

# Management of toxicities associated with novel immunotherapy agents in acute lymphoblastic leukemia

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**Abstract:** The advent of novel immunotherapies, such as blinatumomab, inotuzumab, and chimeric antigen receptor (CAR) T cell therapy, has revolutionized the therapeutic landscape in the treatment of relapsed/refractory B cell acute lymphoblastic leukemia, but can be associated with specific toxicities. We review unique toxicities of each of these in this article. Blinatumomab, a bispecific T cell engager, has been associated with cytokine release syndrome (CRS) and neurological toxicities, both of which can be prevented and managed with corticosteroids. Inotuzumab is a calicheamicin-conjugated CD22 targeting antibody. The calicheamicin component of the drug is likely associated with the hepatotoxicity seen with inotuzumab, especially sinusoidal obstruction syndrome, which can happen both in the context of the drug alone, and also with allogeneic stem cell transplantation. QT prolongation has also been noted with inotuzumab. CAR T therapy uses genetically modified autologous T cells directed against CD19, a known target on B cells. CRS and neurological symptoms, formally termed as immune-effector-cell-associated neurological syndrome, have been described along with hypogammaglobulinemia, cytopenias, and infections.

**Keywords:** blinatumomab, chimeric antigen receptor T cell therapy, inotuzumab

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The therapeutic landscape for relapsed/refractory B cell acute lymphoblastic leukemia (ALL) has evolved considerably in the past few years. After a hiatus in Food and Drug Administration (FDA) approvals for ALL, three novel therapies have recently found their way into the treatment paradigm of relapsed/refractory B cell ALL, while also being studied enthusiastically in the upfront setting. These are inotuzumab (an anti-CD22 antibody drug conjugate), blinatumomab (a bispecific T cell engager), and chimeric antigen receptor (CAR) T cell therapy (tisagenlecleucel, CD19 directed adoptive T cell therapy).

Although these new options have emerged, it is imperative to understand the practical aspects of administration of these therapies, especially regarding toxicity and the management thereof. We review the unique toxicities that have been associated with these novel therapies, and provide

guidance for prevention as well as management options for each. We hope that understanding these toxicities will not only educate readers about early recognition and management, but also allow guidance for use of these therapies in individual scenarios.

Relapsed/refractory B cell ALL in adults has had a relatively poor prognosis with median overall survival under 9 months in the past.<sup>1</sup> Hence, the advent of these new agents has offered renewed hope to patients. By staying cognizant of the potential adverse effects, we can further utilize these agents to the best potential and aim to improve outcomes in these patients.

## Blinatumomab

Blinatumomab is a bispecific antibody with dual binding sites for CD3 and CD19, which enables

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**Table 1.** Reported rates of toxicity with blinatumomab.

	Phase II (n=21) <sup>2</sup>	Phase II (n=36) <sup>3</sup>	Phase II (n=189) <sup>4</sup>	Phase III TOWER study (n=405) <sup>5</sup>	Phase II, Ph positive (n=45) <sup>6</sup>	Phase II, MRD positive patients (n=116) <sup>8</sup>
CRS	NA	All grade: NA Grade ≥ 3: 6%	All grade: NA Grade ≥ 3: 2%	All grade: 14% Grade ≥ 3: 5%	All grade: 7% Grade ≥ 3: 0	All grade: 3% Grade ≥ 3: 2%
Neurotoxicity	20% [grades no specified]	All grade: 36% Grade ≥ 3: 14%	All grade: 52% Grade ≥ 3: 13%	All grade: 45% Grade ≥ 3: 9%	All grade: 47% Grade ≥ 3: 7%	All grade: 53% Grade ≥ 3: 13%

CRS, cytokine release syndrome; NA, not available.

it to engage both cytotoxic T cells and CD19 positive lymphoblasts. This results in T-cell-mediated lysis of tumor cells *via* perforin fusion with the T cell membrane and resulting discharge of cytotoxic granules causing lysis of tumor cells. Minimal residual disease (MRD) negative responses were seen in initial studies leading to the conduct of a phase III trial (TOWER study), where superior responses, as well as overall survival with blinatumomab compared with standard therapy, were found in adult patients with relapsed/refractory B cell ALL (complete remission with hematological recovery 34% *versus* 16%, median overall survival 7.7 *versus* 4 months, HR 0.71, 95% CI 0.55–0.93,  $p=0.01$ ).<sup>2–5</sup> Although initially studied for Philadelphia chromosome negative disease, a recent phase II study has also shown activity in patients with Philadelphia chromosome (Ph+) B cell ALL (ALCANTRA trial), including in patients with prior tyrosine kinase exposure, and in those with T315I mutations.<sup>6</sup> In addition to relapsed/refractory B cell ALL, blinatumomab has also been evaluated and now approved by the FDA for use in MRD-positive B cell ALL.<sup>2,7,8</sup> The basis of this approval was a single arm study, in which of 113 evaluable patients with MRD  $\geq 10^{-3}$  treated with blinatumomab, 88 (78%) achieved an MRD response, resulting in a superior relapse-free survival as well as overall survival. Two distinct toxicities with blinatumomab that are described in the following include cytokine release syndrome (CRS) and neurotoxicity.

#### Cytokine release syndrome

CRS is relatively unique toxicity noted with therapies utilizing T cells for cytotoxicity to tumor cells.

**Incidence.** In early phase II trial using blinatumomab, two patients with high tumor burden (bone marrow blasts 88% and 90%, respectively) developed grade 4 CRS, one of whom had to discontinue treatment permanently while the other was successfully retreated with blinatumomab.<sup>3</sup> Subsequently, treatment prephase with dexamethasone and cyclophosphamide was initiated for patients with high tumor burden, and no further CRS grade  $\geq 3$  was noted thereafter. In the phase II and phase III trials that followed, prephase treatment with dexamethasone for patients with bone marrow blasts  $>50\%$ , peripheral blood blasts  $\geq 15,000$  cells/ $\mu\text{L}$  or elevated lactate dehydrogenase; along with stepwise escalation, that is 9  $\mu\text{g}/\text{day}$  for 1 week, then 28  $\mu\text{g}/\text{day}$  for 3 weeks, along with dexamethasone premedication, was implemented.<sup>4,5</sup> The incidence of CRS with blinatumomab as reported in various trials is shown in Table 1. Common terminology criteria for adverse events (CTCAE) version 4.0 was used for grading toxicities in these studies.

**Pathophysiology.** CRS is a systemic inflammatory response that is thought to be mediated by the increased levels of cytokines and other inflammatory markers. In patients receiving blinatumomab, levels of interleukin (IL)-10, IL-6, and interferon (IFN)-gamma were noted to be elevated after the start of the first cycle.<sup>9</sup> Given that the elevation of IL-6 and IL-10 is not explained entirely by activated cytotoxic T cells, it has also been hypothesized that a hemophagocytic lymphohistiocytosis or macrophage activation syndrome may be implicated in the pathophysiology of CRS following blinatumomab.<sup>10</sup>

**Clinical picture.** As mentioned previously, high disease burden and a higher initial dose of

blinatumomab were identified as risk factors in early studies.<sup>3</sup> Clinical presentation includes high fevers, headache, and malaise, while hypotension, hypoxia, hepatic, or renal dysfunction can occur in higher grades. Pulmonary edema, capillary leak, and disseminated intravascular coagulopathy and hemophagocytic lymphohistiocytosis can be more severe and potentially life threatening.<sup>10</sup>

*Management.* Early recognition is of utmost importance. Prevention strategies such as dose step-up after 7 days of infusion along with dexamethasone prophylaxis, are now widely accepted. Of note, the step-up was performed in studies including patients with morphological disease. For patients where blinatumomab is used for MRD-positive disease, a flat dose of 28 µg for 28 days is recommended, unless dose interruption is required for severe toxicity. Dexamethasone prophylaxis is recommended at the time of initiation of infusion in all patients, at the time of dose increase, and when dose is interrupted for longer than 4 h. Treatment strategies include corticosteroids or temporary discontinuation of infusions. Permanent discontinuation is discouraged given the life-saving potential of treatment of ALL, but is considered in higher grade CRS with life-threatening complications arising from CRS itself. Tocilizumab, an IL-6 receptor blocker, has been used in higher grades of CRS, and in a patient with hemophagocytic lymphohistiocytosis that developed following blinatumomab infusion.<sup>10</sup> Although this has not been commonly used for this indication, it can be considered if no improvement is noted after drug cessation and treatment with steroids.

### Neurotoxicity

Neurological side effects are one of the most feared toxicities with blinatumomab, leading to both drug interruption and discontinuation. However, recovery has been reported in most patients.

*Incidence.* All grades of neurotoxicity can be seen in as many as 36–53% patients treated, of which 7–14% were grade 3 or higher in the various trials.<sup>2–5,8</sup> These are also tabulated for respective trials in Table 1. Not only were neurological events a common occurrence, they were also a common cause of drug interruptions and discontinuations. Most patients recovered neurological status with

interventions, and no deaths were attributed to blinatumomab related neurotoxicity. For example, in the phase III TOWER trial, neurological events led to drug interruption and discontinuations in 6% and 4% patients, respectively, of the 32% interruptions and 12% discontinuations overall. Most of these occurred in cycle 1 of the infusion, and were less common in subsequent cycles.

*Pathophysiology.* The precise mechanism of neurotoxicity with blinatumomab remains unclear. A review of the phase II study showed that more than two prior salvage treatments and prior neurological events were associated with higher neurotoxicity.<sup>11</sup> In the same study, peak levels of IL-6 or tumor burden at baseline were not associated with severity of neurotoxicity. It is, however, plausible that blood brain barrier disruptions due to treatment or disease, and cytokine release upon binding to CD19 positive cells in the central nervous system, may be the underlying mechanism.<sup>12,13</sup>

*Clinical picture.* Given the previous observation that prior neurological events can be associated with a higher risk of neurotoxicity, it is prudent to consider these patients at being at a higher risk.<sup>11</sup> Disease burden or dosing level, however, appear not to be associated with occurrence of neurotoxicity with blinatumomab. Similarly, no laboratory biomarkers are known to predict neurotoxicity.

The typical onset is early, following the initiation of infusion, usually in the first week.<sup>3–5</sup> The clinical presentation can start as tremors or agrapahia, and can also present as headache, delirium, paresthesias, dysarthria, aphasia, encephalopathy, amnesia, seizure, or other neuropsychiatric symptom. The usual time to onset is in the first week, and possibly correlates with the dose escalation in cycle 1. It has also been consistently shown to be most common in the first cycle across most trials.

*Management.* Most trials incorporated drug interruption for grade  $\geq 3$  and a permanent discontinuation for grade  $\geq 4$  neurotoxicity events. Withholding blinatumomab is recommended for grade 3 toxicity until improvement to  $\leq$  grade 1 is noted for three consecutive days, at which time it can be resumed at 9 µg/day, and escalated to 28 µg/day after 7 days if toxicity does not recur. If,

however, neurotoxicity is noted again at 9 µg/day, the drug should be permanently discontinued. Permanent discontinuation is also implemented per package label if the grade 3 toxicity takes more than 7 days to resolve or if more than one seizure occurs.

Steroids remain the cornerstone of treatment of neurological toxicity and is recommended for severe symptoms such as encephalopathy or aphasia. Supportive treatment, such as anti-epileptics for seizures, should be considered as appropriate. Prophylactic anti-epileptics are not required given the low incidence of seizure with blinatumomab.<sup>13</sup> Given the risk of loss of consciousness or seizures amongst other neurological adverse events, patients must be recommended to refrain from driving or operating heavy or potentially dangerous machinery during blinatumomab treatment.

#### *Hypogammaglobulinemia, cytopenias, and infections*

In the phase II studies, immunoglobulin levels were monitored for a prolonged period of time in six patients with MRD-positive B cell ALL.<sup>14</sup> All five responders were noted to have a drop in immunoglobulin G levels to a nadir of 29% (median, range 29–101%) of baseline levels. Immunoglobulin G was not noted to decrease in the one patient who did not achieve a response.<sup>14</sup> Hypogammaglobulinemia was also reported in 6% patients in the TOWER study amongst those who were treated with blinatumomab, compared with 1% of those treated with chemotherapy.<sup>5</sup> In addition, leucopenia as well as neutropenia were reported in both the early phase as well as the TOWER study, although at lower levels than the chemotherapy arm. A variety of infections, including bloodstream infections, catheter site infections, fungal infections, and bacterial sepsis, amongst others have been reported in various studies in as high as 25% of patients. Consideration for immunoglobulin replacement and prophylactic antibiotics must be given on an individual case-by-case basis.

#### **Inotuzumab**

Inotuzumab is an antibody drug conjugate targeting CD22 *via* an anti-CD22 humanized monoclonal antibody and bound to calicheamicin, an

alkylating agent. When this conjugate binds to a CD22 positive cell, the drug is internalized and releases calicheamicin into the cell. Calicheamicin is derived from *Micromonospora echinospora*, and, by causing DNA breaks, results in cell death.<sup>15</sup> In the early phase II studies, MRD-negative responses were noted in around 60% of patients.<sup>16,17</sup> A subsequent phase III trial compared inotuzumab with conventional chemotherapy, and showed superior response as well as median overall survival on a *post hoc* restricted mean survival analysis.<sup>18</sup> We describe the various aspects of hepatic toxicity and QT prolongation with inotuzumab.

#### **Hepatic toxicity (including sinusoidal obstruction syndrome)**

Hepatotoxicity in the form of hyperbilirubinemia, transaminitis, and sinusoidal obstruction syndrome (SOS, also called veno-occlusive disease) has been seen consistently with inotuzumab.

*Incidence.* In the initial phase II trial, inotuzumab was administered at 1.8 mg/m<sup>2</sup> given once every 3–4 weeks (single dose) while subsequent dosing was 0.8 mg/m<sup>2</sup> on day 1 followed by 0.5 mg/m<sup>2</sup> on days 8 and 15 in monthly cycles (weekly dosing).<sup>16,19</sup> The rates of SOS development were noted to be lower with weekly dosing than with the single dose regimen.<sup>16</sup> The risk of SOS is potentially increased by the use of a dual-alkylating conditioning regimen for allogeneic stem cell transplantation (HCT) following inotuzumab therapy.<sup>16,20</sup> The overall rates of hepatic toxicity in various inotuzumab trials are shown in Table 2.

*Pathophysiology.* The mechanism of hepatotoxicity with inotuzumab is likely a result of the calicheamicin component of the drug, as similar toxicity has been seen with gemtuzumab, which is an anti-CD33 antibody drug conjugate also containing calicheamicin.<sup>21,22</sup> In general, SOS is the result of injury to the hepatic endothelium and hepatocytes, resulting in accumulation of red blood cells obstructing the sinusoidal flow, subsequently causing liver damage and hemorrhagic necrosis.<sup>23–25</sup> It has been shown in animal models (cynomolgus monkeys) that antibody-calicheamicin conjugate can result in midzonal degeneration and loss of sinusoidal endothelial cells, along with marked platelet accumulation in sinusoids.<sup>26</sup> In general, Kupffer cells are known to be responsible for antibody dependent cellular phagocytosis,

**Table 2.** Hepatic toxicity observed with inotuzumab.

	Phase II study (n=90) <sup>16</sup>	Phase I/II B1931010 trial (n=72) <sup>17</sup>	Phase III INO-VATE trial (n=326) <sup>18</sup>
Hyperbilirubinemia	All grade: 5% (w); 65% (sd) Grade ≥ 3: 0 (w); 41% (sd)	All grade: 10% Grade ≥ 3: 0	All grade: 15% Grade ≥ 3: 4%
Liver enzyme elevation	All grade: 27% (w); 57% (sd) Grade ≥ 3: 5% (w); 2% (sd)	All grade: 38% Grade ≥ 3: 6%	All grade: 41% Grade ≥ 3: 8%
SOS	7% (w) and 23% (sd) undergoing HCT	8% undergoing HCT; 4% not undergoing HCT	22% undergoing HCT; 8% not undergoing HCT

HCT, allogeneic stem cell transplantation; sd, single dose; SOS, sinusoidal obstructive syndrome; w, weekly.

resulting in clearance of antibody-bound tumor cells in liver.<sup>27</sup> Eventually, the drug conjugate is taken up by Kupffer cells, *via* their Fc receptors, resulting in delivery of the drug conjugate to liver cells.

With busulfan use as conditioning regimen in HCT, glutathione depletion, either as a result of interaction of busulfan and cyclophosphamide, or due to gene polymorphisms in glutathione S transferase, has been implicated in sinusoidal endothelial cell damage resulting in SOS.<sup>28–30</sup> It is currently unclear if a similar mechanism is involved in inotuzumab-mediated hepatotoxicity. In addition, it remains to be studied in greater detail whether the hepatotoxic side effects are specific to the target against which the drug is directed, and whether the toxicity would be different for an alternative dose or dosing schedule warrants further studies.

*Clinical picture.* SOS can occur both after HCT but also without HCT following treatment with inotuzumab, as has been shown in the INO-VATE and B1931010 trials (Table 2).<sup>17,18</sup>

The clinical presentation is of utmost importance in diagnosing SOS, and clinical criteria have been described for bedside evaluation.<sup>23,24,31</sup> Elevated bilirubin, hepatomegaly, right upper quadrant pain, weight gain >5%, and ascites should raise suspicion and warrant evaluation. An ultrasound study can show a decrease in velocity or reversal of portal flow, but is often seen late, and is less often positive for these findings early in the course of the disease. The gold standard for diagnosis is transjugular liver biopsy, which can be fraught with complications, as many patients can have refractory thrombocytopenia as a manifestation

of SOS. Hence, clinical diagnosis remains the mainstay. Laboratory findings may include decreased platelets, antithrombin III, protein C, factor VII, and plasminogen activator inhibitor I (PAI-I), although none of these are validated. Elevation of liver enzymes, and monitoring thereof, requires frequent laboratory monitoring.

In context of an HCT, patients who receive alkylating agents in the conditioning regimen, busulfan-containing conditioning regimen, prior elevation in bilirubin levels, and who are ≥55 years old are associated with an increased risk of developing SOS.<sup>32,33</sup> Of note, SOS typically occurs in the first 21 days following HCT, although late-onset SOS is also described.<sup>31</sup>

*Management.* SOS is a potentially life-threatening condition with a mortality of >80% in patients in whom organ dysfunction ensues as a result. Hence, preventative strategies should be considered, such as avoiding double alkylators with HCT following inotuzumab, avoiding more than two cycles of inotuzumab if HCT is planned, avoiding concomitant hepatotoxic medications such as azoles, and considering use of ursodiol for prophylaxis.<sup>20</sup> Expert panel recommendations on the use of inotuzumab and associated hepatotoxicity are laid out in the referenced publication by Kebriaei and colleagues.<sup>20</sup>

Occurrence of SOS would warrant discontinuation of inotuzumab therapy. Additional supportive measures such as fluid balance maintenance, pain control, and defibrotide for severe SOS, with renal or pulmonary dysfunction, may be considered.<sup>32,34</sup> An elevation of bilirubin >1.5 times upper normal or liver enzymes >2.5 times upper

normal, in the absence of SOS, also requires consideration for drug interruption, dose reduction, or discontinuation of therapy if recovery is not noted on withholding treatment.

#### *QT prolongation*

Prolongation of QTc interval by  $\geq 60$  msec from baseline was noted in 4 out of 162 patients (2%).<sup>18,35</sup> Although no grade  $\geq 3$  or Torsade de Pointes events were reported in the trial, it is recommended to obtain baseline electrocardiograms and electrolytes followed by close monitoring during treatment in order to prevent a life-threatening consequence. Although a cut-off for QTc is not provided as the overall incidence is low, caution should be exercised in patients with a prior history of QTc prolongation, and patients should be apprised of symptoms associated with QTc prolongation, such as dizziness, light-headedness, or syncope. Concomitant use of other medications known to prolong QT interval should also be managed with caution.

#### **Chimeric antigen receptor T cell therapy**

CAR T therapy involves use of T cells consisting of a genetically engineered surface receptor consisting of single chain variable fragment domain that recognizes CD19 and intracellular T cell signaling domains. By virtue of this engineering modification, the CAR T has the ability to recognize CD19 located on the surface of the cancer cell.

‘Chimera’ originally refers to a creature in Greek mythology that is made of more than one animal, for example a lion with the head of a goat and tail that ends with a snake’s head. Chimera in the context of CAR T refers to a receptor made of a combination of an antibody that targets a protein on the tumor cell (also called antigen binding domain), sequences that keep this receptor on the surface of T cell (the hinge region and transmembrane domain), and signals that are responsible for T cell activation (intracellular T cell signaling domain, i.e. CD3zeta, and costimulatory molecules such as CD28 and 4-1BB).

Various constructs are under evaluation, of which CTL019, now called tisagenlecleucel, is FDA approved for relapsed/refractory B cell ALL for patients of age 25 years or less. Clinical trials with tisagenlecleucel have shown unprecedented

response rates of over 80% in single center as well as multi-institute studies.<sup>36–38</sup> Other constructs have been developed and studied at the Memorial Sloan Kettering Cancer Center, National Cancer Institute, and the Fred Hutchinson Cancer Research Center.<sup>39–41</sup> In addition, the role of CAR T has been studied in relapsed/refractory B cell lymphomas (another FDA-approved indication) and multiple myeloma, as well as currently in some solid tumors. Various practical aspects of utilization of CAR T in relapsed/refractory B cell ALL, as well as B cell lymphomas, have been elaborated in two expert opinion papers by the American Society of Transplantation and Cellular Therapy (ASTCT).<sup>42,43</sup> Here, we focus mainly on CRS and immune-effector cell associated neurological syndrome (ICANS), along with available information on hypogammaglobulinemia, infections, and cytopenias reported with tisagenlecleucel for relapsed/refractory B cell ALL. Since these toxicities are potentially life threatening, careful selection of patients and education of staff at treating centers of symptoms and management with a setting of standard institutional algorithms for guidance are important for the safe delivery of CAR T across centers.<sup>44,45</sup>

#### *Cytokine release syndrome*

CRS, as described previously with blinatumomab, is a unique toxicity observed with T-cell-mediated therapies. Incidence and severity can vary depending upon the construct and disease burden. We describe the nuances of CRS associated with tisagenlecleucel for relapsed/refractory B cell ALL.

*Incidence.* In a single institution study at the University of Pennsylvania, as well as in the multi-center ELIANA trial, tisagenlecleucel commonly resulted in CRS; all patients in the single institution study and 77% of treated patients in ELIANA trial developed CRS (Table 3).<sup>37,38</sup> Around one-third of the patients infused with tisagenlecleucel needed intensive care unit management, but all were reversible and no deaths related to CRS were reported.<sup>37,38</sup>

*Pathophysiology.* CRS occurs as a result of immune activation and elevation of inflammatory cytokines. In animal models, the inflammatory cytokines seem to be derived from monocytes and macrophages.<sup>46,47</sup> In severe combined immunodeficient mice grafted with tumor, murine macrophages were seen to be the primary source of

**Table 3.** Toxicities associated with chimeric antigen receptor T cell therapy.

	Single institution study (n = 30) <sup>37</sup>	ELIANA trial (n = 75) <sup>38</sup>
CRS	All grade: 100% Severe (ICU admission): 27%	All grade: 77% (of treated patients) Grade ≥ 3: 46%
Neurotoxicity	43% (grades not specified)	All grade: 40% (of the treated patients) Grade ≥ 3: 13% (no grade ≥ 4)
Hypogammaglobulinemia	90% (100% responders)	81% (100% responders)
Cytopenias	Not reported	Grade ≥ 3: 41% thrombocytopenia, 53% neutropenia
Infections	Not reported	All grade: 43% Grade ≥ 3: 24%

ICU, intensive care unit.

IL-6.<sup>46</sup> IL-1 production appears to precede IL-6 production in another study in a humanized mice model, where blockage of IL-6 receptor *via* tocilizumab was found to be associated with low CRS, but neurotoxicity was still seen. However, when anakinra was used (IL-1 receptor antagonist), both CRS and neurotoxicity were abated.<sup>47</sup> Effector cytokines such as IFN-gamma and granulocyte macrophage colony stimulating factor derived from CART cells as well as nitric oxide as a result of macrophage-derived inducible nitric oxide synthase are thought to be other mediators of this toxicity.<sup>46,48</sup> The pathophysiology of CRS, as understood so far, is shown in Figure 1.

The result of this increase in cytokines is exposure of endothelial cells to these endothelial-activating cytokines such as IL-6 and IFN- $\gamma$ . Endothelial cells may themselves produce IL-6 when activated, resulting in a positive feedback loop.<sup>49</sup> Evidence of endothelial activation has been shown as elevated levels of von Willebrand factor and angiopoietin-2 in the serum in patients with severe CRS.<sup>50</sup> Angiopoietin-2 excess causes further endothelial activation, and increases microvascular permeability, further resulting in a capillary-leak-like phenomenon, resulting in hypotension and tachycardia amongst other symptoms of CRS.<sup>46,47</sup>

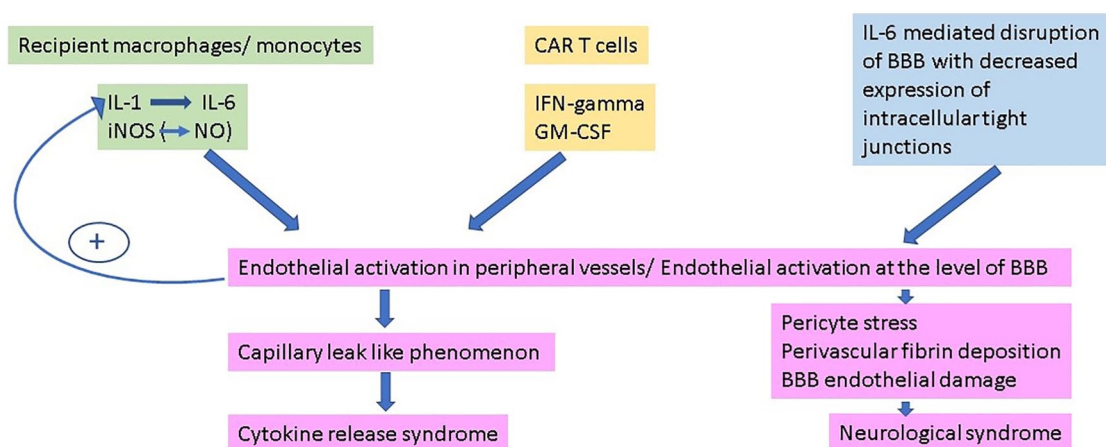
*Clinical picture.* A higher risk has been shown with high disease burden (bone marrow blasts >50%), not only with tisagenlecleucel, but also other CART constructs studied in B cell ALL.<sup>38–40</sup> Additional risk factors noted have been high T

cell dose, active infections or high inflammation markers at the time of CART infusion.<sup>44</sup>

Median time to onset of CRS with tisagenlecleucel in the ELIANA trial was 3 days (range, 1–22 days) while median duration was 8 days (range, 1–36 days).<sup>38</sup> Cases were reported with onset up to 8 weeks from infusion. Clinical presentation usually starts with fever, myalgias, and generalized weakness, but can rapidly progress to hypotension, tachycardia, and hypoxia, eventually causing organ dysfunction involving liver, kidneys or heart, with cytopenias or coagulopathy.<sup>37,38</sup> As noted previously, laboratory markers such as C-reactive protein, ferritin, IL-6, IL-10, and IFN-gamma, amongst others, are elevated. Not all of these are usually monitored in clinical practice, and should not supersede clinical suspicion as the elevations can be delayed after clinical presentation.

*Grading and management.* Various grading systems were used in early trials, which limits the interpretation of severity or grading of CRS across trials. To address that, and to harmonize reporting of toxicity in clinical trials as well as other studies, the ASTCT has developed a consensus grading criteria for toxicity related to immune effector cells including CART.<sup>51</sup> We encourage use of this system to report and describe these toxicities.

Appropriate management again relies heavily on astute clinical judgement and early recognition of clinical symptoms and signs. Supportive strategies, such as antipyretics, supplemental oxygen,



**Figure 1.** Potential mechanisms for CAR T related CRS and ICANS.

CAR, chimeric antigen receptor; CRS, Cytokine release syndrome; ICANS, immune-effector cell associated neurological syndrome.

analgesics etc., are used for lower-grade CRS. Since the initial desperate, but successful, use of tocilizumab in response to elevated IL-6 levels in a patient critically ill after CAR T infusion for B cell ALL, and the consequential response from this, tocilizumab has remained the mainstay of treatment of CRS in these patients. Tocilizumab was FDA approved, alongside tisagenlecleucel, to be used for treatment of severe or life-threatening CRS from CAR T therapy. Prophylactic use of tocilizumab was studied as a safety study in 34 patients, and showed decreased incidence of CRS, albeit with increased ICANS.<sup>52</sup> Hence, prophylactic use of tocilizumab is not currently recommended. Other prevention strategies under consideration include cyto-reduction prior to CAR T, inverse dose adjustment, using disease burden or fractionated dosing.<sup>44</sup> Siltuximab, a direct IL-6 inhibitor, has also been used to treat CRS in clinical practice, but formal studies of its use in prevention and management are awaited.

#### *Immune-effector cell associated neurological syndrome*

ICANS is likely the most feared complication of CAR T therapy. In a now discarded CAR T product, JCAR015, cerebral edema led to death in five patients, leading to termination of the trial.<sup>53,54</sup>

**Incidence.** The rate of ICANS with tisagenlecleucel in two trials is shown in Table 3. Although around 40% patients developed neurological

symptoms following tisagenlecleucel, no lethal toxicity was noted with this product.

**Pathophysiology.** The precise mechanism of ICANS following tisagenlecleucel remains to be detailed. As described in the CRS section, IL-1 and IL-6 derived from host macrophages are now thought to be the major mediators of ICANS.<sup>46,47</sup> Similar inflammatory cytokines that mediate CRS, such as IL-6, also likely disrupt the blood brain barrier endothelium, exposing the pericytes to circulating cytokines and possible pericyte damage.<sup>55,56</sup> Autopsy studies of patients who died from neurological syndrome and resulting cerebral edema also showed dilation of perivascular space, with the presence of acellular exudate, endothelial damage, and astrocyte injury.<sup>57</sup> This is also depicted in Figure 1.

**Clinical picture.** ICANS is commonly noted to coincide with CRS, but can also happen following resolution of CRS, or in the absence of CRS. Common manifestations include inattention, aphasia, agraphia, somnolence, encephalopathy, seizures, obtundation, or cerebral edema, quite similar to the neurotoxicity noted with blinatumomab. Inflammatory markers are expected to be elevated as in CRS, but are not always used in clinical practice for diagnosis as clinical presentation is the most suggestive.

**Grading and management.** Like CRS, ASTCT consensus grading is encouraged to harmonize



grading and interpretation for various studies.<sup>51</sup> Periodic neurological assessment, potentially using tools such as the Immune Effector Cell-Associated Encephalopathy (ICE) score, as described in this ASTCT consensus grading, is encouraged for early recognition. Treatment relies mainly on use of corticosteroids, while tocilizumab can be used if there is concurrent CRS.<sup>58</sup> Support with analgesics and anti-seizure medications can be used as appropriate. Additional work up can include imaging, electroencephalography, funduscopy, or lumbar puncture to evaluate for alternative etiology.<sup>58</sup> Elevation of head end of the bed to an angle of 30 degrees, hyperosmolar therapy such as acetazolamide or mannitol, and hyperventilation to attain a PaCO<sub>2</sub> of 28–30 mmHg have also been described for raised intracranial pressure.<sup>58</sup>

#### *Hypogammaglobulinemia*

Hypogammaglobulinemia resulting from B cell aplasia is an almost universal ‘off tumor’ ‘on target’ toxicity from CD19-directed CAR T cells. In addition to ALL cells, CD19 is also a target on normal mature B cells, and the use of CD19 CAR T cells resulted in prolonged B cell aplasia in all responders.<sup>37,38</sup> Given limited data on immunoglobulin replacement in CAR T therapy, recommendations are currently derived from practices in HCT or other immunodeficiency states. Consideration should be given to intravenous replacement when the levels of immunoglobulins is less than 400, especially in the early period following CAR T, or if recurrent infections are reported.<sup>43,59</sup>

#### *Cytopenias and infections*

Prolonged cytopenias have been reported in patients receiving CAR T cells in various studies.<sup>38,50,60</sup> In the ELIANA trial, grade 3–4 thrombocytopenia and neutropenia lasting at least 28 days was seen in 41% and 53% patients, and had resolved to grade 2 or lower in 73% and 66% patients by 3 months, respectively.<sup>38</sup> This was also associated with infections in 43% patients. In another study of using a different CAR construct (19–28z, not yet FDA approved), infections were reported in 42% patients, and were significantly associated with grade 3–4 CRS.<sup>61</sup> Currently, no evidence-based guidelines are established for prophylactic antibiotic use with CAR T therapy, but

prophylaxis against viral infections and *Pneumocystis jiroveci* for all patients, while bacterial and fungal prophylaxis upon onset of neutropenia have been suggested by expert panels.<sup>42,43</sup> The use of lymphodepleting chemotherapy, such as a fludarabine-based regimen, prior to CAR T cell infusion may also drive the need for prophylaxis against *Pneumocystis jiroveci*, regardless of the construct.

#### **Conclusions and future directions**

Notable, and potentially life-threatening, toxicities are possible with novel immunotherapy agents used in relapsed/refractory B cell ALL. Given the encouraging responses in this area of significant unmet need, the use of these agents is only expected to increase, further underscoring the need for clinicians utilizing these agents to be acquainted with their potential toxicities, early recognition thereof, and instigation of appropriate management strategies.

Clinical questions that remain unanswered include the role of HCT in patients who achieve a complete response to immunotherapy agents. All of these agents are being studied in earlier lines of therapy in B cell ALL, either alone or in combination with a chemotherapy backbone (NCT03367299, NCT03541083, NCT02877303, NCT02143414, NCT01371630, NCT03488225, NCT03150693). Mitigating toxicities as well as improving management strategies are areas of ongoing investigation. Additional CAR constructs are under evaluation that allow for a ‘switch off’ mechanism to turn the CAR T off once response is achieved, or to manage toxicity, such as JCAR017, which includes a truncated form of epidermal growth factor receptor that allows for a turn off using cetuximab.<sup>62</sup> Although dose escalation was noted to decrease the incidence of toxicity with blinatumomab, fractionated dosing with CAR T cells is of interest in decreasing the risk of toxicities. The role of siltuximab in prevention and management of IL-6-mediated CRS and ICANS is also of interest. Data on the long-term toxicities of these agents is also being collected, both by the Center for International Blood and Marrow Transplant Research (CIBMTR) as well as manufacturing companies, to understand long-term neurological or other organ toxicity, as well as any potential secondary malignancies from insertional oncogenesis, as has been reported with gene therapy for X-linked

severe combined immunodeficiency and chronic granulomatous disease.<sup>63</sup>

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