

# Nephrotoxicity in Bispecific Antibodies Recipients: Focus on T-Cell-Engaging Bispecific Antibodies

Xiaoli Wen, Gaosi Xu

Department of Nephrology, The Second Affiliated Hospital, Jiangxi Medical College, Nanchang University, Nanchang City, Jiangxi Province, People's Republic of China

Correspondence: Gaosi Xu, The Second Affiliated Hospital, Jiangxi Medical College, Nanchang University, No. 1, Minde Road, Donghu District, Nanchang, 330006, People's Republic of China, Tel/Fax +860791 86312770, Email [gaosixu@163.com](mailto:gaosixu@163.com)

**Abstract:** Recently, bispecific antibodies (BsAbs) are evolving the landscape of cancer treatment and have significantly improved the outcomes of relapsed or refractory cancer patients. As increasing BsAbs entered clinical practice, specific toxicities have emerged, and renal side-effects have been described. However, there are a lack of studies analyzing the nephrotoxicity in the anti-cancer BsAbs recipients systematically. In this review, we demonstrate the etiologies, mechanisms, other risk factors and treatment options of kidney injury in the BsAbs recipients to provide a more comprehensive insight into the nephrotoxicity post-BsAbs therapy. Significantly, due to the limited clinical trial data on each subject, we mainly conclude the related etiologies, mechanisms, and risk factors of nephrotoxicity that occur in T-cell-engaging BsAbs recipients. Nephrotoxicity associated with non-T-cell BsAbs may be associated with adverse nephrotoxicity of related monoclonal antibodies to two specific antigens. The aim of this paper is to provide nephrologists and oncologists with theoretical knowledge to provide better medical management for recipients who receive BsAbs, especially T-cell-engaging BsAbs treatment.

**Keywords:** bispecific antibodies, nephrotoxicity, acute kidney injury, cytokine release syndrome, tumor lysis syndrome, cancer

## Introduction

Monoclonal antibodies (mAbs) were widely used in the neoplastic diseases and have achieved favorable treatment outcomes since Köhler and Milstein first developed a method to produce monoclonal antibodies via a hybridoma technique.<sup>1</sup> However, the treatment effect has not been as effective as the first expected in the mAbs recipient who experiences drug resistance, tumor relapse, and treatment-related adverse events. The presence of bispecific antibodies (BsAbs) overcomes the limitations of conventional mAbs and enhance anti-cancer efficacy. In the last few decades, the rapid development of T-cell immunotherapy greatly promotes the application of novel T-cell-engaging BsAbs in cancer patients.<sup>2</sup>

BsAbs simultaneously target two different epitopes of an antigen, or two different antigens by a single antibody-like molecule, therefore having synergistic or emergent therapeutic effects and finally improving the antitumor abilities. T-cell-engaging BsAbs remain one of the specific BsAbs, which target a tumor associated antigen with one arm, and simultaneously bind to the CD3 subunit within the T-cell receptor (TCR) complex with the other arm.<sup>3</sup> After linking two different antigens, the BsAbs activate multiple immune pathways to eliminate the tumor cells.<sup>4</sup> A bispecific antibody can be seen as the combination therapy of two drugs merging into one superior entity with fewer side-effects. Compared to chimeric antigen receptor (CAR)-T-cell therapy, T-cell-engaging BsAbs enable the triggering of T-cell signaling and precisely target the killing of tumor cells as a result, providing more favorable efficacy and safety.<sup>5</sup> As these benefits are acknowledged, increasing BsAbs are in preclinical studies or clinical trial phases and approved for therapeutic applications of cancer.

However, although the presence of BsAbs changes the landscape of cancer therapy, there are some treatment-associated adverse events including cytokine release syndrome (CRS), neurological symptoms and so on.<sup>2</sup> Of note, while rarely reported, nephrotoxicity such as acute kidney injury (AKI), proteinuria, and creatinine increase were recorded and induced a fatal

outcome in some clinical trials of BsAbs.<sup>6,7</sup> Nephrotoxicity is closely associated with the dosage of antitumor drugs and can significantly affect the future quality-of-life of cancer patients.

In this review, we summarize BsAbs-engagement nephrotoxicity that has been reported in clinical trials of bispecific antibodies and describe the causes of nephrotoxicity in recipients of BsAbs immunotherapy<sup>6–19</sup> (Table 1). Physicians must strive to provide the best standard of care and improve the prognosis of these patients.

## Nephrotoxicity of T-Cell-Engaging BsAbs

T-cell-engaging BsAbs are engineered, artificial antibodies that consist of two single-chain variable arms which direct against both the TCR complex and tumor associated antigen, respectively. As a subunit of the TCR, CD3 is the most common epitope in the T cell's surface.<sup>20</sup> Up to now, the common T-cell-engaging BsAbs include Blinatumomab (CD19 x CD3), Mosunetuzumab/Odronektamab (CD20 x CD3), Ertumaxomab (Her-2 x CD3), Teclistamab (BCMA x CD3), and so on.

After simultaneously linking the tumor-associated antigen and CD3, BsAbs recruit immune cells close to the tumor, leading to the formation of an immune synapse. The formed synapse further induces activation and release of perforins and granzymes by activating immune activity of T-cell, and finally results in T-cell-dependent cytotoxic lysis of the tumor cell.<sup>21–23</sup> Additionally, immune synapse can drive T-cell proliferation and expansion via epitope spreading and cellular memory.<sup>24</sup> Cytokines such as interferon (IFN)- $\gamma$  released from activated immune T-cells stimulate macrophages to release inflammatory mediators such as interleukin (IL)-10, IL-6, and tumor necrosis factor (TNF)- $\alpha$  which function in turn by activating upper-stream T cells. It is well-acknowledged that activation of T-cells and release of cytokines are prerequisites for T-cell-engaging BsAbs to play a role in tumor cell killing<sup>25,26</sup> (Figure 1).

However, the reactions that accompany T-cell activation and the role of cytokines in the body are not specific, which means normal tissues can also be attacked and treatment-engagement adverse events may occur. As a vast number of T-cell-engaging BsAbs enter clinical or pre-clinical trials, a spectrum of specific toxicities also catch peoples eyes. CRS and immune effector cell associated neurotoxicity syndrome (ICANS) are the most common adverse events resulting from excessive activation of immune cells or non-immune cells. Non-specific toxicities from on-target effects can also occur, such as sepsis and TLS. These complications put BsAbs recipients at a degree of risk of nephrotoxicity including proteinuria, creatinine increased, and AKI. Although reports of nephrotoxicity are rare, just one report describing the adverse event of AKI and demonstrating the incidence of 1%,<sup>27</sup> the outcomes may be irreversible and fatal to patients. CRS and TLS are the most essential mechanisms of AKI in patients receiving T-cell-engaging BsAbs. Other factors including fluid loss, such as vomiting, diarrhea, and fever, and infection can also be considered as risk factors of nephrotoxicity in cancer patients receiving BsAbs (Figure 2).

## Cytokine Release Syndrome

CRS is a common complication of T-cell-engaging BsAbs treatment.<sup>28–30</sup> The most common symptoms of BsAbs-induced CRS are fever, chills, headache, dizziness, and fatigue.<sup>30</sup> The clinical features of this syndrome are associated with high levels of inflammatory markers and cytokines, including TNF- $\alpha$ , IFN- $\gamma$ , IL-2, IL-6, and IL-10,<sup>31</sup> which can induce activation of bystander immune and non-immune cells as monocytes/macrophages, dendritic cells, NK cell, T-cell, and endothelial cells, great importantly macrophages.<sup>32</sup> Activated macrophages produce excessive amounts of additional cytokines such as IL-6, TNF- $\alpha$ , and IL-10. In return, these cytokines enhance the function of T-cells and other immune cells to kill cancer cells. Nevertheless, a cascade of amplification of the cytokines may occur and lead to a cytokine storm if beyond the body's compensatory capacity.<sup>33</sup>

In the clinical trial of APVO436 (CD123 x CD3), one patient with grade 2 CRS subsequently developed acute kidney failure (grade 5) with fatal outcome.<sup>6</sup> Similarly, in the Phase I study of Ertumaxomab (Her-2 x CD3), almost all patients experienced CRS in any grade and one of the patients who underwent a systemic inflammatory response of AKI, which is fully reversible.<sup>7</sup> In another clinical trial of Odronektamab (CD20 x CD3), creatine increased in 30/145 (20.7%) patients, 20.0% in grade 1–2 and 0.7% in grade 3, accompanying the presence of CRS of 61.4%.<sup>10</sup> Additionally, proteinuria was detected in four out of the 41 patients in the Phase II study of Catumaxomab (EpCAM x CD3), 7.3% in the proteinuria of grade 1–2, and 2.4% in grade 3.<sup>9</sup> We also found that clinical studies with nephrotoxic adverse events tended to report higher incidence of CRS or severe CRS (grade 3 or higher). Although there is no more detailed and precise description of

**Table 1** Summary of published data of cytokine release syndrome (CRS), nephrotoxicity and other risks of nephrotoxicity in the clinical trials of bispecific antibodies (BsAbs) approved for use or not

NO	Drug Name	Target Antigen	Author	Clinical Trial Stage	Target Disease	% /Incidence of CRS	% /Incidence of Nephrotoxicity	Relevant Manifestation	Other Risk of Nephrotoxicity
1	APVO436	CD123 x CD3	Fatih M. Uckun	Phase I	R/R Acute myeloid leukemia or myelodysplastic syndrome	CRS: 10/46 (21.7%)	AKI: 2/46 (4.3%) proteinuria: 1/46 (2.2%)	8.7% CRS in grade 3–4 One AKI in grade 3 and one in grade 5	TLS (grade 3): 1/46 (2.2%), sepsis (grade 3): 1/46 (2.2%), shock (grade 3): 1/46 (2.2%)
2	Ertumaxomab	Her-2 x CD3	Philipp Kiewe	Phase I	Metastatic breast cancer	CRS: almost all patients	AKI: 1/17 (5.9%)	Fever (94.1%), rigors (47.1%), headache (35.3%), nausea (29.4%), vomiting (29.4%), most of CRS are mild and transient	Systolic hypertension: 2/17 (11.8%)
3	Catumaxomab	EpCAM x CD3	Morten Mau-Sørensen	Phase I	Epithelial cancers with known EpCAM expression	Many have CRRS	Creatinine increased: 4/16 (25.0%)	CRRS including chills, pyrexia, vomiting, nausea. creatinine increased: 1/5 (20.0%) in the 2 µg cohort and 3/7 (42.9%) in the 7 µg cohort	Hypertension: 6/16 (37.5%), hypotension: 6/16 (37.5%) diarrhea: 4/16 (25%), vomiting: 10/16 (62.5%)
4	Catumaxomab	EpCAM x CD3	J Sehouli	Phase II	Epithelial ovarian cancer	Pyrexia: 30/41 (73%), nausea: 21/41 (51.2%)	Proteinuria: 4/41 (9.8%)	3 (7.3%) proteinuria in grade 1–2, 1 (2.4%) in grade 3. No one developed severe renal insufficiency	Infection: 8/41 (19.5%), diarrhea: 13/41 (31.7%), vomiting: 19/41 (46.3%)
5	Odronextamab	CD20 x CD3	Rajat Bannerji	Phase I	CD20-positive R/R B-cell malignancies	CRS: 89/145 (61.4%)	Creatinine increased: 30/145 (20.7%)	20.0% creatinine increased in grade 1–2 0.7% in grade 3	Hypotension: 40/145 (27.6%), infections: 71/145 (49.0%), vomiting: 30/145 (20.7%), diarrhea: 29/145 (20.0%) sepsis: 2/145 (1.4%), grade 4; TLS: 1/145 (1.4%), grade 5
6	Bintrafusp Alfa	PD-L1 x TGF-β	Luis Paz-Ares	Phase I	NSCLC previously treated with platinum	N/A	AKI: 2/80 (2.5%)	One AKI in grade 3, one in grade 1	Diarrhea: 5/80 (6.3%), IRR: 1/80 (1.25%)

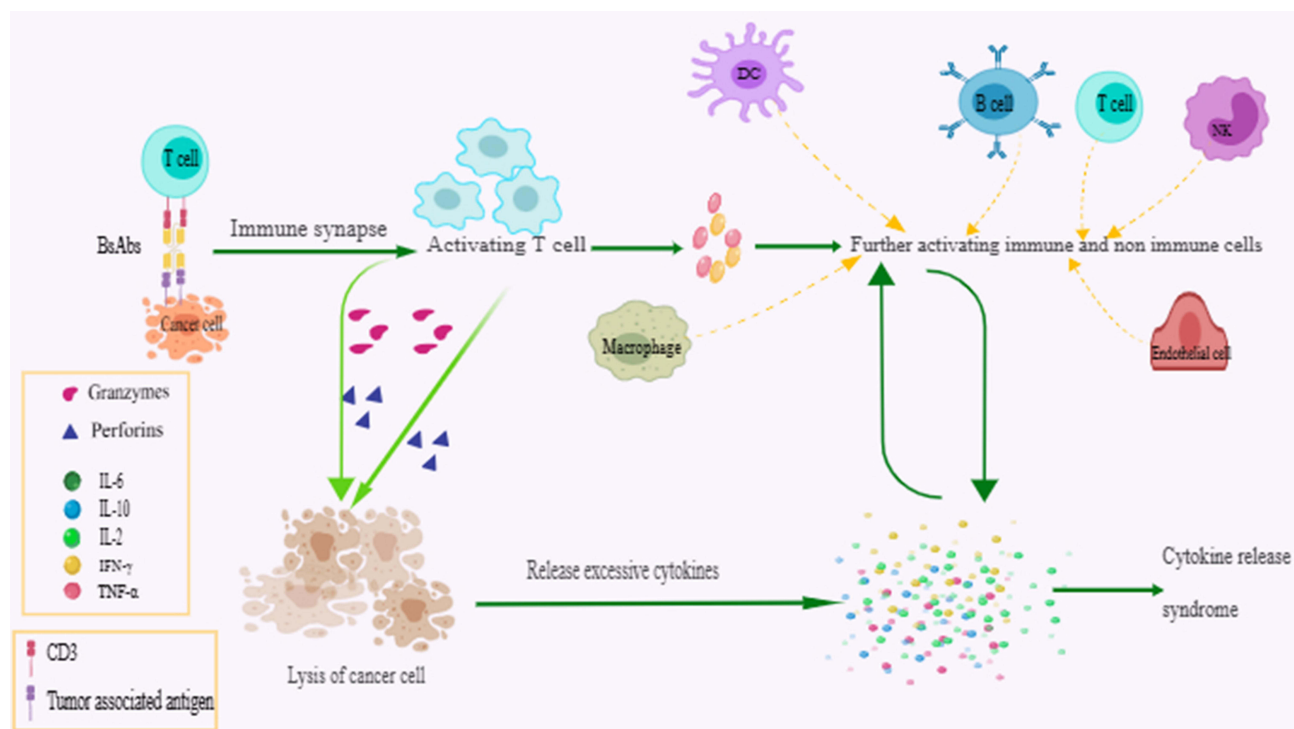
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Table I (Continued).

NO	Drug Name	Target Antigen	Author	Clinical Trial Stage	Target Disease	% /Incidence of CRS	% /Incidence of Nephrotoxicity	Relevant Manifestation	Other Risk of Nephrotoxicity
7	Bintrafusp Alfa	PD-L1 x TGF- $\beta$	Changhoo- nYoo	Phase II	Locally advanced/ metastatic biliary tract cancers	N/A	Immune-related nephritis and renal dysfunction: 3/159 (1.3%)	One AKI is the complications of cirrhosis, one is immune related, all of 3 in grade 3	Hypertension: 1/159 (0.6%), diarrhea: 6/159 (3.8%) tubulointerstitial nephritis: 1/159 (0.6%)
8	SHR-1701	PD-L1 x TGF- $\beta$ RII	Dan Liu	Phase I	Advanced solid tumors	N/A	Proteinuria: 9/171 (5.3%)	All proteinuria in grade 1–2 and improved or resolved at data cutoff	Protein urine present: 15/ 171 (8.8%)
9	SHR-1701	PD-L1 x TGF- $\beta$ RII	Jifeng Feng	Phase I	Recurrent or metastatic cervical cancer	N/A	Proteinuria: 5 /32 (15.6%) creatinine increased: 2/32 (6.3%)	All proteinuria in grade 1–3 One creatinine increased in grade 1–2, one in grade 3	Treatment-related bleeding events: 8/32 (25.0%)
10	Dilpacimab	DLL4 x VEGF	Michael S. Gordon	Phase I	Advanced solid tumors	N/A	Proteinuria: 6/55 (10.9%)	Manifestation of proteinuria is persistent with anti-VEGF-like toxicity	Hypertension: 35/55 (63.6%), diarrhea: 20/55 (36.4%), vomiting: 9/55 (16.4%)
11	KN046	PD-L1 x CTLA- 4	Anwen Xiong	Phase II	NSCLC	N/A	Renal failure: 2/64 (3.1%)	One in the 5 mg/kg cohort died due to renal failure related to KN046	Lung infection: 2/64 (3.1%), fever: 7/64 (10.9%)
12	BI 836880	Ang-2 x VEGF	Noboru Yamamoto	Phase I	Advanced solid tumors	N/A	Hypertension and proteinuria: 3/9 (33.3%)	Patients simultaneously experienced hypertension and proteinuria	Vomiting: 2/9 (22.2%)
13	Vanucizumab	Ang-2 x VEGF- A	Manuel Hidalgo	Phase I	Advanced solid tumors	N/A	Proteinuria: 5/42 (11.9%)	Four proteinuria in grade 1–2, one in grade 3–4	Hypertension: 25/42 (59.5%), diarrhea: 11/42 (26.2%), vomiting: 8/42 (19.0%)
14	MEDI-573	IGFI x IGFI	Paul Haluska	Phase I	Advanced solid tumors	N/A	Creatinine increased: 1/43 (2.3%)	Increased serum creatinine is the treatment-related serious adverse events by severity according to CTCAE criteria	Diarrhea: 7/43 (16.3%), vomiting: 4/43 (9.3%)

**Notes:** The major manifestations of nephrotoxicity associated with bispecific antibodies (BsAbs) remain acute kidney injury (AKI), proteinuria, and increased serum creatinine. Cytokine release syndrome (CRS), tumor lysis syndrome (TLS), and spesis tend to be more common in clinical studies of T-cell engaging BsAbs with kidney adverse events, and feature of nephrotoxicity occurring in non-T-cell BsAbs recipients closely like the reported events in studies of monoclonal antibody drugs targeting specific antigen.

**Abbreviations:** Her-2, Human epidermal growth factor receptor 2; TGF- $\beta$ , Transforming growth factor-beta; PD-L1, Programmed cell death 1 ligand 1; NSCLC, Non-small cell lung cancer; R/R, Relapsed or refractory; IRR, Infusion-related reaction; DLL4, Delta-like 4; VEGF, Vascular endothelial growth factor; TGF- $\beta$ RII, Transforming growth factor receptor-2; CTLA-4, Cytotoxic T-lymphocyte antigen-4; ICIs, Immune checkpoint inhibitors; Ang-2, Angiopoietin-2; EpCAM, Epithelial Cell Adhesion Molecule; CRRS, Cytokine release-related symptoms; IGFI/II, Insulin-like growth factor-I/II; CTCAE, Common terminology criteria for adverse events; TLS, Tumor lysis syndrome; N/A, Data not available.



**Figure 1** Reaction mechanism of anti-cancer T-cell engaging bispecific antibodies (BsAbs) after simultaneously link the tumor-associated antigen and CD3, bispecific antibodies (BsAbs) recruit immune cells such as T-cells close to the tumor and lead to the formation of an immune synapse. Formed synapses further induce activation and release of perforins and granzymes by activating immune activity of T-cells and finally result in T-cell-dependent cytotoxic lysis of the cancer cell. The products of cancer lysis also trigger the release of cytokines. Activated T-cells release interferon (IFN)- $\gamma$  and tumor necrosis factor (TNF)- $\alpha$ , which further promotes the maturation of other immune cells including dendritic cells (DC), macrophages, nature kill (NK) cells, and endothelial cells. Mature immune cells release large amounts of cytokines, and these cytokines in turn activate T-cells and other immune cells.

nephrotoxicity and CRS in each person due to the limited data information, we have reason to believe that CRS is closely related to T-cell-engaging BsAbs-associated nephrotoxicity.

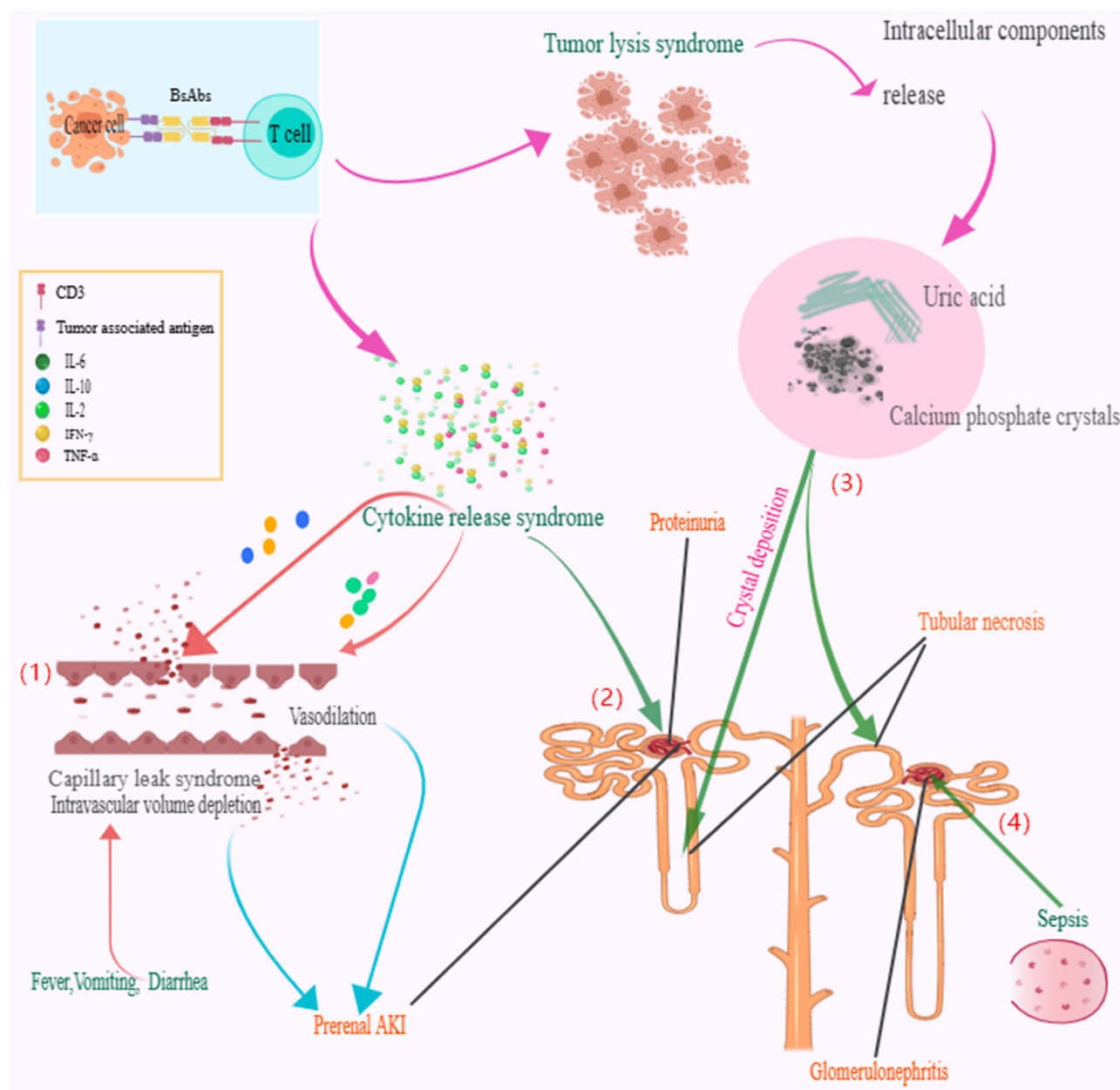
Excessive cytokines such as IL-2 will cause cytokine-driven capillary leak syndrome, which can lead to hypotension and intravascular volume depletion and finally induce prerenal AKI or a transient creatinine increase. Simultaneously, ischemic acute tubular injury (ATI) such as tubular necrosis can also develop with severe hypotension.<sup>34</sup> Of note, cytokine-mediated inflammatory kidney injury may also occur if cytokines exist in the blood beyond the body's control. Relevant research indicates that BsAbs are occasionally associated with the collapsing glomerulopathy, which in this context may result from cytokine-induced podocyte and endothelial injury.<sup>27,35,36</sup>

There are exciting similarities about the mechanism of CRS associated with immune effector cells between BsAbs and CAR-T therapy.<sup>31</sup> But the incidences post the use of T-cell-BsAbs is lower and the majority appear in mild or moderate as compared to CAR-T cell therapy (Table 2), which may result in nephrotoxicity infrequently.

A novel grading scheme for the severity of CRS associated with immune effector cells is found in the American Society for Transplantation and Cellular Therapy (ASTCT) consensus.<sup>37</sup> Importantly, with the deeper understanding of relevant CRS, after increasing research on T-cell-BsAbs, early interventions such as step dosing strategy, disease cytoreduction, and pretreatment with glucocorticoids have radically decreased the incidence and improved the severity of CRS in cancer patients who receive T-cell-BsAbs.<sup>31</sup> Additionally, the usage of tocilizumab, a IL-6 inhibitor, in the management of T-cell-BsAbs-induced CRS alone or in conjunction with corticosteroids may also improve the prognosis and decrease the risk of AKI to some extent.<sup>38,39</sup>

## Tumor Lysis Syndrome

TLS is another potential mechanism for nephrotoxicity in patients with a high tumor burden receiving T-cell-BsAbs. TLS occurs infrequently in patients treated with T-cell-BsAbs, as described in non-Hodgkin lymphoma patients treated with



**Figure 2** Proposed major mechanisms of nephrotoxicity in bispecific antibodies (BsAbs) recipients. 1) Cytokine release syndrome with excessive cytokines will function on blood vessels and cause cytokine-driven capillary leak syndrome as well as intravascular volume depletion, which can lead to hypotension and induce prerenal acute kidney injury (AKI) or transient creatinine increased. 2) Excessive cytokines will infiltrate, attack glomerulus tissue, destroy the filtration barrier, and finally induce proteinuria. 3) Too much or too fast lysis of cancer cells will produce excessive calcium salts, phosphate, and uric acid. The accumulation of uric acid, calcium, and phosphate cause the formation of crystals in the kidney tubules, blocking the kidney tubules, inducing infection, and finally leading to tubules necrosis. 4) Under the infection situation, sepsis may be a risk factor of glomerulonephritis.

CD20 $\times$ CD3 BsAbs.<sup>10</sup> A grade 3 TLS event was recorded in the phase I study of APVO436 (CD123  $\times$  CD3) and 1% of 145 patients who received Odrnextamab (CD20  $\times$  CD3) experienced grade 5 TLS.<sup>6,10</sup> Cancer, especially malignant hematologic cells, may contain up to four times more intracellular phosphate compared with normal mature lymphoid cells.<sup>40</sup>

TLS is a metabolic disorder characterized by hyperuricemia, hyperphosphatemia, hyperkalemia, and hypocalcemia, brought about by rapid tumor cell destruction that may result in a variety of systematic manifestations including musculoskeletal, cardiac, neurologic, and kidney injury.<sup>41</sup> Hyperuricemia can cause nephropathy/nephrocalcinosis-induced renal failure, and damaged glomerular filtration secondary to preceding urate nephropathy/nephrocalcinosis-induced renal failure can



**Table 2** Comparison of severity, cause, main symptoms, and treatment measure of cytokine release syndrome (CRS) associated with T-cell-engaging bispecific antibodies (BsAbs) and chimeric antigen receptor T-cells (CAR-T)

Immunotherapy platform causing CRS	T cell-engaging bispecific antibodies (BsAbs)	Chimeric antigen receptor T-cells (CAR-T)
Severity of CRS	Mild or moderate, few in grade 3 or higher	More severe, half of the recipients in grade 3–4 death is possible
Cause of CRS	Overactivation of immune and non-immune cells	Uncontrolled CAR-T cell activation
Prime cytokines	TNF- $\alpha$ , IFN- $\gamma$ , IL-6, IL-2, IL-10	IFN- $\gamma$ , TNF- $\alpha$ , IL-6, IL-8, IL-1, MCP1
Risk factor of CRS	Tumor burden, higher initial starting dose of infusion	Tumor burden, dose of drugs
Main symptom of CRS	Pyrexia, malaise, headache, nausea, hypotension, hypoxia, renal impairment, most commonly occur with initial infusion or in the first cycle	Pyrexia, hypotension, pulmonary edema, reduced various cardiovascular, systemic organ injury, occur immediately or be delayed days or weeks after infusion
Treatment measure	Mild or moderate patients: supportive care Severe patients: corticosteroids or tocilizumab	Tocilizumab, corticosteroids, administration of anti-inflammatory drugs, renal perfusion, modified CAR-T therapy
Effect of treatment on curative effect	BsAbs can be held and adjusted in response to toxicity Relative strategies would not impair the efficiency of BsAbs	Therapeutic of CRS do not decrease the curative effect of CAR-T therapy

**Abbreviations:** TNF- $\alpha$ , tumor necrosis factor- $\alpha$ ; IFN- $\gamma$ , interferon- $\gamma$ ; IL-6, interleukin-6; IL-2, interleukin-2; IL-4, interleukin-4; IL-10, interleukin-10; IL-1, interleukin-1; IL-8, interleukin-8; MCP1, monocyte chemoattractant protein-1.

subsequently occur.<sup>41</sup> There is a high risk of kidney damage caused by precipitation of uric acid and calcium phosphate crystals in renal tubules.<sup>42</sup>

Although TLS can usually be readily discriminated from CRS on the basis of characteristic laboratory abnormalities such as hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia, it can sometimes be difficult to determine if CRS and TLS occur concurrently.<sup>43</sup> Early identification of patients at risk and prevention of its development is critical. The syndrome is seen most frequently in patients with lymphoproliferative malignancies.<sup>44</sup> Of note, some suggest that TLS itself can also develop life threatening conditions including sudden cardiac failure through induction of hypocalcemia, hyperkalemia, and hyperuricemia,<sup>45</sup> which may be a risk factor of AKI.

The dominant treatment strategy includes correction of electrolyte disorder, promoting excretion of phosphate, calcium, and uric acid. Preventive management of TLS is risk-based: for low-risk TLS, consistent monitoring is enough, with oral hydration or intravenous injection (IV) if patient cannot tolerate this, and allopurinol and rasburicase should be used if uric acid is elevated for intermediate-risk patients.<sup>41,44</sup> Dialysis is necessary when a general resolution of tumor lysis-induced acute renal failure is ineffective or life-threatening electrolyte disorders or volume overload occur (Table 3).

**Table 3** Management measures of different mechanism about nephrotoxicity in bispecific antibodies (BsAbs) recipients.

Mechanism of nephrotoxicity	Management measure
Cytokine release syndrome	Grade 1–2: antihistamines, antipyretics, fluids, vasopressors, oxygen supplementation Grade 3–4: +tocilizumab and corticosteroids, admitted to ICU if necessary Grade 5: Admitted to ICU
Tumor lysis syndrome	Management: electrolyte management, alkalinized urine, RRT Prevention: monitor, oral/Intravenous hydration, allopurinol; rasburicase
Infection/sepsis	Anti-bacterial, viral, and fungal infections treatment Antimicrobial prophylaxis and IVIG

**Notes:** Reducing drug dose or discontinuing treatment should be considered carefully.

**Abbreviations:** ICU, intensive care unit; RRT, renal replacement therapy; IVIG, intravenous immunoglobulin.

## Sepsis

Although reported infrequently as well as no event of sepsis-induced nephrotoxicity been found in the existing clinical trials, sepsis has been recorded in some studies of T-cell-BsAbs, including one patient in the APVO436' phase I study who experienced sepsis of grade 3 and another one who suffered from grade 4 sepsis in a phase II clinical trial of Odronextamab.<sup>6,10</sup> Moreover, infection, as a cause of sepsis, occurs with a high incidence due to the conditioning regime and neutropenia in the T-cell-engaging BsAbs recipients.<sup>46</sup> A pooled analysis on risk of infections associated with the use of bispecific antibodies in multiple myeloma has found that half of the patients treated with BsAbs developed an infection, and a quarter developed grade III/IV infections.<sup>46</sup>

Mechanisms of sepsis-induced nephrotoxicity are various, normally inflammation, metabolic reprogramming, and microvascular endothelial dysfunction are considered as three fundamental mechanisms in the development of sepsis-acute kidney injury.<sup>36,47</sup>

Proadministration of antimicrobial prophylaxis and IVIG may play a role in decreasing the risk of infections. But there are no official guidelines for the implement of antimicrobial prophylaxis and IVIG in patients receiving BsAbs.

## Nephrotoxicity of Non-T Cell-BsAbs

Apart from T-cell-engaging BsAbs, the most established class of bispecific immunotherapies, there are clinically three other classes of BsAbs: (a) NK-cell redirectors; (b) Tumor-targeted immunomodulators; and (c) Dual immunomodulators.<sup>5</sup> NK-cell redirectors redirect NK cells to malignant cells by targeting a tumor antigen and CD16A, and tumor-targeted immunomodulators direct potent costimulation to the tumor infiltrating immune cells by targeting a tumor antigen and costimulatory molecules, and dual immunomodulators simultaneously bind two distinct immunomodulating targets resulting in dual blockade of inhibitory targets.

In contrast to T-cell-engaging BsAbs, the other three classes are mainly in the early stages of research and development, only Cadonilimab (PD-1× CTLA-4) was approved in China in June 2022 for use in patients with relapsed or metastatic cervical cancer.<sup>48</sup> Adverse events of proteinuria and nephritis, described associated with the therapy of BsAbs, occurred in the clinical trials of Cadonilimab,<sup>49,50</sup> and one study indicated that the toxicity spectrum of cadonilimab was consistent with those of the monotherapy and combination therapies targeting PD-1 and CTLA-4.<sup>50</sup> Moreover, In the phase II study of KN046 (PD-L1 x CTLA-4), renal failure occurred in 2/64 (3.1%) patients and one of the patients in the 5 mg/kg cohort died due to renal failure related to KN046.<sup>16</sup> Again, vanucizumab (Ang-2 x VEGF-A)-associated proteinuria accounts for 11.9% (5/42) in the phase I research, and a study demonstrated that the therapeutic strategy of this agent did not increase the incidence or grade of proteinuria with agents targeting the Ang/Tie2 pathway or VEGF-R.<sup>18</sup> These BsAbs, obviously, target two different non-T-cell redirector antigens, which itself owns the possibility of agents-induce nephrotoxicity post the administration, as well as may induce the nephrotoxicity in the course of therapy.

## Other Potential Risk Factors of Nephrotoxicity

As an important organ in the human body, the kidney mainly plays the role of regulating endocrine and excreting human waste and plays an irreplaceable role in regulating human electrolyte homeostasis. The kidney is the main organ for drug excretion. Because of the specificity of disease and treatment in tumor patients, the risk factors of nephrotoxicity in these patients also increase.

## Hemophagocytic Lymph Histiocytosis/Macrophage Activation Syndrome

A large proportion of BsAbs were administered to improve the prognosis in patients with hematological malignancies. Hemophagocytic lymph histiocytosis/macrophage activation syndrome (HLH/MAS), which is more common in the hematological malignancies than other cancers, is a unique toxicity that also can cause AKI, glomerulopathy, and nephrotic syndrome.<sup>51</sup> The clinical manifestations of HLH are mainly excessive inflammatory response and organ damage caused by infected cytokines.<sup>52</sup> As a special organ, the kidney is not immune from its influence. AKI from HLH/MAS has not been well characterized by kidney biopsy but may develop from hemodynamic-related tubular injury, glomerulonephritis, or AIN.<sup>34</sup> In an exploratory study performed in cynomolgus monkeys and in genetically engineered triple humanized mice, cytokine release, lymphocyte margination, and T-cell activation were observed in monkeys



administered the CD28 super agonist (10 mg/kg) alone, with maximum cytokine release and lymphocyte margination seen at about 5 hours after CD28 super-agonist administration.<sup>53</sup> Biopsy results of subjects in a similar study demonstrated that mononuclear or mixed cell infiltrates were observed in the kidneys, brain, and seminal vesicles of animals administered the CD28 super-agonist.<sup>54</sup> Current treatments focus on suppressing systemic inflammation and reducing capillary leakage. Management options include systemic glucocorticoids, transfusion, and blood volume supplementation. For refractory cases, more effective immunosuppression such as cyclosporin, intravenous immunoglobulin, or plasmapheresis is recommended.<sup>55</sup>

## Other Medications Used

Based on the specificity of the tumor, most patients will use a variety of treatments to slow the progression of the tumor and improve the prognosis. Antitumor therapy of BsAbs combined with chemoradiotherapy is widely used in the clinic.<sup>56</sup> The nephrotoxicity of chemoradiotherapy drugs is well known, so, when using bispecific antibodies, we need to take into account the kidney damage of other drugs. Notably, hematopoietic stem cell transplantation, the preferred treatment for hematologic malignancies, can also cause nephrotoxicity.<sup>57</sup> To achieve reduction of nephrotoxicity caused by combination drugs, drug toxicology studies should be strictly followed and the treatment regimen with the least impact on the kidney should be selected under the available conditions. Reduced or adjusted medication according to kidney function also plays a significant role in preventing kidney damage in patients who simultaneously receives BsAbs and other drugs.

## Risk Factor of Prerenal Injury

Acute cardiac dysfunction with reduced cardiac output and hypotension may result in reduced blood flow to the kidney, which can lead to acute kidney injury if not improved in time.<sup>58</sup> Additionally, fluid loss induced by vomiting, diarrhea, or high fever probably increased the risk of AKI.<sup>34</sup> For the prevention of possible prerenal risk factors, we should strengthen body fluid management to prevent fluid deficiency caused by diarrhea, vomiting, and fever. It is also important to pay close attention to blood pressure changes in patients and detect capillary leakage syndrome.

## Conclusion

In recent years, the immunotherapy of cancer has made great progress. It has a significant effect on prolonging the survival time of tumor patients. However, immunotherapy in tumors can lead to complications, including renal toxicity. Kidney complications may force a reduction in drug doses, a change in treatment, or permanent disqualification from a given treatment regimen. It is important to predict the nephrotoxicity of immunotherapy drugs, but the pathological mechanism of renal damage in immunotherapy drugs is limited.

By analyzing the existing data from published literature, we found that there exist nephrotoxicity in T-cell-engaging BsAbs recipients, which mainly include AKI, increased creatinine, and proteinuria. The suggested mechanisms of kidney injury in T-cell-engaging BsAbs recipients are discussed in many aspects, including CRS, TLS, and sepsis. Hemophagocytic lymph histiocytosis/macrophage activation syndrome, using other medications and fluid loss, can be a risk factor for kidney damage. In addition, there are often other risk factors for AKI such as age and comorbidities. There is a lack of guidelines for the treatment of nephrotoxicity in the BsAbs recipients. Prevention or treatment of CRS, TLS, and sepsis can significantly reduce the occurrence of nephrotoxicity in patients receiving T-cell-engaging BsAbs. Nephrotoxicity associated with non-T-cell-BsAbs is likely due to the combination of two relevant monoclonal antibodies targeting specific antigens. Close monitoring is still needed to detect kidney injury as early as possible and give effective remedial measures. Similarly, management of using medication and fluid can help reduce factors that aggravate renal toxicity. With the increasing number of cancer patients worldwide, T-cell-engaging BsAbs will be increasingly put into the market due to its double-target effect. Nephrologists and oncologists should strengthen their understanding of this drug, and have a certain understanding of the mechanisms, risk factors, and management strategies of relevant nephrotoxicity to better address adverse nephrotoxic events that may occur in the clinic.

## Abbreviations

BsAbs, Bispecific antibodies; mAbs, Monoclonal antibodies; TCR, T-cell receptor; AKI, Acute kidney injury; CRS, Cytokine release syndrome; TLS, Tumor lysis syndrome; CAR-T, Chimeric antigen receptor T-cell; Her-2, Human epidermal growth factor receptor 2; BCAM, Basal cell adhesion molecule; IFN- $\gamma$ , Interferon- $\gamma$ ; TNF- $\alpha$ , Tumor necrosis factor- $\alpha$ ; IL, Interleukin; ICANS, Immune effector cell associated neurotoxicity syndrome; IV, Intravenous injection; EpCAM, Epithelial Cell Adhesion Molecule; ATI, Acute tubular injury; NK cell, Nature kill cell; DC, Dendritic cell; PD-1, Programmed cell death 1; PD-L1, Programmed cell death 1 ligand 1; CTLA-4, Cytotoxic T-lymphocyte antigen-4; ASTCT, American Society for Transplantation and Cellular Therapy; IVIG, Intravenous immunoglobulin; VEGF-A, Vascular endothelial growth factor A; Ang-2, Angiopoietin-2; HLH/MAS, Hemophagocytic lymph histiocytosis/macrophage activation syndrome; AIN, Acute interstitial nephritis; ICU, Intensive care unit; RRT, Renal replacement therapy.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare that they have no competing interests in this work.

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