DRUGS IN CONTEXT
RIGOROUS • RAPID • RESPONSIVE

A continuous publication, open access, peer-reviewed journal

ACCESS ONLINE

REVIEW

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

Diego Conde-Royo MD[1], Luis Miguel Juárez-Salcedo MD[2], Samir Dalia MD[3]

[1]Hematology Department, Principe de Asturias General Hospital, Madrid, Spain; [2]Hematology Department, Gregorio Marañón University Hospital, Madrid, Spain; [3]Hematology/Oncology Department, Mercy Clinic Oncology and Hematology – Joplin, MO, USA

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.

Citation

Conde-Royo D, Juárez-Salcedo LM, Dalia S. Management of adverse effects of new monoclonal antibody treatments in acute lymphoblastic leukemia. Drugs in Context 2020; 9: 2020-7-2. DOI: 10.7573/dic.2020-7-2

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;[4] however, 40–50% of these patients will relapse.[5]

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.[11] 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.[12] 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 chemotherapy regimens, with most patients (45%) receiving fludarabine, high-dose cytosine arabinoside, 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).[13] 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.[14]

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.[15]

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).[16] Furthermore, maintenance treatment with blinatumomab in high-risk ALL patients after allogenic stem cell transplantation (HCT) has also been tested in a small series.[17] In newly diagnosed ALL patients, the combination of blinatumomab with hyper-CVAD and high-dose methotrexate/cytarabine showed preliminary CR and MRD rates of 100% and 96%, respectively, with a median follow-up of 17 months.[18] 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.[19]

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.[20] 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 anticonvulsant 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]

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.

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-γ 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] Dose step escalation, dexamethasone premedication, and

Table 1. Management of neurologic adverse events secondary to blinatumomab.

	NAE management	
	When?	**How?**
Seizure prophylaxis	Primary prophylaxis	Not required unless specified by hospital treatment protocol
	Secondary prophylaxis	Therapeutic dose - Phenytoin - Levetiracetam
Treatment	NAE Grade 3	- Interrupt blinatumomab - DXM: 8 mg every 8 hours x 3 days with dose tapering for 4 days - When resolved: restart at 9 mcg/day and, if no recurrence in 7 days, escalate to 28 mcg/day
	NAE Grade 4	- Permanent discontinuation of blinatumomab - DXM: same as grade 3
	≥1 seizure	Permanent discontinuation of blinatumomab

DXM, dexamethasone; NAE: neurological adverse event.

Table 2. CRS rates secondary to blinatumomab in r/r and MRD-positive ALL trials.

CRS Grade	**CRS rates in blinatumomab trials**				
	r/r ALL Ph$^-$ (ref.[30]) **Phase II** ***n*=36**	**r/r ALL Ph$^-$ (ref.[12])** **Phase II** ***n*=189**	**r/r ALL Ph$^-$ (ref.[13])** **Phase III** ***n*=267**	**r/r ALL Ph$^+$ (ref.[14])** **Phase II** ***n*=45**	**MRD-positive ALL (ref.[15])** **Phase II** ***n*=116**
Grade ≤3 *n* (%)	NA	NA	25 (9)	3 (6.7)	2 (1.7)
Grade ≥3 *n* (%)	3 (8)	3 (2)	13 (5)	0	2 (1.7)

ALL, acute lymphoblastic leukemia; CRS, cytokine release syndrome; MRD, minimal residual disease; NA, not available; Ph, Philadelphia; r/r, relapsed/refractory.

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

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

	CRS management	
	When?	**How?**
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 ≤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 ≥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 ≥15,000/μL, 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.

studies, blast counts on peripheral blood ≥15,000/μL, extramedullary high tumor load, or rapid increase in 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 cytoreduction 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 discontinuation of blinatumomab and avoid progression in clinical severity. Blinatumomab interruption, supported by its short half-life of ~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]

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.[34] 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).[35] 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 was reported.[7] Febrile neutropenia rates in ALL patients treated with blinatumomab range between 24% and 28%, while a rate of 39% is reported with SoC.[12,13] It is important to highlight the high rate of catheter-related bloodstream infections observed with blinatumomab, ranging from 3% to 11% in different trials.[14,36] Immunoglobulin levels are decreased in blinatumomab patients, related to CD19 targeting, with hypogammaglobulinemia rates of 6% compared with 0.6% in SoC patients.[37]

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.[13]

Hematologic toxicity

Overall, the incidence rate of cytopenia 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 ($p<0.001$).[7]

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.[38] 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 myocardiocytes. 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.[39]

Hemophagocytic lymphohistiocytosis possibly developed by CRS has been reported in the blinatumomab context. Teachey et al.[39] reported a case of hemophagocytic lymphohistiocytosis after blinatumomab administration triggered by the massive production of cytokines. The authors observed similar clinical features in patients treated with CAR T-cell therapy, with positive results when tocilizumab was administered.[40]

Bone marrow necrosis is an infrequent complication of childhood ALL, being described in 0.5% of cases.[41] 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.[42] 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.[43] 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.[44] Calicheamicin is derived from *Micromonospora echinospora* and acts by causing DNA breaks, resulting in cell death.[45] The interaction of CD22-positive cells with the conjugate antibody produces the internalization and release of

Table 4. Hematologic toxicity in blinatumomab trials.

	Hematologic toxicity of blinatumomab					
	Phase III[13] *n*=267		Phase II[72] *n*=189		Phase II[15] *n*=116	
	Any grade *n* (%)	Grade ≥3 *n* (%)	Any grade *n* (%)	Grade ≥3 *n* (%)	Any grade *n* (%)	Grade ≥3 *n* (%)
Leukopenia	NA	8(3)	19 (10)	15 (8)	8 (7)	7 (6)
Neutropenia					18 (15.5)[a]	18 (15.5)[a]
Febrile neutropenia	64 (24)	57 (21.3)	53 (28)	48 (25.4)		
Neutropenia	53 (20)	47 (17.6)	33 (17.4)	30 (16)		
Anemia	69 (25.8)	53 (19.8)	38 (20)	27 (14.2)	7 (6)	5 (4.3)
Thrombocytopenia	47 (17.5)	39 (14.5)	21 (11)	16 (8.4)	6 (5)	5 (4.3)

[a]No distinction between febrile neutropenia and neutropenia.
NA, not available.

calicheamicin into lysosomes in the cytoplasm cell, where it leads to double-strand DNA cleavage and subsequent apoptosis.[46,47,48] A phase II trial administered InO initially at 1.8 mg/m^2 every 3–4 weeks and subsequently at 0.8 mg/m^2 on day 1 followed by 0.5 mg/m^2 on days 8 and 15, every 21 days.[49,50] The overall response rate of the 49 patients was 58%. In the phase III INO-VATE study, the efficacy of InO was assessed in patients with relapsed or refractory B-cell ALL. Patients (*n*=326) were randomized to receive single-agent InO on days 1, 8, and 15 in 21-day or 28-day cycles *versus* standard intensive chemotherapy as first and second salvage therapy. The primary endpoints for the trial were CR with or without count recovery and OS. High response rates (81% *versus* 29%) and high MRD negativity (78% *versus* 28%) were observed in the InO group compared with standard therapy.[50] The median OS was 7.7 months for InO *versus* 6.7 months for standard therapy and, in a post-hoc survival analysis, median OS was 13.9 *versus* 9.9 months, respectively.

The percentage of patients who experienced AEs in the INO-VATE study was 94.4% in the InO group; of these AEs, 87.8% were related to InO (severe AEs were reported in 51.2%) and 3% of the patients required dose reduction due to AEs related to treatment. The most common AEs were pneumonia, febrile neutropenia, hepatotoxicity (including sinusoidal obstruction syndrome [SOS]), and sepsis.[51] However, the good results obtained in r/r cases, despite the AEs observed, contributed to the FDA approval of InO in August 2017.

Since its approval, many groups have developed guidelines for the early identification of toxicities and their rapid management, avoiding treatment suspension. In 2018, Kebriaei et al.[52] published the European Society for Blood and Marrow Transplantation (EBMT) guidelines for the management of the main AEs associated with InO treatment, highlighting the importance of complication-preventive management as well as the early identification of AEs and their adequate management.

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%.[53] 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.[54] The median time to SOS was 15 days after HCT among patients receiving InO who proceeded to follow-up HCT.[54] 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.[54] 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%).[55]

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.[56,57] 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.[58,59] This theory has been probed in animal models, with midzonal degeneration

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: (1) Painful hepatomegaly (2) Weight gain >5% (3) Ascites	No more than two InO cycles prior to HCT preferable	Supportive therapy for fluid balance and pain control
After HCT: Symptoms as the criteria Histological diagnosis of SOS Ultrasound evidence of SOS	Avoid concomitant hepatotoxic medication use (e.g. antifungal treatment) Use of prophylactic agents such as ursodiol during HCT	Paracentesis in cases of respiratory compromise due to ascites Defibrotide for severe 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.

and loss of sinusoidal endothelial cells, along with marked platelet accumulation in sinusoids, secondary to the conjugate antibody.[60] 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.[61,62] 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.[63] 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.[54,63] In cases of InO use, conditioning regimens containing thiotepa 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.[52]

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.[58,59] 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/m^2 for cycle 1 followed by 0.8 mg/m^2 for subsequent cycles. This regimen resulted safe and active in older patients, with a lower frequency of SOS than what was reported.[58,64] Jabbour et al.[59] 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.[59,65]

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 6. InO dose modifications for hematologic toxicities.

Criteria	Dose modification
ANC ≥1x10^9/L	If ANC decreases, interrupt the next cycle until recovery of ANC to ≥1x10^9/L Discontinue InO if low ANC persists for ≥28 days and is suspected to be related to InO
Platelet counts was ≥50x10^9/L	If platelet count decreases, interrupt the next cycle until recovery to ≥50x10^9/L. If count persist for >28 days and is suspected to be related to InO, discontinue the treatment
ANC was <1x10^9/L and platelet counts was <50x10^9/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 ≥1x10^9/L and platelet count recovers to ≥50x10^9/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.[62] When ascites compromise respiration, paracentesis is recommended and, in severe cases, a transjugular intrahepatic portosystemic shunt could be considered.[62] 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.[66] 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).[61,67,68] 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 mseconds from baseline was noted in the group of patients receiving InO.[50] 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).[69] 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%).[50] 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[50] 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.[51] 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.[51] Patients with an absolute neutrophil count below 1000/mm^3 secondary to InO treatment may be treated with G-CSF.[70] The prophylactic use of G-CSF may be

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 Assessment and monitoring with EKG	Primary prophylaxis is not recommended, but to assess individually according to comorbidities Screening for HBV	Premedication with corticosteroids, antipyretics, and antihistamines	Hydration and allopurinol Cytoreduction with a combination of HU, steroids, or vincristine is recommended for patients with circulating lymphoblasts (≥10,000/mm^3) Rasburicase
Monitoring	Monitoring of ion levels Beware of concomitant drugs (procainamide, amiodarone, macrolides, antihistamines, antidepressants)	Monitor related signs and symptoms Treatment in accordance with standard medical practice	Monitor signs and symptoms during infusion Treatment in accordance with standard medical practice	Monitor related signs and symptoms 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.

considered for patients with expected neutropenia or a risk of fever ≥20%.[71] 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,[50] 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

cancer treatment.[70,71] Cytoreduction with hydroxyurea or cyclophosphamide is recommended before the first dose of InO in patients with circulating lymphoblasts >10,000/mm^3. 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.[70,71]

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.

Contributions: Diego Conde-Royo and Luis Miguel Juárez-Salcedo contributed equally to this manuscript. Luis Miguel Juárez-Salcedo and Samir Dalia should be considered joint corresponding authors. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Disclosure and potential conflicts of interest: The authors declare that they have no conflicts of interest relevant to this manuscript. The International Committee of Medical Journal Editors (ICMJE) Potential Conflicts of Interests form for the authors is available for download at: https://www.drugsincontext.com/wp-content/uploads/2020/09/dic.2020-7-2-COI.pdf

Acknowledgements: None.

Funding declaration: There was no funding associated with the preparation of this article.

Article URL: https://www.drugsincontext.com/management-of-adverse-effects-of-new-monoclonal-antibody-treatments-in-acute-lymphoblastic-leukemia

Correspondence: Luis Miguel Juárez-Salcedo, Hematology Department, Gregorio Marañón University Hospital, Madrid, Spain. dr.luisjuarez@gmail.com

Provenance: Invited; externally peer reviewed.

Submitted: 3 July 2020; **Peer review comments to author:** 8 July 2020; **Revised manuscript received:** 15 September 2020; **Accepted:** 16 September 2020; **Publication date:** 14 October 2020.

Drugs in Context is published by BioExcel Publishing Ltd. Registered office: Plaza Building, Lee High Road, London, England, SE13 5PT.

BioExcel Publishing Limited is registered in England Number 10038393. VAT GB 252 7720 07.

For all manuscript and submissions enquiries, contact the Editorial office editorial@drugsincontext.com

For all permissions, rights and reprints, contact David Hughes david.hughes@bioexcelpublishing.com

References

1. Acute Lymphocytic Leukemia – Cancer Stat Facts. SEER. https://seer.cancer.gov/statfacts/html/alyl.html. Accessed June 11, 2020.
2. Sant M, Allemani C, Tereanu C, et al. Incidence of hematologic malignancies in Europe by morphologic subtype: results of the HAEMACARE project. *Blood*. 2010;116(19):3724–3734. https://doi.org/10.1182/blood-2010-05-282632
3. DeAngelo DJ, Jabbour E, Advani A. Recent advances in managing acute lymphoblastic leukemia. *Am Soc Clin Oncol Educ Book*. 2020;(40):330–342. https://doi.org/10.1200/EDBK_280175
4. Rowe JM, Buck G, Burnett AK, et al. Induction therapy for adults with acute lymphoblastic leukemia: results of more than 1500 patients from the international ALL trial: MRC UKALL XII/ECOG E2993. *Blood*. 2005;106(12):3760–3767. https://doi.org/10.1182/blood-2005-04-1623

5. Paul S, Kantarjian H, Jabbour EJ. Adult acute lymphoblastic leukemia. *Mayo Clin Proc*. 2016;91(11):1645–1666. https://doi.org/10.1016/j.mayocp.2016.09.010
6. Gökbuget N, Stanze D, Beck J, et al. Outcome of relapsed adult lymphoblastic leukemia depends on response to salvage chemotherapy, prognostic factors, and performance of stem cell transplantation. *Blood*. 2012;120(10):2032–2041. https://doi.org/10.1182/blood-2011-12-399287
7. Stein AS, Larson RA, Schuh AC, et al. Exposure-adjusted adverse events comparing blinatumomab with chemotherapy in advanced acute lymphoblastic leukemia. *Blood Adv*. 2018;2(13):1522–1531. https://doi.org/10.1182/bloodadvances.2018019034
8. Scheuermann RH, Racila E. CD19 antigen in leukemia and lymphoma diagnosis and immunotherapy. *Leuk Lymphoma*. 1995; 18(5–6):385–397. https://doi.org/10.3109/10428199509059636
9. Raponi S, De Propris MS, Intoppa S, et al. Flow cytometric study of potential target antigens (CD19, CD20, CD22, CD33) for antibody-based immunotherapy in acute lymphoblastic leukemia: analysis of 552 cases. *Leuk Lymphoma*. 2011;52(6):1098–1107. https://doi.org/10.3109/10428194.2011.559668
10. Dinner S, Liedtke M. Antibody-based therapies in patients with acute lymphoblastic leukemia. *Hematol Am Soc Hematol Educ Program*. 2018;2018(1):9–15. https://doi.org/10.1182/asheducation-2018.1.9
11. Hoffmann P, Hofmeister R, Brischwein K, et al. Serial killing of tumor cells by cytotoxic T cells redirected with a CD19-/CD3-bispecific single-chain antibody construct. *Int J Cancer*. 2005;115(1):98–104. https://doi.org/10.1002/ijc.20908
12. Topp MS, Gökbuget N, Stein AS, et al. Safety and activity of blinatumomab for adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia: a multicentre, single-arm, phase 2 study. *Lancet Oncol*. 2015;16(1):57–66. https://doi.org/10.1016/S1470-2045(14)71170-2
13. Kantarjian H, Stein A, Gökbuget N, et al. Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia. *N Engl J Med*. 2017;376(9):836–847. https://doi.org/10.1056/NEJMoa1609783
14. Martinelli G, Boissel N, Chevallier P, et al. Complete hematologic and molecular response in adult patients with relapsed/refractory Philadelphia chromosome-positive B-precursor acute lymphoblastic leukemia following treatment with blinatumomab: results from a phase II, single-arm, multicenter study. *J Clin Oncol*. 2017;35(16):1795-1802. https://doi.org/10.1200/JCO.2016.69.3531
15. Gökbuget N, Dombret H, Bonifacio M, et al. Blinatumomab for minimal residual disease in adults with B-cell precursor acute lymphoblastic leukemia. *Blood*. 2018;131(14):1522–1531. https://doi.org/10.1182/blood-2017-08-798322
16. Ribera JM, Mercadal S, Barba P, et al. Blinatumomab use during consolidation in adult patients with high-risk, Philadelphia chromosome-negative acute lymphoblastic leukemia: preliminary results of the BLIN01 TRIAL. *EHA Library*. 06/12/20; 294320; EP401
17. Kebriaei P, Banerjee PP, Ganesh C, et al. Blinatumomab is well tolerated maintenance therapy following allogeneic hematopoietic cell transplantation for acute lymphoblastic leukemia. *Blood*. 2019;134(Suppl 1):1298. https://doi.org/10.1182/blood-2019-125931
18. Richard-Carpentier G, Kantarjian HM, Short NJ, et al. Updated results from the phase II study of hyper-CVAD in sequential combination with blinatumomab in newly diagnosed adults with B-cell acute lymphoblastic leukemia (B-ALL). *Blood*. 2019;134(Suppl 1):3807. https://doi.org/10.1182/blood-2019-129657
19. Chiaretti S, Bassan R, Vitale A, et al.; A dasatinib-blinatumomab combination for the front-line treatment of adult Ph+ ALL patients. Preliminary results of the GIMEMA LAL2116 D-ALBA TRIAL; on behalf of GIMEMA ACUTE LEUKEMIA WORKING PARTY *EHA Library*. 06/16/19; 267371; S1617.
20. Jain T, Litzow MR. No free rides: Management of toxicities of novel immunotherapies in ALL, including financial. *Blood Adv*. 2018;2(22):3393–3403. https://doi.org/10.1182/bloodadvances.2018020198
21. Stein AS, Schiller G, Benjamin R, et al. Neurologic adverse events in patients with relapsed/refractory acute lymphoblastic leukemia treated with blinatumomab: management and mitigating factors. *Ann Hematol*. 2019;98(1):159–167. https://doi.org/10.1007/s00277-018-3497-0
22. Turtle CJ, Hanafi L-A, Berger C, et al. CD19 CAR-T cells of defined CD4+:CD8+ composition in adult B cell ALL patients. *J Clin Invest*. 2016;126(6):2123–2138. https://doi.org/10.1172/JCI85309
23. Klinger M, Zugmaier G, Nägele V, et al. Adhesion of T cells to endothelial cells facilitates blinatumomab-associated neurologic adverse events. *Cancer Res*. 2020;80(1):91–101. https://doi.org/10.1158/0008-5472.CAN-19-1131
24. Prescribing information of Blinatumomab. AMGEN. https://www.pi.amgen.com/~/media/amgen/repositorysites/pi-amgen-com/blincyto/blincyto_pi_hcp_english.pdf. Accessed April 23, 2020.
25. Alfayez M, Kantarjian HM, Short NJ, et al. Safety and efficacy of blinatumomab in patients with Central Nervous System (CNS) disease: a single institution experience. *Blood*. 2018;132(Suppl 1):2702. https://doi.org/10.1182/blood-2018-99-117400
26. Aldoss I, Khaled SK, Budde E, Stein AS. Cytokine release syndrome with the novel treatments of acute lymphoblastic leukemia: pathophysiology, prevention, and treatment. *Curr Oncol Rep*. 2019;21(1):4. https://doi.org/10.1007/s11912-019-0753-y
27. Frey N. Cytokine release syndrome: who is at risk and how to treat. *Best Pract Res Clin Haematol*. 2017;30(4):336–340. https://doi.org/10.1016/j.beha.2017.09.002

28. Topp MS, Gökbuget N, Zugmaier G, et al. Phase II trial of the anti-CD19 bispecific T cell-engager blinatumomab shows hematologic and molecular remissions in patients with relapsed or refractory B-precursor acute lymphoblastic leukemia. *J Clin Oncol*. 2014;32(36):4134–4140. https://doi.org/10.1200/JCO.2014.56.3247
29. Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. *Biol Blood Marrow Transplant*. 2019;25(4):625–638. https://doi.org/10.1016/j.bbmt.2018.12.758
30. Brandl C, Haas C, d'Argouges S, et al. The effect of dexamethasone on polyclonal T cell activation and redirected target cell lysis as induced by a CD19/CD3-bispecific single-chain antibody construct. *Cancer Immunol Immunother CII*. 2007;56(10):1551–1563. https://doi.org/10.1007/s00262-007-0298-z
31. Choudhry J, Parson M, Wright J. A retrospective review of tocilizumab for the management of blinatumomab (a bispecific T cell engager)-induced Cytokine Release Syndrome (CRS). *Blood*. 2018;132(Suppl 1):5211. https://doi.org/10.1182/blood-2018-99-117353
32. Offidani M, Corvatta L, Malerba L, Marconi M, Leoni P. Infectious complications in adult acute lymphoblastic leukemia (ALL): experience at one single center. *Leuk Lymphoma*. 2004;45(8):1617–1621. https://doi.org/10.1080/10428190410001683660
33. Zugmaier G, Topp MS, Alekar S, et al. Long-term follow-up of serum immunoglobulin levels in blinatumomab-treated patients with minimal residual disease-positive B-precursor acute lymphoblastic leukemia. *Blood Cancer J*. 2014;4:244. https://doi.org/10.1038/bcj.2014.64
34. Klinger M, Brandl C, Zugmaier G, et al. Immunopharmacologic response of patients with B-lineage acute lymphoblastic leukemia to continuous infusion of T cell-engaging CD19/CD3-bispecific BiTE antibody blinatumomab. *Blood*. 2012;119(26):6226–6233. https://doi.org/10.1182/blood-2012-01-400515
35. Kantarjian HM, Stein AS, Bargou RC, et al. Blinatumomab treatment of older adults with relapsed/refractory B-precursor acute lymphoblastic leukemia: results from 2 phase 2 studies. *Cancer*. 2016;122(14):2178–2185. https://doi.org/10.1002/cncr.30031
36. Mikulska M, Lanini S, Gudiol C, et al. ESCMID Study Group for Infections in Compromised Hosts (ESGICH) consensus document on the safety of targeted and biological therapies: an infectious diseases perspective (agents targeting lymphoid cells surface antigens [I]: CD19, CD20 and CD52). *Clin Microbiol Infect*. 2018;24(Suppl 2):S71–S82. https://doi.org/10.1016/j.cmi.2018.02.003
37. Giebel S, Thomas X, Hallbook H, et al. The prophylactic use of granulocyte-colony stimulating factor during remission induction is associated with increased leukaemia-free survival of adults with acute lymphoblastic leukaemia: a joint analysis of five randomised trials on behalf of the EWALL. *Eur J Cancer*. 2012;48(3):360–367. https://doi.org/10.1016/j.ejca.2011.11.023
38. Darvishi B, Farahmand L, Jalili N, Majidzadeh-A K. Blinatumomab provoked fatal heart failure. *Int Immunopharmacol*. 2016;41: 42–46. https://doi.org/10.1016/j.intimp.2016.10.017
39. Teachey DT, Rheingold SR, Maude SL, et al. Cytokine release syndrome after blinatumomab treatment related to abnormal macrophage activation and ameliorated with cytokine-directed therapy. *Blood*. 2013;121(26):5154–5157. https://doi.org/10.1182/blood-2013-02-485623
40. Bumma N, Papadantonakis N, Advani AS. Structure, development, preclinical and clinical efficacy of blinatumomab in acute lymphoblastic leukemia. *Future Oncol Lond Engl*. 2015;11(12):1729–1739. https://doi.org/10.2217/fon.15.84
41. Paydas S, Ergin M, Baslamisli F, et al. Bone marrow necrosis: clinicopathologic analysis of 20 cases and review of the literature. *Am J Hematol*. 2002;70(4):300–305. https://doi.org/10.1002/ajh.10114
42. Yarali N, Isik M, Arman-Bilir O, Guzelkucuk Z, Oguz-Erdogan AS. Bone marrow necrosis in a patient following blinatumomab therapy. *J Pediatr Hematol Oncol*. 2020;42(3):e167–e169. https://doi.org/10.1097/MPH.0000000000001532
43. Shor B, Gerber H-P, Sapra P. Preclinical and clinical development of inotuzumab-ozogamicin in hematological malignancies. *Mol Immunol*. 2015;67(2 Pt A):107–116. https://doi.org/10.1016/j.molimm.2014.09.014
44. Guerra VA, Jabbour EJ, Ravandi F, Kantarjian H, Short NJ. Novel monoclonal antibody-based treatment strategies in adults with acute lymphoblastic leukemia. *Ther Adv Hematol*. 2019;10:2040620719849496. https://doi.org/10.1177/2040620719849496
45. DiJoseph JF, Armellino DC, Boghaert ER, et al. Antibody-targeted chemotherapy with CMC-544: a CD22-targeted immunoconjugate of calicheamicin for the treatment of B-lymphoid malignancies. *Blood*. 2004;103(5):1807–1814. https://doi.org/10.1182/blood-2003-07-2466
46. de Vries JF, Zwaan CM, De Bie M, et al. The novel calicheamicin-conjugated CD22 antibody inotuzumab ozogamicin (CMC-544) effectively kills primary pediatric acute lymphoblastic leukemia cells. *Leukemia*. 2012;26(2):255–264. https://doi.org/10.1038/leu.2011.206
47. Zein N, Sinha AM, McGahren WJ, Ellestad GA. Calicheamicin gamma 1I: an antitumor antibiotic that cleaves double-stranded DNA site specifically. *Science*. 1988;240(4856):1198–1201. https://doi.org/10.1126/science.3240341
48. Kantarjian H, Thomas D, Jorgensen J, et al. Inotuzumab ozogamicin, an anti-CD22-calecheamicin conjugate, for refractory and relapsed acute lymphocytic leukaemia: a phase 2 study. *Lancet Oncol*. 2012;13(4):403–411. https://doi.org/10.1016/S1470-2045(11)70386-2

49. Kantarjian H, Thomas D, Jorgensen J, et al. Results of inotuzumab ozogamicin, a CD22 monoclonal antibody, in refractory and relapsed acute lymphocytic leukemia. *Cancer*. 2013;119(15):2728–2736. https://doi.org/10.1002/cncr.28136
50. Kantarjian HM, DeAngelo DJ, Stelljes M, et al. Inotuzumab Ozogamicin versus standard therapy for acute lymphoblastic leukemia. *N Engl J Med*. 2016;375(8):740–753. https://doi.org/10.1056/NEJMoa1509277
51. Coppell JA, Richardson PG, Soiffer R, et al. Hepatic veno-occlusive disease following stem cell transplantation: incidence, clinical course, and outcome. *Biol Blood Marrow Transplant*. 2010;16(2):157–168. https://doi.org/10.1016/j.bbmt.2009.08.024
52. Kebriaei P, Cutler C, de Lima M, et al. Management of important adverse events associated with inotuzumab ozogamicin: expert panel review. *Bone Marrow Transplant*. 2018;53(4):449–456. https://doi.org/10.1038/s41409-017-0019-y
53. Kantarjian HM, DeAngelo DJ, Advani AS, et al. Hepatic adverse event profile of inotuzumab ozogamicin in adult patients with relapsed or refractory acute lymphoblastic leukaemia: results from the open-label, randomised, phase 3 INO-VATE study. *Lancet Haematol*. 2017;4(8):e387–e398. https://doi.org/10.1016/S2352-3026(17)30103-5
54. Jabbour EJ, DeAngelo DJ, Stelljes M, et al. Efficacy and safety analysis by age cohort of inotuzumab ozogamicin in patients with relapsed or refractory acute lymphoblastic leukemia enrolled in INO-VATE. *Cancer*. 2018;124(8):1722–1732. https://doi.org/10.1002/cncr.31249
55. Carreras E. How I manage sinusoidal obstruction syndrome after haematopoietic cell transplantation. *Br J Haematol*. 2015;168(4):481–491. https://doi.org/10.1111/bjh.13215
56. Mohty M, Malard F, Abecassis M, et al. Sinusoidal obstruction syndrome/veno-occlusive disease: current situation and perspectives-a position statement from the European Society for Blood and Marrow Transplantation (EBMT). *Bone Marrow Transplant*. 2015;50(6):781–789. https://doi.org/10.1038/bmt.2015.52
57. Mohty M, Malard F, Abecassis M, et al. Revised diagnosis and severity criteria for sinusoidal obstruction syndrome/veno-occlusive disease in adult patients: a new classification from the European Society for Blood and Marrow Transplantation. *Bone Marrow Transplant*. 2016;51(7):906–912. https://doi.org/10.1038/bmt.2016.130
58. Kantarjian H, Ravandi F, Short NJ, et al. Inotuzumab ozogamicin in combination with low-intensity chemotherapy for older patients with Philadelphia chromosome-negative acute lymphoblastic leukaemia: a single-arm, phase 2 study. *Lancet Oncol*. 2018;19(2):240–248. https://doi.org/10.1016/S1470-2045(18)30011-1
59. Jabbour E, Sasaki K, Ravandi F, et al. Chemoimmunotherapy with inotuzumab ozogamicin combined with mini-hyper-CVD, with or without blinatumomab is highly effective in patients with Philadelphia chromosome-negative acute lymphoblastic leukemia in first salvage. *Cancer*. 2018;124(20):4044–4055. https://doi.org/10.1002/cncr.31720
60. Richardson PG, Riches ML, Kernan NA, et al. Phase 3 trial of defibrotide for the treatment of severe veno-occlusive disease and multi-organ failure. *Blood*. 2016;127(13):1656–1665. https://doi.org/10.1182/blood-2015-10-676924
61. Curigliano G, Spitaleri G, de Braud F, et al. QTc prolongation assessment in anticancer drug development: clinical and methodological issues. *Ecancermedicalscience*. 2009;3:130. https://doi.org/10.3332/ecancer.2009.130
62. Roden DM. Drug-induced prolongation of the QT interval. *N Engl J Med*. 2004;350(10):1013–1022. https://doi.org/10.1056/NEJMra032426
63. Hibma JE, Kantarjian HM, DeAngelo DJ, Boni JP. Effect of inotuzumab ozogamicin on the QT interval in patients with haematologic malignancies using QTc-concentration modelling. *Br J Clin Pharmacol*. 2019;85(3):590–600. https://doi.org/10.1111/bcp.13832
64. Mehta HM, Malandra M, Corey SJ. G-CSF and GM-CSF in Neutropenia. *J Immunol Baltim Md 1950*. 2015;195(4):1341–1349. https://doi.org/10.4049/jimmunol.1500861
65. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of America. *Clin Infect Dis*. 2011;52(4):e56–e93. https://doi.org/10.1093/cid/cir073
66. Advani A, Coiffier B, Czuczman MS, et al. Safety, pharmacokinetics, and preliminary clinical activity of inotuzumab ozogamicin, a novel immunoconjugate for the treatment of B-cell non-Hodgkin's lymphoma: results of a phase I study. *J Clin Oncol*. 2010;28(12):2085–2093. https://doi.org/10.1200/JCO.2009.25.1900
67. Fayad L, Offner F, Smith MR, et al. Safety and clinical activity of a combination therapy comprising two antibody-based targeting agents for the treatment of non-Hodgkin lymphoma: results of a phase I/II study evaluating the immunoconjugate inotuzumab ozogamicin with rituximab. *J Clin Oncol*. 2013;31(5):573–583. https://doi.org/10.1200/JCO.2012.42.7211
68. Drgona L, Gudiol C, Lanini S, Salzberger B, Ippolito G, Mikulska M. ESCMID Study Group for Infections in Compromised Hosts (ESGICH) consensus document on the safety of targeted and biological therapies: an infectious diseases perspective (agents targeting lymphoid or myeloid cells surface antigens [II]: CD22, CD30, CD33, CD38, CD40, SLAMF-7 and CCR4). *Clin Microbiol Infect*. 2018;24(Suppl 2):S83–S94. https://doi.org/10.1016/j.cmi.2018.03.022
69. Lenz H-J. Management and preparedness for infusion and hypersensitivity reactions. *Oncologist*. 2007;12(5):601–609. https://doi.org/10.1634/theoncologist.12-5-601

70. Coiffier B, Altman A, Pui C-H, Younes A, Cairo MS. Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. *J Clin Oncol*. 2008;26(16):2767–2778. https://doi.org/10.1200/JCO.2007.15.0177
71. Mirrakhimov AE, Voore P, Khan M, Ali AM. Tumor lysis syndrome: a clinical review. *World J Crit Care Med*. 2015;4(2):130–138. https://doi.org/10.5492/wjccm.v4.i2.130
72. Topp MS, Gökbuget N, Stein AS, et al. Safety and activity of blinatumomab for adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia: a multicentre, single-arm, phase 2 study. *Lancet Oncol*. 2015;16(1):57–66. https://doi.org/10.1016/S1470-2045(14)71170-2