful in guiding management as clinical symptoms and laboratory tests including urinalysis/urine microscopy are insufficient to differentiate many of the causes of ICI-associated AKI.

Table 4. American society of clinical oncology grading and treatment of renal immune-related adverse events (adapted from [66]).

	Grade 1	Grade 2	Grade 3	Grade 4
Diagnosis	Creatinine level increase of >0.3 mg/dL.; creatinine 1.5–2× above baseline	Creatinine 2–3× above baseline	Creatinine > 3 × baseline or > 4.0 mg/dL.; hospitalization indicated	Life-threatening consequences; dialysis indicated; creatinine 6× above baseline
Management *	Consider temporarily holding ICI	Hold ICI temporarily. Administer corticosteroids (0.5–1 mg/kg/day prednisone equivalents). If worsening or no improvement after 1 week, increase to 1–2 mg/kg/day and permanently discontinue ICI.	Permanently discontinue ICI Administer corticosteroids (initial dose of 1–2 mg/kg/d prednisone or equivalent). If elevations persist or worsen, consider additional immunosuppression (e.g., infliximab, azathioprine, cyclophosphamide (monthly), cyclosporine, and mycophenolate).	

* Non-specific management include exclusion of potential alternative etiologies, fluid status optimization and nephroprotective therapy.

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Follow up

	Management
G1	If improved to baseline, resume routine creatinine monitoring
G2	If improved to G1, taper corticosteroids over at least 3 weeks before resuming treatment with routine creatinine monitoring If elevations persist > 7 days or worsen and no other cause found, treat as G3
G3	If improved to G1, taper corticosteroids over at least 4 weeks If elevations persist > 3-5 days or worsen, consider additional immunosuppression (eg, mycophenolate)
G4	If improved to G1, taper corticosteroids over at least 4 weeks If elevations persist > 2-3 days or worsen, consider additional immunosuppression (eg, mycophenolate)

J Clin Oncol. 2018

Management of renal irAEs in patients treated with ICPis

- For any suspected immune mediated adverse reactions, exclude other causes
- Monitor patients for elevated serum creatinine prior to every dose
- Routine urinalysis is not necessary, other than to rule out UTIs
- If no potential alternative cause of AKI identified, one should forego biopsy and proceed directly with immunosuppressive therapy
- Swift treatment of autoimmune component is important

Biomarkers, Clinical Features and Rechallenge for Immune Checkpoint Inhibitor Renal Immune-Related Adverse Events

ISN INTERNATIONAL SOCIETY OF NEPHROLOGY

Methods

Single center
Retrospective

Treated with ICI
2014 to 2020

ICI-AKI
Biopsy confirmed acute interstitial nephritis (AIN) or AKI attributed to ICI

non-ICI-AKI
Biopsy confirmed or not treated with steroids & no progression with ICI resumption

ICI, Immune checkpoint inhibitors

Results

Kidney function & biomarkers	Creatinine (mg/dL)	CRP (mg/L)	uRBP/Cr (mcg/g)
n=37 ICI-AKI	2.0 [IQR 1.7, 2.9]	54.0 [IQR 33.7, 90.0]	1,927 [IQR 1,174, 46,522]
	p<0.05	*p<0.05*	*p<0.05*
n=13 non-ICI-AKI	1.5 [IQR 1.3, 1.6]	3.5 [IQR 3.0, 7.9]	233 [IQR 127, 989]

ICI-AKI outcomes

39%
Complete recovery at 3 months after ICI withdrawal

43%
Rechallenge with ICI

19%
Recurrence of AKI after rechallenge

KI REPORTS
Kidney International Reports

Isik et al, 2021

Visual abstract by:
Omar Taco, MD Msc
@Errantnephron

Conclusion: These biomarkers could assist with discriminating ICI-AKI from other causes and may also help aid clinical decision-making related to both management and recurrence. We also described distinguishing clinical characteristics of patients with ICI-AKI, which may help with the diagnosis and possible prevention of ICI-AKI.

Treatment and Outcomes of ICI-Related AKI

- In general, permanent discontinuation of ICPis is recommended with grade 4 toxicities, with the exception of endocrinopathies that have been controlled by hormone replacement.
- Pulse corticosteroids are usually not necessary but may be used if there is concurrent second organ system involvement or if the patient is deteriorating rapidly.
- Importantly, medications associated with AIN (proton pump inhibitors, nonsteroidal anti-inflammatory drugs, antibiotics) should be discontinued, if possible, as they may be the inciting antigen.

ICIs in Kidney Transplantation

- Several cases of kidney injury have now been reported when Ipilimumab, Nivolumab and Pembrolizumab were used in kidney transplant patients.
- Although Lipson et al. had initially reported the successful administration of ipilimumab to 2 kidney transplantation patients with metastatic melanoma without any signs of rejection, they recently reported a case of tumor regression but allograft rejection after administration of pembrolizumab.

ICIs in Kidney Transplantation

- In addition, 3 cases of rejection were reported with the use of nivolumab in kidney transplant patients with melanoma.
- Based on the 6 cases, it appears that PD-1 inhibitors could be more prone to causing rejection in the transplanted kidney compared to CTLA-4 antagonists, especially when the patients have received anti CTLA-4 agents prior to PD-1 inhibitor treatment.

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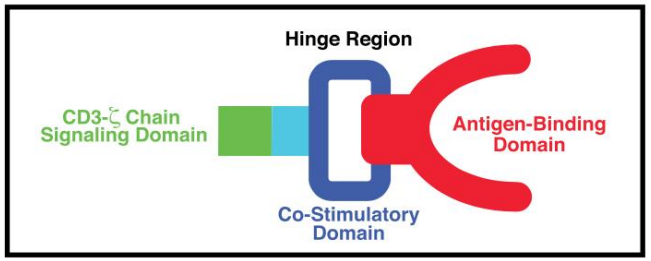
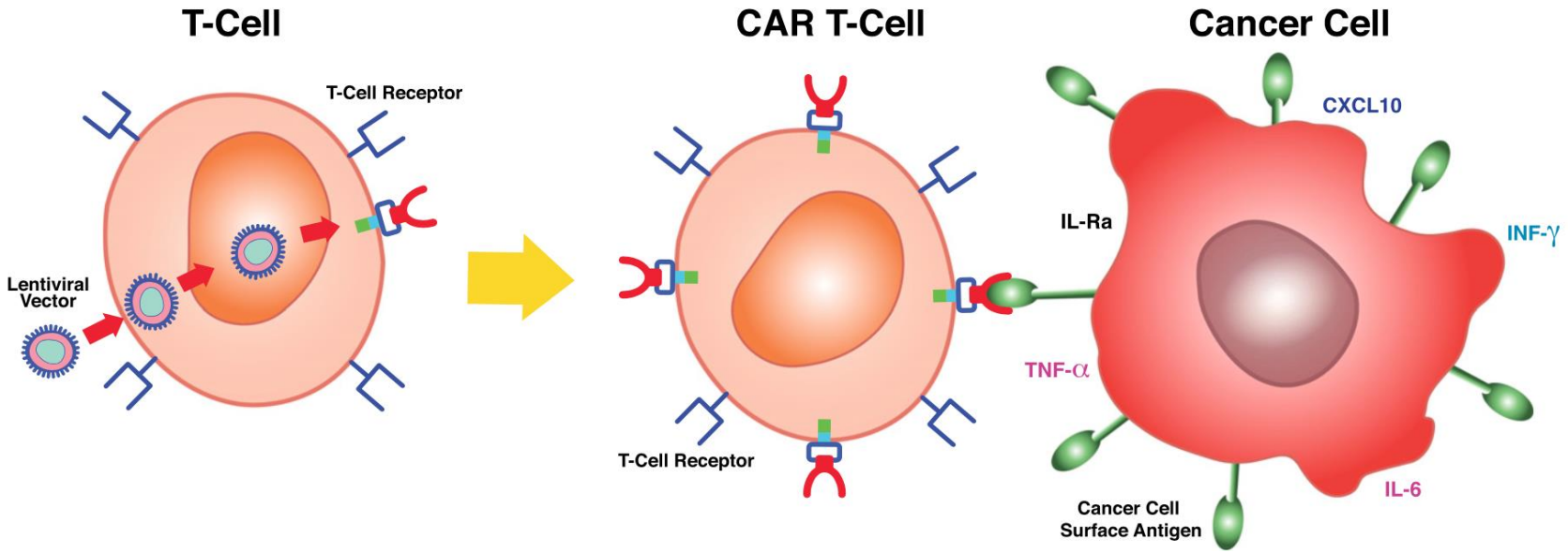
Chimeric Antigen Receptor T Cells: CAR T cell therapy represents a novel use of immunotherapy to treat various cancers.





T cells harvested from patients are genetically modified using lentiviral vector to place an antigen binding domain (recognizes tumor antigen), which is linked to an intracellular costimulatory domain (CD28 or 4–1BB) and CD3-z signaling domain to **amplify the immune response against tumor cells**.

J Am Soc Nephrol 29: 2039–2052, 2018

Table 4. Chimeric antigen receptor T cell–associated nephrotoxicity

Potential Nephrotoxicity
AKI
Prerenal AKI/acute tubular injury
Cytokine release syndrome with capillary leak and hypotension
Hemophagocytic lymphohistiocytosis with inflammation
Acute cardiac dysfunction with reduced cardiac output and hypotension
Intravascular volume depletion from fever, N/V, and diarrhea
Tumor lysis syndrome
Electrolyte disorders
Hypokalemia, hypophosphatemia, and hyponatremia
Prevention/treatment of toxicity
Chemotherapy to reduce tumor burden
Corticosteroids to reduce inflammatory response
Supportive care for hypotension with vasopressors, iv fluids, and oxygen
IL-6 blockade with tocilizumab for cytokine release syndrome and hemophagocytic lymphohistiocytosis

N/V, nausea and vomiting.

J Am Soc Nephrol 29: 2039–2052, 2018

Cytokine Release Syndrome (CRS)

- Effective targeted cancer killing by CAR-T cells carries risk for systemic toxicity, which includes potential nephrotoxicity.
- Cytokine release syndrome (CRS) is a systemic inflammatory response that occurs on activation of CAR-T cells and destruction of tumor cells.
- In this setting, IL-6, IL-10, and IFN-γ as well as inflammatory markers C-reactive protein and ferritin are produced.
- This syndrome manifests with high fever, myalgias, and tachycardia within 1–14 days of CAR T cell infusion and can progress to vasodilatory shock and capillary leak with multiorgan failure.

Cytokine Release Syndrome (CRS)

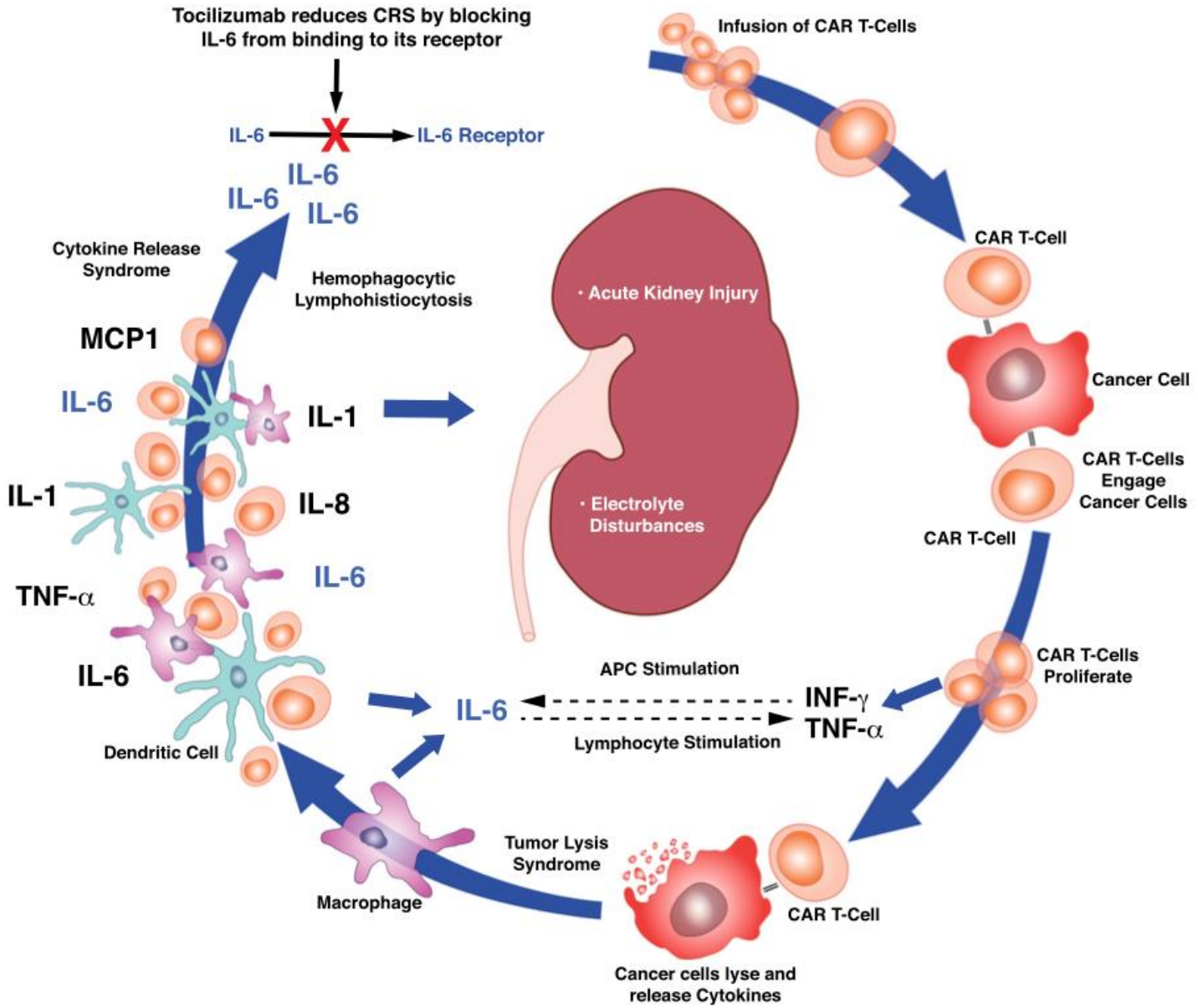
- Increased lactate dehydrogenase and hyperuricemia were observed after approximately 22 days in initial clinical trials.
- A subset of patients with CRS also developed hepatosplenomegaly and liver dysfunction, increased ferritin levels, and decreased fibrinogen levels with coagulopathy.
- These clinical findings coupled with elevations of IL-6, IL-10, and IFN-g suggest a secondary form of hemophagocytic lymphohistiocytosis (HLH).

Cytokine Release Syndrome (CRS)

- Rhabdomyolysis may develop, whereas rapid, effective cancer killing may also cause tumor lysis syndrome (TLS).
- TLS has been described in patients with ALL, CLL, and other hematologic malignancies after CAR-T cell therapy.
- Adverse kidney effects include AKI and various electrolyte abnormalities.
- Lack of biopsy data likely acute tubular injury

Prevention/treatment strategies

- Prevention includes pretreatment with chemotherapy to decrease the tumor burden and steroids to dampen inflammation.
- When indicated, intravenous fluid resuscitation and vasopressors to maintain systemic hemodynamics and renal perfusion are helpful.
- Tocilizumab, a monoclonal anti–IL-6 receptor antibody, is indicated for severe grade 3/4 CRS and catecholamine-dependent vasodilatory shock to improve BP and prevent multiorgan failure.
- Additionally, corticosteroids can be used in patients with only partial response to tocilizumab or who develop recurrent symptoms.



IFN-g and TNF-a stimulate macrophage activation. CAR T cells also cause lysis of cancer cells

Tocilizumab blocks IL-6 from binding to its receptor, reducing the effects of cytokine release syndrome (CRS).

J Am Soc Nephrol 29: 2039–2052, 2018

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BCG Therapy

- Intravesical BCG therapy has been used since 1976 for non- muscle invasive bladder cancer and represents one of the first immunotherapeutic intervention in the modern era of cancer treatment.
- Acute kidney injury complicates around 40% of BCGitis and usually presents with acute interstitial nephritis, with or without granuloma .
- BCG can disseminate and cause renal infection, but it is assumed that BCGitis and granulomas are more often caused by type 4 hypersensitivity reactions, as evidenced by the lack of mycobacterial isolation in urine culture or kidney biopsy.
- Anecdotal reports of mesangial glomerulonephritis, membranous nephropathy and hemolytic uremic syndrome have also been published, possibly in relation with an autoimmune response to BCG.

Immunotherapy Related Acute Kidney Injury

ACKD
Advances in Chronic Kidney Disease

Immunotherapy	Clinical features	Histology of AKI (acute kidney injury)
Immune checkpoint inhibitors CTLA 4 inhibitors PD-1 inhibitors PDL1 inhibitors	↑S.Creatinine Nephritic / Nephrotic syndrome Electrolyte derangements	AIN (Acute interstitial nephritis) Glomerular diseases
CAR-T cell therapy Tisagenlecleucel Axicabtagene ciloleucel	Cytokine release syndrome Macrophage activation syndrome	Likely ATI (acute tubular injury)
Pro-inflammatory cytokines High dose IL-2 INF-alpha	Hypotension, vascular leak Vascular injury	Acute tubular injury

Reference: S.Manohar et al.ACKD.2021
VA by Mythri Shankar.,MD.,DNB

@nephromythri

Conclusion: The incidence of ICI-related AKI is ~2-4% with more than 80% cases being from AIN. CAR-T cell therapy is growing in importance as an effective immunotherapy for cancer and causes AKI, primarily acute tubular injury and prerenal azotemia.

Adv Chronic Kidney Dis. 2021;28(5):429-437

Summary

- Checkpoint inhibitor-related renal toxicity is an immune-mediated process.
- While initial studies noted a small incidence of AKI (2–3%), recent data suggest a higher incidence rate closer to 13–29% with ICI.
- AIN is the most common biopsy finding reported.
- Ipilimumab has been associated with AIN and podocytopathies such as lupus like nephritis, minimal change disease, and TMA.
- Hyponatremia related to hypophysitis has been reported as well.
- The time of onset is 2–3 months in a majority of the cases.
- Most cases are responsive to steroids if identified early in the course of renal injury.
- Few patients may remain dialysis dependent.

Summary

- The renal injury related to anti PD-1 therapy is AIN.
- It usually appears later, 3–10 months into treatment.
- Steroids are also effective in the treatment of this immune-mediated adverse effect.
- When both CTLA-4 and PD-1 inhibitor drugs are combined, granulomatous or diffuse AIN can be found on kidney biopsy with partial response to steroids.
- While biopsy-proven interstitial nephritis related to these drugs is a complication associated with some degree of morbidity, one must keep in mind common causes of AKI in cancer patients such as volume depletion, dehydration, and sepsis.


Thank You
for
listening