Management of adverse effects of new monoclonal antibody treatments in acute lymphoblastic leukemia

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Abstract
Therapeutic options for relapsed/refractory B-cell acute lymphoblastic leukemia have evolved in the past few years. The FDA has approved three novel therapies for this disease: inotuzumab ozogamicin (an anti-CD22 antibody–drug conjugate), blinatumomab (a bispecific T-cell engager), and chimeric antigen receptor T-cell therapy. Although these novel immunotherapies have revolutionized the therapeutic landscape, it is important to understand the crucial aspects of administration, especially toxicity. In this article, we review the unique toxicities and adverse effects of blinatumomab and inotuzumab ozogamicin and provide recommendations for prevention of adverse effects as well as the management options for each medication.

Keywords: acute lymphoblastic leukemia, immunotherapy, blinatumomab, inotuzumab, side effects.

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Introduction
Acute lymphoblastic leukemia (ALL) is an uncommon disease, with 1.7 new cases per 100,000 in the USA between 2013 and 2017, representing 0.3% of all new cancers.¹ ALL presents a bimodal incidence pattern with the majority of cases being in the pediatric population and a second peak in the fifth decade of life.² Depending on the cell of origin, ALL is subdivided into B-cell or T-cell ALL. The precursor B-cell phenotype (B-ALL) accounts for around 80% of all ALL cases. Frontline treatment in newly diagnosed cases, based on the combination of several chemotherapeutic agents, achieves complete remission (CR) rates of >90% and 5-year event-free survival rates of ~85% in pediatric patients. Despite the outcome improvement with the use of treatment combinations inspired on pediatric regimens compared to historical results, the adult population has survival rates of ~40%, worse than in pediatric patients.³ Using standard chemotherapy regimens, >90% of adults with newly diagnosed ALL achieve CR; however, 40–50% of these patients will relapse.³

Relapsed/refractory (r/r) ALL after conventional chemotherapy regimens is associated with poor prognosis, with a remission rate and median overall survival (OS) of 45% and 9 months, respectively. In the salvage setting, CR rates of 18–25% have been reported with a median OS of 3–4 months.⁶ Risk factors for shorter survival in the r/r setting include primary refractory to induction therapy, relapse after allogeneic hematopoietic stem cell transplantation or within 12 months of remission, and relapse after numerous lines of treatment.⁷ Improved salvage therapies were needed to improve CR rates that could be used as a ‘bridge’ to transplant and improved long-term survival. Immunotherapy has become the new cornerstone in cancer treatment due to the improved knowledge of tumor-specific cellular responses by the immune system. Targeting the CD20 antigen was one of the first attempts to improve survival with the use of immunotherapy. Other targets, including CD19 and CD22, have been explored as plausible targets with the aim of improving survival.⁸ The significant expression of CD19 in ALL lymphoblasts (~90%) justifies the development of therapies, such as blinatumomab or chimeric antigen receptor (CAR) T-cell therapy. On the other hand, CD22 is also expressed on the surface of B cells and, in particular, in >90% of B-ALL malignant cells. Its internalization after ligand binding makes it an optimal target for cell lysis mediated by cytotoxic drug delivery – the mechanism of action of inotuzumab ozogamicin (InO).⁹,¹⁰
Both blinatumomab (CD3/CD19 bispecific T-cell engager) and InO (CD22-directed conjugated antibody) are monoclonal targeted therapies tested in patients with r/r ALL. In phase III clinical trials (TOWER and INO-VATE), both agents showed survival improvement and the FDA and EMA have indicated their use for the treatment of B-cell precursor ALL in first or second CR with minimal residual disease (MRD) ≥0.1% in adults and children. Although these treatments offer a new landscape on treatment, this improvement in therapeutic options has been associated with fear of the accompanying toxicities, limiting their use. To date, various adverse events (AEs) related to both treatments as well as a series of recommendations for their early identification and management have been described.

In this review of the literature, we summarize and analyze the management of two promising therapies – blinatumomab and InO – highlighting the importance of prompt recognition of toxicities and their adequate management.

**Blinatumomab**

Blinatumomab is a bispecific T-cell engager (BiTE®) antibody construct conformed by two antigen-binding regions: one for CD3-positive T cells and another for CD19-positive B cells. Attaching these two different sites, blinatumomab can recruit cytotoxic T cells and redirect them against malignant B cells, leading to their lysis. The activation of T cells induces perforin-mediated apoptosis of the targeted B cells. The single current approved indication of blinatumomab is in adult and pediatric ALL patients, in three different scenarios: r/r Philadelphia negative (Ph−), r/r Philadelphia positive (Ph+), and positive MRD cases.

In the setting of r/r Ph− ALL, a larger phase II trial included 189 patients showing CR rates of 33% and a median OS of 6.1 months. The safety profile of blinatumomab was confirmed with a low treatment-related mortality. The multicenter phase III TOWER trial compared salvage treatments in r/r Ph− ALL patients (n=405), specifically blinatumomab and standard of care (SoC) chemotherapy. The SoC arm included four different chemotherapies, high-dose cytarabine, and granulocyte colony-stimulating factor with or without anthracycline (FLAG/FLAG-Ida). After two cycles of continuous intravenous infusion of blinatumomab during 4 weeks (each cycle) with 2 weeks off between cycles, the CR rate (incomplete, partial, or full hematologic recovery) was higher in the blinatumomab arm than in the SoC arm (44% versus 25%; p<0.001). This benefit was also observed in terms of OS: 7.7 months in the blinatumomab group and 4 months in SoC patients with a 0.71 hazard ratio for death (p<0.01). The approval for the use of blinatumomab in r/r Ph− ALL cases was supported by data from the ALCANTARA study. This phase II single-arm trial included 45 patients r/r to at least one second-generation or later tyrosine kinase inhibitor or intolerant to second-generation or later tyrosine kinase inhibitors and intolerant or refractory to imatinib. Blinatumomab achieved CR/partial hematologic recovery in 36% of cases after the first 2 cycles, equivalent to 88% of all those with MRD negativity. Median relapse-free survival (RFS) and OS were 6.7 and 7.1 months, respectively. In the context of MRD-positive ALL, a single-arm phase II study including 116 patients in first or subsequent CR with MRD positivity (≥10−3) was performed. Overall, 78% of patients achieved an MRD negative status after one cycle, showing a significant improvement compared to MRD non-responders in terms of RFS (23.6 versus 5.7 months; p=0.002) and OS (38.9 versus 12.5 months; p=0.002). Median OS was 36.5 months and, at 18 months, 54% of patients met the criteria for the RFS event. Ongoing trials are evaluating the role of blinatumomab in other lines of therapy in ALL. Recently, interim results of the BLIN01 trial were published. This trial looked at blinatumomab infusions as consolidation treatment intercalated with high-dose chemotherapy and showed that treatment with blinatumomab was safe and effective (reduction of MRD levels after each of the two cycles of blinatumomab). Furthermore, maintenance treatment with blinatumomab in high-risk ALL patients after allogenic stem cell transplantation (HCT) has also been tested in a small series. In newly diagnosed ALL patients, the combination of blinatumomab with hyper-CVAD and high-dose methotrexate/ctytarabine showed preliminary CR and MRD rates of 100% and 96%, respectively, with a median follow-up of 17 months. In ALL Ph+ patients included in the GIMEMA LAL2116 D-ALBA TRIAL, blinatumomab was administered with dasatinib as induction chemo-free therapy. Preliminary results reported potential benefit of the combination in terms of safety and efficacy. Although blinatumomab has shown a benefit in survival, there are many AEs to consider in the management of patients on this treatment. The major toxicities produced by this drug that clinicians should be aware of are neurological adverse events (NAEs) and cytokine release syndrome (CRS). Prompt management should be started to minimize the potential risk of these conditions. Many strategies have been described to minimize toxicities, the most important of which is the progressive escalation of the blinatumomab dose from 9 mcg/day in the first week to 28 mcg/day from the second week until the end of treatment.

**Neurological adverse events**

NAEs are one of the main reasons for blinatumomab interruptions. The presentation of NAEs encompasses a wide range of symptoms, from headache, tremor, confusion, or disorientation to more severe clinical manifestations as aphasia, seizure, or stupor. The pathogenesis of blinatumomab-related neurotoxicity remains obscure. As similar NAEs have been described in patients treated with CD19-targeted CAR T cells, it could be hypothesized that NAEs may occur due to the CD19-target dependence. A possible two-step model has been proposed trying to improve the understanding of NAE biology with blinatumomab. In the first instance, blinatumomab induces
the redistribution of peripheral T cells to vessel endothelium and then due to endothelial activation to perivascular space; this migration is B-cell independent. Subsequently, in a B-cell-dependent phenomenon, blinatumomab promotes T-cell activation and cytokine release triggering neurotoxicity.\(^{21,22}\) Another possible two-step model has also been proposed. First, blinatumomab induces the redistribution of peripheral T cells to vessel endothelium and then to the perivascular space due to endothelial activation; this migration is B-cell independent. Subsequently, in a B-cell-dependent phenomenon, blinatumomab promotes T-cell activation and cytokine release, triggering neurotoxicity.\(^{23}\)

In the clinical trials, Topp et al.\(^{12}\) described that NAEs were recorded in 98 (52%) patients, 39% with grade 1/2, 11% with grade 3, and 2% with grade 4. NAEs occurred generally during cycle 1, with the median time to onset and median duration being 9 and 5 days, respectively. However, grade ≥3 NAEs had a longer onset time (16.5 days) and shorter duration (3 days)\(^{12}\). Per protocol, blinatumomab was stopped after grade 3 or serious NAEs. Subsequently, a restart, with dose reduction (dose escalation was not permitted), was allowed after a 2-week blinatumomab-free interval if the NAEs returned to grade ≤1. Temporary discontinuations or interruptions occurred in 29 (15%) patients, 9 of whom were permanently discontinued due to NAEs. A 3-day dexamethasone course (at least 8 mg/day) was administered in this context, with a prophylactic anticoagulant if the NAE was a seizure. Treatment interruptions did not necessarily impair the achievement of remission. Of the 29 patients with blinatumomab discontinuation, 10 achieved CR/partial hematologic recovery before interruption and 6 achieved it after treatment resumption.\(^{12}\) Stein et al.\(^{21}\) performed multivariate analysis for baseline characteristics as risk factors for NAEs. Prior NAEs, race other than white, and more than two prior salvage therapies were statistically significant.\(^{24}\)

In the TOWER trial including 405 r/r Ph\(^+\) ALL patients, similar exclusion criteria regarding central nervous system (CNS) involvement/pathology were described as well as blinatumomab discontinuation related to NAEs. The incidence of any grade NAEs was higher in the blinatumomab group than in the SoC arm (61% versus 50%, respectively); as was the interruption rate due to NAEs (6% versus 1%). Nevertheless, the rate of grade ≥3 NAEs was similar in both treatment groups (blinatumomab 9.4% versus SoC 8.3%).\(^{13}\) Interestingly, considering treatment exposure time, the exposure adjusted event rate (EAER) for grade ≥3 NAEs was higher in SoC patients (0.38 versus 0.95 events per patient-year; \(p=0.008\)).\(^{7}\) As in the TOWER trial, the use of dexamethasone achieved successful results in NAE treatment, with no fatal events related to neurotoxicity.\(^{13}\)

### Cytokine release syndrome

Immunotherapy has become the cornerstone for the new landscape in the treatment of hematologic malignancies, being also responsible for the related toxicities. CRS, secondary to blinatumomab or CAR T-cell therapy, is one of the most significant unique toxicities together with NAEs.

CRS is the consequence of a systemic inflammatory response resulting from dramatic inflammatory cytokine production. The antigen–antibody interaction caused by blinatumomab triggers the activation of cytotoxic T cells and subsequently of macrophages and monocytes, inducing the massive cytokine release.\(^{22}\) The underlying mechanism remains uncertain, although a peak in IL-6, IL-10, and interferon-\(\gamma\) levels has been reported in ALL patients treated with blinatumomab.\(^{27}\)

Clinical signs due to previous events encompass fever, chills, hemodynamic instability, and symptoms related to capillary leak syndrome.\(^{28}\)

The rate of CRS events was constant among different trials.\(^{12,13}\)

### Management and prophylaxis of blinatumomab NAEs

In cases of grade 1–2 neurological toxicity, symptomatic management (intravenous fluids, respiratory support, anti-inflammatory) is recommended and the initiation of treatment with steroids (dexamethasone 8 mg every 8 hours) should be considered to avoid progression to grade 3. Discontinuation of blinatumomab is not recommended unless there is progression with more severe symptoms.

Once a grade 3 NAE is confirmed, blinatumomab needs to be stopped until toxicity improvement to grade ≤1 for at least 3 days. Blinatumomab can be restarted at baseline dose, escalating the dosage after 7 days if there is no recurrence. In grade 4 NAEs, patients in whom grade 3 neurotoxicity lasts for more than 7 days or there is recurrence during blinatumomab reintroduction, permanent discontinuation is recommended.\(^{25}\) Along with treatment interruption, dexamethasone 8 mg every 8 hours for 3 days with tapering dose during 4 days is frequently used and recommended.

Primary seizure prophylaxis is not indicated at present due to its low incidence rate (<1%);\(^{13}\) however, secondary prophylaxis should be carried out in specific cases. NAE management is summarized in Table 1. Further approaches, such as imaging studies (CT scan, magnetic resonance), electroencephalogram, or cerebrospinal fluid analysis, need to be conducted with the aim of discarding other possible neurological diseases.

Patients with CNS involvement were excluded from the earlier-mentioned trials; however, some experience with blinatumomab in such cases has been reported. In a small retrospective series, blinatumomab was administered to ten ALL patients with active CNS disease or a history of CNS involvement. Grade ≥3 NAEs were observed in two patients, leading to blinatumomab discontinuation. The use of blinatumomab remained effective despite CNS status.\(^{26}\) Using blinatumomab in patients with CNS involvement of ALL remains controversial and should be discussed with an ALL expert prior to initiation.
pre-phase dexamethasone treatment in high-burden disease patients were implemented in those studies as grade 4 CRS cases were described after blinatumomab infusion.²⁹

In a phase III trial,¹³ the relative incidence rate of any grade CRS was 16% with a grade ≥3 CRS rate of 5%. Any grade events were most common during cycle one compared with cycle 2 (13% versus 3%); likewise for grade ≥3 CRS (4% versus 1%). In contrast to NAEs, CRS toxicity had a faster onset time, with a median of 2 days from blinatumomab administration for any grade CRS and 4 days for grade ≥3.⁷ The rates of treatment interruption and discontinuation due to CRS were 5% and 1%, respectively.¹³

It is important to highlight that, in MRD-positive ALL patients, the CRS rate was lower compared with previous studies in r/r ALL patients (any grade CRS rate of 3% and 1.7% grade ≥3 events);¹⁵ this could be explained by the difference in tumor burden between both populations, with higher release cytokines in r/r ALL patients (Table 2).

### Management and prophylaxis of blinatumomab CRS

Limiting the incidence and severity of CRS must be one of the goals when blinatumomab is administered. For this purpose, guidelines incorporate several measures, including cytoreduction, prophylactic treatment, pre-phase dexamethasone, and dose modification/interruptions. Simultaneously, adopting international or institutional guidelines for CRS management in CAR T-cell patients is also crucial.³⁰

Cytoreduction is recommended in patients who have a high tumor burden: more than 50% of blasts in bone marrow.
studies, blast counts on peripheral blood $\geq 15,000/\mu L$, extramedullary high tumor load, or rapid increase of lactate dehydrogenase, which could indicate progressing disease.12,13 Dexamethasone, a maximum of 24 mg/day during 5 days or cyclophosphamide have been proposed as cytoadherence therapies. In the premedication setting, 20 mg of dexamethasone 1 hour before the first dose of blinatumomab and prior to dose escalation is also suggested.25

As has been noted, most preventive strategies involve the use of steroids. Even during the management of the initial CRS grades, the administration of dexamethasone three times daily could prevent the discontinued use of blinatumomab and avoid progression in clinical severity. Blinatumomab interruption, supported by its short half-life of 1–2 hours, along with other supportive care interventions, allows quicker CRS completion. If grade 3 CRS is diagnosed, interruption is mandatory along with dexamethasone administration 8 mg/8 hours for up 3 days with 3-day tapering. At its recovery, blinatumomab can be restarted at a lower dose with dexamethasone premedication. Permanent discontinuation is considered in grade 4 events.

The complete impact of corticosteroids on blinatumomab efficacy is not well described, but some studies conjecture that the reduction of cytokine production is not followed by an impairment of T-cell activation.31 Tocilizumab, an IL-6 antagonist, is widely used in CRS caused by CAR T-cell therapy and is approved by the FDA. Among blinatumomab clinical trials sponsored by Amgen, approximately 1000 patients were treated with BiTE; 39 of them were diagnosed with CRS and 15% were treated with tocilizumab. For all cases, CRS resolved. Once blinatumomab was approved in December 2017, almost 4600 ALL patients received blinatumomab with 160 CRS cases reported; 24 of them were managed with tocilizumab (15/16 CRS events for which outcome was provided were resolved).32 The management of CRS is summarized in Table 3.

### Infectious adverse events

Infection is an important cause of morbidity and mortality in ALL patients in the SoC chemotherapy era, becoming a real challenge in the management of this disease.33

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### Table 3. Management of cytokine release syndrome secondary to blinatumomab.

| CRS management                                                                 |
|-------------------------------------------------------------------------------|
| **When?**                                                                     |
| Prephase                                                                       |
| High tumor burden disease$^a$                                                 |
| - DXM: 10 mg/m$^2$/day or maximum of 24 mg/day for up to 5 days               |
| - Cy: 200 mg/m$^2$/day for up to 4 days                                       |
| Premedication                                                                 |
| r/r                                                                           |
| - DXM: 20 mg                                                                  |
| MRD positive                                                                  |
| - PRD: 100 mg                                                                 |
| - DXM: 16 mg                                                                  |
| Dose escalation                                                               |
| r/r                                                                           |
| - First cycle                                                                  |
| - Days 1–7: 9 mcg/day                                                         |
| - Days 8–28: 28 mcg/day                                                       |
| Continued cycles                                                              |
| - Days 1–28: 28 mcg/day                                                       |
| MRD positive                                                                  |
| Days 1–28: 28 mcg/day                                                        |
| Treatment                                                                      |
| CRS Grade 3                                                                    |
| - Interrupt blinatumomab until grade $\leq$1 and at least 3 days             |
| - Restart at 9 mcg/day and, if no recurrence in 7 days, escalate to 28 mcg/day|
| - Permanent discontinuation of blinatumomab if NAE occurred at 9 mcg/day or need $\geq$7 days to resolve|
| - DXM: 8 mg/8 hour/3 days with dose tapering for 4 days                      |
| - Tocilizumab 8 mg/kg, maximum 3 doses separated by 12 hours                 |
| CRS Grade 4                                                                    |
| - Permanent discontinuation of blinatumomab                                  |
| - DXM and tocilizumab: same as grade 3                                       |

$^a$>50% of blasts in bone morrow, blast counts on peripheral blood $\geq 15,000/\mu L$, extramedullary high tumor load or rapidly increase of lactate dehydrogenase.

CRS, cytokine release syndrome; Cy, cyclophosphamide; DXM, dexamethasone, MRD, minimal residual disease; NAE, neurological adverse event; PRD, prednisone; r/r, relapsed/refractory.
Considering that blinatumomab targets CD19-positive cells, all B-cells are depleted, including CD19-positive plasmablast and precursors, with a subsequent decrease in plasma cell numbers. As a result, a drop in immunoglobulin levels is observed, with a slow recovery. A study of lymphocyte subpopulations in ALL patients during blinatumomab treatment showed different trends in B-cell and T-cell counts. B cells experience a drop at the beginning of the infusion and remain suppressed over the duration of immunotherapy. Conversely, after an initial decline, T-cell counts recover to baseline in less than 10 days and, within 2–3 weeks, experience an expansion (doubling of their number on average). Further investigation to correlate the latter results with the incidence of infections is necessary. Another immunosuppressive effect of blinatumomab, which has an impact on infections, is neutropenia; this will be discussed later.

Compared with SoC, blinatumomab showed a better infection profile with a lower infection grade ≥3 rate (34% versus 52%), confirmed when infection rates were adjusted by treatment exposure time (1.63 versus 6.49 events per patient-year in blinatumomab and SoC arms, respectively). Despite similar fatal AE rates in both arms for infections and sepsis (blinatumomab 11% versus SoC 12% and blinatumomab 3% versus SoC 4%, respectively), a lower EAER for blinatumomab in relation to SoC (52% versus 56% (p < 0.01)) was demonstrated, as well as a lower infection grade ≥3 rate (34% versus 39% is reported with SoC.)

A lower EAER for blinatumomab in relation to SoC (52% versus 56% (p < 0.01)) was demonstrated, as well as a lower infection grade ≥3 rate (34% versus 39% is reported with SoC.), which was confirmed when infection rates were adjusted by treatment exposure time (1.63 versus 6.49 events per patient-year in blinatumomab and SoC arms, respectively). Despite similar fatal AE rates in both arms for infections and sepsis (blinatumomab 11% versus SoC 12% and blinatumomab 3% versus SoC 4%, respectively), a lower EAER for blinatumomab in relation to SoC was reported. Febrile neutropenia rates in ALL patients treated with blinatumomab range between 24% and 28%, while a rate of 39% is reported with SoC. It is important to highlight the high rate of catheter-related bloodstream infections observed with blinatumomab, ranging from 3% to 11% in different trials. Immunoglobulin levels are decreased in blinatumomab patients, related to CD19 targeting, with hypogammaglobulinemia rates of 6% compared with 0.6% in SoC patients.

### Management and prophylaxis of blinatumomab infectious AEs

Blinatumomab is not associated with a relevant increment in the risk of infection; thus, no additional preemptive measure other than following institutional or expert prophylaxis guidelines is mandatory. Nevertheless, physicians need to be aware of catheter-related bloodstream infections; careful management of these devices is warranted due to blinatumomab continuous administration (4 weeks per cycle), which implies a higher risk. Finally, as a slow recovery of immunoglobulin levels has been reported, its replacement should be considered in persistent hypogammaglobulinemia or with increased infection rates.

### Hematologic toxicity

Overall, the incidence rate of cytopenias with blinatumomab was lower than for patients treated with SoC (60 versus 70%). Particularly, for grade ≥3 neutropenia, thrombocytopenia, and anemia, the rates were 18 versus 27%, 15% versus 28%, and 20% versus 35%, respectively, in the blinatumomab and SoC arms. Indeed, considering treatment exposure, EAERs of any grade for cytopenias were 5.25 versus 23.99 events per patient-year (p<0.001) and, in grade ≥3 cytopenias, 3.64 versus 20.07 events per patient-year (p<0.001).

In moderate or severe neutropenia, the use of granulocyte colony-stimulating factor (G-CSF) is recommended instead of blinatumomab interruption. The administration of G-CSF in ALL patients is safe and could decrease the infection risk associated with neutropenia. The incidence rates of hematologic toxicities in blinatumomab trials are summarized in Table 4.

### Other AEs

Organ damage secondary to CRS can occur, and there is a particular plausible correlation with cardiac dysfunction due to the effect of several inflammatory cytokines on myocardocytes. The decrease in cardiac contractility and the induction of fibrosis as well as cardiac hypertrophy are produced by IL-1β, IL-2, IL-6, and tumor necrosis factor-α. As a result, all these alterations could develop inotropic and chronotropic impairment, leading to cardiac failure and death; indeed, a case of fatal cardiac failure was reported in a patient treated with blinatumomab.

Hemophagocytic lymphohistiocytosis possibly developed by CRS has been reported in the blinatumomab context. It is important to highlight the high rate of catheter-related bloodstream infections observed with blinatumomab, ranging from 3% to 11% in different trials. Immunoglobulin levels are decreased in blinatumomab patients, related to CD19 targeting, with hypogammaglobulinemia rates of 6% compared with 0.6% in SoC patients.

Bone marrow necrosis is an infrequent complication of childhood ALL, being described in 0.5% of cases. The mechanism of the underlying pathophysiology remains unknown, yet microvascular damage, thrombosis, or hypoxic injury have been hypothesized as a potential mechanism for this condition. The direct toxic effect of chemotherapy on bone marrow cells probably also plays a role as a trigger. Elevated levels of IL-6 and tumor necrosis factor-α were observed in bone marrow necrosis cases in ALL, including in a 15-year-old patient after blinatumomab therapy, likely due to the release of chemokines and cytokines following BiTE administration. Thus, it is important to be aware of this complication in ALL patients treated with blinatumomab with similar symptoms (bone pain and severe cytopenias).

### Inotuzumab

InO is composed of an anti-CD22 monoclonal antibody linked by an acid labile linker to N-acetyl-γ-calicheamicin dimethylhydrazide, a derivate of the antitumor antibiotic calicheamicin. Calicheamicin is derived from *Micromonospora echinospora* and acts by causing DNA breaks, resulting in cell death. The interaction of CD22-positive cells with the conjugate antibody produces the internalization and release of...
In this section, we will describe the main AEs and summarize the recommendations of the main cooperative groups for the early identification and early management of toxicities.

### Hepatic toxicity and sinusoidal obstruction syndrome

Hepatotoxicity with the use of InO is represented in the form of hyperbilirubinemia, transaminitis, and SOS. SOS is a serious and potentially fatal complication associated with allogenic stem cell transplantation with a mortality rate of 84%. The INO-VATE study reported an incidence of any grade SOS in 13% of patients in the InO group compared with 11% in the standard therapy group, with almost the same percentage of grade ≥3 cases for both groups. The median time to SOS was 15 days after HCT among patients receiving InO who proceeded to follow-up HCT. The presentation after HCT was reported in 8% of patients receiving one InO cycle, 19% of patients receiving two cycles, and 29% receiving more than two InO cycles. SOS incidence in patients who underwent HCT after InO was higher in the older group (≥55 years) compared with those who were younger (41% versus 17%).

In this syndrome, sinusoidal endothelial cells and hepatocytes in zone 3 of the hepatic acinus are damaged by toxic metabolites generated during the conditioning regimen, resulting in the penetration of red blood cells into the space of Disse beneath the endothelial cells and obstructing the sinusoidal flow downstream. In the case of patients receiving InO, the pathophysiology is not completely understood. However, the observation of VOD related to the use of gemtuzumab ozogamicin (a humanized anti-CD-33 antibody) conjugated with calicheamicin suggests that this complication is due to the direct effect of the antibiotic. This theory has been probed in animal models, with midzonal degeneration...
and loss of sinusoidal endothelial cells, along with marked platelet accumulation in sinusoids, secondary to the conjugate antibody. This process is mediated by the direct action of the Kupffer cells (responsible for antibody-dependent cellular phagocytosis), via their Fc receptors, resulting in the delivery of the drug conjugate to liver cells.

Clinical presentation is characterized by the presence of elevated bilirubin, hepatomegaly, abdominal pain (right upper quadrant), weight gain >5%, and ascites. In severe cases of SOS, the association with less common symptoms, such as hypoxia, encephalopathy, pleural effusion, and renal insufficiency or failure, could be observed. SOS can be diagnosed through a variety of diagnostic methods, yet the gold standard is by transjugular liver biopsy, a technique with complications due to the high presence of refractory thrombocytopenia as a manifestation of SOS. Ultrasound can also provide useful information, especially to identify the decrease in velocity or reversal of portal flow; however, this finding is often seen at later stages of SOS.

The main risk factors for classical SOS are the use of myeloablative conditioning regimens for HCT, including busulfan or total body irradiation, patients undergoing a second HCT, unrelated donor transplantation, older age, poorer Karnofsky performance scores, and a preexisting liver disease. Of all these factors, two have been the most identified in patients with SOS after InO use, namely the use of pre-HCT conditioning regimens with alkylating agents and elevated levels of bilirubin before HCT. In cases of InO use, conditioning regimens containing thiopeta and melphalan should be avoided, if possible. Other preventative strategies should be considered, for example, avoiding concomitant hepatotoxic medications such as azoles and considering the use of prophylaxis with ursodiol.

The Center for International Blood and Marrow Transplant Research developed and assessed a risk score to identify patients at high risk of SOS after an allogenic HCT; however, this did not include InO exposure. Therefore, close monitoring for signs and symptoms is necessary. The EBMT guidelines published in 2018 identified the close relationship between the number of InO cycles and the rate of SOS, recommending limiting the administration of InO to two cycles if feasible. New strategies have been developed to minimize the high risk of SOS associated with InO. One of those is the possibility of reducing or dividing the total dose or increasing the interval time between the last cycle of InO and the performance of HCT.

In 2018, Kantajarian et al. published the results of InO administration in combination with low-intensity chemotherapy (mini-hyper CVD) for older patients with ALL. InO was administered on just 1 day per cycle at a total dose of 1.3 mg/m² for cycle 1 followed by 0.8 mg/m² for subsequent cycles. This regimen resulted safe and active in older patients, with a lower frequency of SOS than what was reported. Jabbour et al. confirmed, in 2019, that the combination of low-intensity chemotherapy with InO was safe, with a low rate of early mortality. The strategy of using lower weekly doses of InO instead of the sequential use of blinatumomab led to a decrease in the rate of SOS.

Blood tests should be performed to monitor bilirubin levels and liver function tests at least once before the start of each InO dose. Furthermore, patient weight should be monitored during their time in hospital, both before and after transplantation.

### Table 5. Management of sinusoidal obstruction syndrome associated with inotuzumab ozogamicin.

| Diagnosis                      | Prevention                                      | Treatment                                      |
|--------------------------------|-------------------------------------------------|------------------------------------------------|
| Previous to HCT                | Avoid double alkylator conditioning regimens     | Permanent discontinuation of InO               |
| During to HCT:                 |                                                 |                                                |
| Bilirubin ≥2 mg/dL plus two of:| No more than two InO cycles prior to HCT preferable | Supportive therapy for fluid balance and pain control |
| (1) Painful hepatomegaly       |                                                 |                                                |
| (2) Weight gain >5%            |                                                 |                                                |
| (3) Ascites                    |                                                 |                                                |
| After HCT:                     |                                                 |                                                |
| Symptoms as the criteria       | Avoid concomitant hepatotoxic medication use (e.g. antifungal treatment) | Paracentesis in cases of respiratory compromise due to ascites |
| Histological diagnosis of SOS  | Use of prophylactic agents such as ursodiol during HCT | Defibrotide for severe SOS                     |
| Ultrasound evidence of SOS     |                                                 | Limit fluid removal with paracentesis to <1 L to avoid disruption of renal perfusion |

HCT, allogenic stem cell transplantation; InO, inotuzumab ozogamicin; SOS, sinusoidal obstruction syndrome.
Table 6. **InO dose modifications for hematologic toxicities.**

| Criteria | Dose modification |
|----------|-------------------|
| ANC ≥1x10⁹/L | If ANC decreases, interrupt the next cycle until recovery of ANC to ≥1x10⁹/L. Discontinue InO if low ANC persists for ≥28 days and is suspected to be related to InO. |
| Platelet counts was ≥50x10⁹/L | If platelet count decreases, interrupt the next cycle until recovery to ≥50x10⁹/L. If count persist for >28 days and is suspected to be related to InO, discontinue the treatment. |
| ANC was <1x10⁹/L and platelet counts was <50x10⁹/L | If ANC or platelet count decreases, then interrupt the next cycle of treatment until at least one of the following occurs:  
  • ANC and platelet count recover to at least baseline levels for the prior cycle.  
  • ANC recovers to ≥1x10⁹/L and platelet count recovers to ≥50x10⁹/L.  
  • Stable or improved disease (based on most recent bone marrow assessment) and the ANC and platelet count decrease are considered to be due to the underlying disease (not considered to be InO-related toxicity). |

ANC, absolute neutrophil count; InO, inotuzumab ozogamicin.

The initial management of SOS should include symptomatic supportive care and careful attention to fluid balance. The use of diuretics, oxygen, and hemodialysis/hemofiltration is also feasible. When ascites compromise respiration, paracentesis is recommended and, in severe cases, a transjugular intrahepatic portosystemic shunt could be considered. Patients should also continue to receive ursodiol prophylactically.

Defibrotide, a mixture of single-stranded oligonucleotides, is recommended in patients with severe SOS and those with renal or pulmonary dysfunction. The use of this drug in a prophylaxis setting is currently under investigation for patients at high risk of developing SOS and it is not recommended outside clinical trials (Table 5).

**QT prolongation**

Anticancer agents have the potential to cause adverse electrocardiographic effects, particularly QT interval prolongation, which serves as a surrogate marker for potentially fatal arrhythmia (Torsade de Pointes). Preclinical studies did not indicate a potential for dimethylhydrazide to induce QT prolongation or grade ≥3 or Torsade de Pointes events. However, prolongation of the corrected QT interval by ≥ 60 milliseconds from baseline was noted in the group of patients receiving InO. It is recommended to obtain baseline electrocardiograms and electrolytes followed by close monitoring of symptoms associated with corrected QT prolongation (dizziness, light-headedness, or syncope). The use of concomitant medication known to prolong QT interval, including antiarrhythmic drugs (e.g. quinidine, procainamide, amiodarone), antibiotics (e.g. macrolides, ketoconazole), antihistamines (e.g. terfenadine, astemizole), antidepressants (e.g. tricyclic antidepressants), and antipsychotics (e.g. haloperidol), should be managed with caution.

**Hematological toxicity**

One of the most common AEs associated with the myelosuppressive action of cancer treatment is cytopenias, the most common of which are neutropenia and thrombocytopenia. In the INO-VATE study, neutropenia was reported in 48% of InO patients, with a similar percentage of cases in the standard therapy arm. However, the rate of febrile neutropenia was lower in the InO group (27%) compared with the standard therapy group (52%). Thrombocytopenia of any grade was reported in 45% of patients in the InO arm compared with 61% of patients in the standard arm. The platelet transfusion rate was major in the standard therapy group (95% of patients) compared with 64% in the InO group and hemorrhagic events were reported in 33% of patients administered InO.

The EBMT guidelines recommend that complete blood counts should be performed at least before each InO cycle. The monitorization of signs and symptoms of febrile neutropenia or bleeding episodes related to thrombocytopenia is also recommended. In cases of severe infections and severe cytopenias, interruption, reduction, or discontinuation of InO doses may be necessary. Patients with an absolute neutrophil count below 1000/mm³ secondary to InO treatment may be treated with G-CSF. The prophylactic use of G-CSF may be
considered for patients with expected neutropenia or a risk of fever $\geq 20\%$. Recommendations and dose modifications are summarized in Table 6.

### Infectious AEs

The reduction in B-cell levels observed after the use of anti-CD20 monoclonal antibodies is expected to also be observed in patients treated with anti-CD22 agents. A rapid decrease in the number of circulating CD22-positive B cells has been reported after InO administration.\(^{67,72}\) As a consequence, hematologic cytopenias were the most reported AEs associated with InO, although febrile neutropenia was less than standard therapy. Furthermore, the incidence of infections (sepsis or pneumonia) was similar in both arms of the study or slightly lower with InO, confirming that this agent does not increase the risk of infection.

No benefit is expected from the universal use of antibacterial, antiviral, or anti-pneumocystis prophylaxis for patients receiving CD22-targeted therapy; however, infection risk should be individually evaluated considering patient comorbidities.

Screening for chronic and resolved hepatitis B virus (HBV) infection should be performed before starting treatment with InO. In HBsAg-positive patients, antiviral prophylaxis should be indicated in order to prevent HBV reactivations, while HBV-DNA monitoring and preemptive antiviral treatment may be appropriate for HBsAg-negative but anti-HBc-positive patients.\(^{68}\) Recommendations are summarized in Table 7.

### Other AEs

Severe or mild infusion-related reactions can occur in almost all cancer treatments, with a variety of signs and symptoms ranging from flash or rash to severe life-threatening reactions.\(^{69}\) The INO-VATE study reported the presence of infusion-related reactions of any grade in 1% of patients.\(^{52}\) Premedication with steroids, antipyretics, and antihistamines is recommended. In cases of severe reactions, interruption or suspension of the infusion must be evaluated.

Tumor lysis syndrome is usually common after the first dose of cancer treatment is given and is a life-threatening emergency. It can occur spontaneously or due to cell death following

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**Table 7. General recommendations for other InO adverse events.**

| Other adverse events | Prolonged QT syndrome | Infections | Infusion-related reactions | Tumor lysis syndrome |
|----------------------|-----------------------|------------|---------------------------|----------------------|
| Before starting the InO treatment | Caution in patients with a history or predisposition to prolonged QT syndrome | Primary prophylaxis is not recommended, but to assess individually according to comorbidities | Premedication with corticosteroids, antipyretics, and antihistamines | Hydration and allopurinol |
| | Assessment and monitoring with EKG | Screening for HBV | | Cytotherapy with a combination of HU, steroids, or vincristine is recommended for patients with circulating lymphoblasts ($\geq 10,000/mm^3$) |
| | | | | Rasburicase |
| Monitoring | Monitoring of ion levels | Monitor related signs and symptoms | Monitor signs and symptoms during infusion | Monitor related signs and symptoms |
| | Beware of concomitant drugs (procainamide, amiodarone, macrolides, antihistamines, antidepressants) | Treatment in accordance with standard medical practice | Treatment in accordance with standard medical practice | Treatment in accordance with standard medical practice |
| Severe cases | Discontinue InO infusion and start appropriate medical treatment | Discontinue InO infusion and start appropriate medical treatment | Discontinue InO infusion and start appropriate medical treatment | Discontinue InO infusion and start appropriate medical treatment |

EKG, electrocardiogram; HBV, hepatitis B virus; HU, hydroxyurea; InO, Inotuzumab ozogamicin.
Cytoreduction with hydroxyurea or cyclophosphamide is recommended before the first dose of InO in patients with circulating lymphoblasts >10,000/mm³. In patients with a high tumor burden or elevated uric acid levels >7.5 mg/dL, the administration of rasburicase should be considered to prevent tumor lysis syndrome. Additional preventive measures, such as hydration or allopurinol prescription, may also be recommended (Table 7).

**Conclusion**

There has been a dramatic change in the clinical settings of ALL treatment, especially in r/r cases. Immunotherapeutic agents have distinct mechanisms of action and toxicity profiles compared with conventional cytotoxic chemotherapy agents. The toxicities related to these drugs are unique, with the most important being on-target and secondary to the mechanism of action. Blinatumomab is associated with CRS and neurotoxicity, both of which need prompt recognition and management with corticosteroids. The principal AE with InO is SOS following HCT. Close follow-up and early detection are recommended to prevent long-term morbidity and mortality. Management should be provided in accordance with the EBMT recommendations. As the use of these agents continues to expand, an increased awareness of the toxicities will be important so that they are effectively managed to optimize patient outcomes and limit the AEs of these agents in ALL.

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