Current Oncology Reports (2019) 21: 4
https://doi.org/10.1007/s11912-019-0753-y

LEUKEMIA (A AGUAYO, SECTION EDITOR)

Cytokine Release Syndrome With the Novel Treatments of Acute Lymphoblastic Leukemia: Pathophysiology, Prevention, and Treatment

Ibrahim Aldoss[1] · Samer K. Khaled[1] · Elizabeth Budde[1] · Anthony S. Stein[1]

Published online: 21 January 2019

Abstract

Purpose of Review T cell-based therapies (blinatumomab and CAR T cell therapy) have produced unprecedented responses in relapsed and refractory (r/r) acute lymphoblastic leukemia (ALL) but is accompanied with significant toxicities, of which one of the most common and serious is cytokine release syndrome (CRS). Here we will review the pathophysiology, prevention, and treatment of CRS.

Recent Findings Efforts have been initiated to define and grade cytokine release syndrome (CRS), to identify patients at risk, to describe biomarkers that predict onset and severity, to understand the pathophysiology, and to prevent and treat severe cases to reduce T cell immunotherapy-related morbidity and mortality.

Summary Optimizing the timing of T cell-based therapies in ALL, identifying new biomarkers, and investigating novel anti-cytokine agents that have anti-CRS activity are likely to be fruitful avenues of study.

Keywords Acute lymphoblastic leukemia · Cytokine release syndrome · Chimeric antigen receptor · T cell therapy · Immunotherapy · Blinatumomab

Introduction

Advanced acute lymphoblastic leukemia (ALL) carries a dismal prognosis, with only a small fraction of patients enjoying long-term survival [1]. Leukemia relapsing after or unresponsive to initial therapy usually represents chemo-resistant disease, and historically, the response to available salvage conventional chemo-based regimens was disappointing, as only a small fraction of patients were successfully able to proceed to allogeneic hematopoietic cell transplantation (HCT) [1, 2]. The management of relapsed and refractory (r/r) B cell ALL has markedly evolved over the last few years with newly approved effective novel therapies, among which are two CD19-targeted immunotherapies, namely, CD19 chimeric antigen receptor (CAR) T cell and CD19 bispecific T cell engager (BiTE®) therapy.

Blinatumomab is a CD3/CD19 BiTE that brings endogenous T cells to close proximity with CD19+ leukemic cells to allow formation of cytolytic synapses that leads to T cell activation and ALL cell lysis. This activation occurs separately from the TCR receptor and independent of co-stimulation and antigen-presenting cells. The activation leads to polyclonal proliferation, which recruits additional T cells in the process. Blinatumomab has shown astonishing activity in minimal residual disease (MRD)-positive r/r ALL, with an MRD-negative complete response (CR) rate of 80% [3]. For r/r morphologic ALL (≥ 5% blasts), blinatumomab induces CR/CR with incomplete count recovery (CRi) in approximately half of treated patients [4, 5]. Blinatumomab activity was observed across different leukemia genetics, patient ages, and disease settings.

On the other hand, CAR T cell therapy involves adoptive transfer of genetically engineered T cells expressing a receptor

This article is part of the Topical Collection on *Leukemia*

✉ Anthony S. Stein
astein@coh.org

Ibrahim Aldoss
ialdoss@coh.org

Samer K. Khaled
skhaled@coh.org

Elizabeth Budde
ebudde@coh.org

[1] Gehr Family Center for Leukemia Research, City of Hope, 1500 Duarte Rd, Duarte, CA 91010, USA

of interest that can be redirected to the targeted cells (e.g., CD19CAR in CD19+ ALL). There are various CAR T cell platforms with different properties influencing the timing of expansion, peak levels, and persistence of CAR T cells in vivo. Nonetheless, all CD19 CAR T cell platforms have universally yielded unprecedented high rates of deep remissions in relapsed/refractory ALL [6–10]. Furthermore, ongoing studies are exploring immunotherapies using other ALL-specific targets, including CD22 [11].

The successful utilization of T cell-based therapy in ALL was accompanied with undesired consequences; the most serious ones are neurotoxicity and cytokine release syndrome (CRS), each potentially presenting life-threatening complications. Here, we focus our discussion on CRS.

Pathophysiology, Biomarkers, and Manifestations of CRS

CRS is the result of massive inflammatory cytokine production that substantially exceeds physiological levels and is triggered by the activation of effector T cells upon their interaction with targets. Stimulation of T cells and bystander immune cells such as monocytes/macrophages induces the release of cytokines and chemokines, and thus mediate systemic inflammatory responses. Additionally, non-CAR T cells seem to be activated as well and potentially play a role in CRS pathophysiology [12]. Interleukin-6 (IL-6) is central in mediating CRS; however, other cytokine levels also rise during the course of CRS and drive some of its manifestations, including IL-2, interferon-ɣ, tumor necrosis factor, GM-CSF, MIP1α, MCP1, IL-5, IL-8, and IL-10 [6, 13•, 14•, 15–17]. Furthermore, patients with severe CRS (≥ grade 4) have pronounced evidence of consumptive coagulopathy with prolonged thrombocytopenia, elevation of d-dimer, prolongation of prothrombin time (PT) and partial thromboplastin time (PTT), hyperfibrinogenemia, and elevation in endothelial activation markers [13•].

The peak level of IL-6 following CAR T cell infusion correlates with CRS severity and intensive care unit (ICU) admission [10]. Serum IL-6 measurement is not readily available in a timely manner to guide therapy; therefore, C-reactive protein (CRP) levels, which are easily measured and available, have served as a reliable, widely used surrogate for IL-6 levels that is closely monitored during CRS onset and progression [18, 19]. The upsurge and fluctuations in CRP level correlate with CRS severity and resolution of manifestations of the syndrome [6, 8, 10, 20]. However, CRP is not specific to CRS, and the level is increased by infectious and non-infectious inflammatory causes. Other markers including ferritin, interferon, and TNF correlate with CRS as well [6, 10, 15].

The rise of cytokines can provide a diagnostic support for early CRS following T cell therapy. Furthermore, the dynamic change in cytokine levels can also be utilized as a tool to predict forthcoming severe CRS, and therefore, this feature might promote early administration of anti-cytokine-based therapies as preemptive therapy to reduce treatment morbidities, yet this approach need to be studied systemically [13•, 14•].

Signs and symptoms of CRS vary by the severity; however, the syndrome is usually multi-systemic. High-grade fever as well as constitutional symptoms occur in the majority of CRS cases, and it can be challenging to distinguish symptoms from underlying infectious processes. Therefore, it is crucial to administer empiric anti-microbial therapy concurrently in the majority of CRS cases. Any organ can be affected during CRS, and the patient can develop skin rash, nausea, vomiting, respiratory failure, cardiac dysfunction, renal failure, disseminated intravascular coagulopathy, hepatic dysfunction, and neurological deficit [13•]. Although neurotoxicity can be an independent complication of CD19 T cell therapies, it can be part of CRS manifestation. Indeed, severe neurotoxicity is observed more frequently in patients with severe CRS during CAR T cell therapy than in patients unaffected by this syndrome [9, 13•]. Furthermore, the occurrence of severe CRS is associated with delayed count recovery after treatment [13•], and the severity of CRS was the only independent factor associated with increased infectious complications after CAR T cell therapy [21].

Symptoms and laboratory findings of CRS can overlap and mimic macrophage activating syndrome (MAC)/hemophagocytic lymphohistocytosis (HLH) [22, 23], and at least in one case, a predisposing mutation in the *perforin* gene was identified in a patient who developed severe CRS during CAR T cell therapy [23].

Incidence and Predictors of CRS

CRS is observed during the various T cell therapies in ALL, irrespective of the target. The incidence of CRS varies by the type of immunotherapy, and it is encountered more frequently during CAR T cell therapy compared to the rate in bispecific T cell engagers. Any grade and severe CRS were reported in 76–100% and 23–47% in patients enrolled on different CD19CAR T cells studies, respectively [6, 8–10]. In contrast, the rate of CRS is much lower in blinatumomab studies, with only 0–6% experiencing severe manifestations [3–5, 15, 24]. The occurrence of CRS is not restricted to T cell therapy targeting the CD19 antigen. CD22-based CAR T cells in ALL were associated with CRS in 76% of treated patients, including 33% that were considered severe [11]. Refer to Table 1 for the incidence of any grade and severe CRS and the median onset of CRS as well as the incidence of CRS death during blinatumomab and CAR T cell therapy studies.

Other factors influence the risk of CRS during T cell therapy, including patient and leukemia characteristics as well as

Table 1 CAR T cell and blinatumomab studies and associated CRS events

Study	No.	Age	Median onset by days	CRS any grade	Severe CRS[a]	ICU admission	CRS death	CRS therapy	Notes
CAR T cells									
U Penn [6]	30	14 (5–60)	1 for severe and 4 for non-severe	100%	27[10]%	27%	0	Tocilizumab = 9, steroid = 6	CRS severity correlated with disease burden, higher levels of CTL019+ CD8 and CD3 cells
MSKCC [7]	53	44 (23–74)		45 (85%)	14 (26%)		1	Tocilizumab = 19, steroid = 17	Possible association with age (did not reach significance). Severe CRS correlated with disease burden
NCI [8]	21	4 (1–7)	3 (1–22)	16 (76%)	6 (28.6%)	NR	0	Tocilizumab = 4, steroid = 2	CRS severity correlated with peak circulating CAR T cells, higher peak of CRP, and higher disease burden
FHCRC [10]	32	40 (20–73)	NR	25 (83%)	7 (23%)	7 (23%)	1	Tocilizumab = 7, steroid = 3	Severe CRS correlated with higher disease burden, peak of IL-6 and INF-γ, higher PB CD4 and CD8 CAR T cell expansion, higher CRS and ferritin
Multicenter tisagenlecleucel [9]	75	11 (3–23)	3 (1–22)	58 (77%)	35 (47%)	35 (47%)	1	Tocilizumab = 28 (37%)	The majority of neurotoxicity occurred during or shortly after CRS. Severe neurotoxicity occurred more frequently in patients with severe CRS
CD22CAR T cells [11]	21	19 (7–30)	After day 5	16 (76%)	7 (33%) grade II	NR	None	NR	
Blinatumomab									
Pilot MRD study [25]	21	47 (20–77)	NR	NR	0	0	0	None	
BLAST (MRD) study	113		During cycle 1	4 (3.5%)	2 (1.8%)	NR	0	NR	
Pilot R/R ALL study	36	32 (18–77)	NR	NR	2	NR	0	NR	
ALCANTARA in r/r Ph + ALL	45	55 (23–78)	NR	3 (6.7%)	0	0	0	None	
Confirmatory phase II in r/r ALL	189	39 (18–79)	NR	NR	3 (2%)	NR	NR	NR	Lower incidence of severe CRS compared to the pilot study after implementing pre-treatment dexamethasone and dose escalation
TOWER, phase 3 study in r/r ALL	271	41 (18–80)	NR	38 (14.2%)	13 (4.9%)	NR	NR	Treatment interruption in 5%	
Pediatric in r/r ALL	70	8 (1–17)	NR	8 (11%)	4 (6%)	NR	1 (cardiac failure related to CRS)	Treatment interruption in 2 and permanently held in 2, tocilizumab = 1	Introduced step-wise dose escalation. Peak levels of IL-10, IL-6, and INF-γ were higher in patients with CRS

U Penn University of Pennsylvania, MSKCC Memorial Sloan Kettering Cancer Center, NCI National Cancer Institute, FHCRC Fred Hutchinson Cancer Research Center, MDACC MD Anderson Cancer Center, MRD minimal residual disease, NR not reported, CRS cytokine release syndrome, ICU intensive care unit, PB peripheral blood

[a] Defined as requiring intensive care

delivered pre-infusion intervention (salvage therapy between collection and infusion as well as lymphodepletion intensity). Leukemia burden at the time of lymphodepletion significantly correlated with increased risk of severe CRS, as shown consistently across CAR T cell studies [6–8, 10, 13•]. This correlation is in part due to higher in vivo CAR T cell expansion compared with that in low leukemia burden, resulting in correspondingly higher cytokine release [6, 8, 10]. The incorporation of CAR T cell therapy following HCT in ALL patients where the majority of patients were in remission at the time of starting conditioning regimen produced no CRS [26]. Likewise, the CRS rate was lower in patients receiving blinatumomab in the MRD setting, compared to the rate in those with fully r/r ALL [3, 4, 15].

The addition of fludarabine to cyclophosphamide during lymphodepletion resulted in increased CRS severity following CAR T cell infusion [13•]. Other factors potentially associated with severe CRS include the infused dose of CAR T cells, using unselected bulk $CD8^+$ T cells, older patient age, and severe thrombocytopenia [6, 13•, 27], but more studies are needed to confirm these observations. No association between the incidence of severe CRS and the co-stimulatory domain used in the CAR product was noted [27]; however, it has been observed that the onset of CRS typically occurs earlier with CARs using the CD28 co-stimulatory domain compared to CARs using the 4-1BB co-stimulatory domain, and this event is likely related to the timing of peak T cell expansion [28•].

CRS during T cell therapies occurs early during the course of treatment, and the onset typically appears during the first week of therapy and lasts for a week before CRS symptoms subside [9]. In one study, severe CRS occurred earlier compared to non-severe forms of CRS, with a median onset of 1 versus 4 days, respectively [6]. During blinatumomab therapy, CRS occurs predominantly during the first cycle of therapy, and classically upon starting infusion and when the dose is escalated on day 8 of therapy. Beyond cycle 1, it is uncommon to encounter blinatumomab-induced CRS if the patient attained remission.

Grading of CRS

Several grading systems were proposed and utilized in rating the severity of CRS across the different T cell therapy studies [20, 29, 30]. The Common Terminology Criteria for Adverse Events (CTCAE), version 4 was used during blinatumomab studies, but these criteria were not designed specifically for T cell-based therapy per se. Efforts were initiated to reach a consensus in defining and grading the severity of CRS to allow comparing toxicities across different studies with different T cell-based therapy products and to standardize prevention and management of CRS.

Lee et al. proposed a CAR T specific CRS grading system in 2014, which is now a commonly used system to capture severity during CAR T cell therapy [30]. This grading system restricts grade 1 to non-life-threatening symptoms that only require symptomatic therapy. Grade 2 includes hypotension that is managed with intravenous fluids or a low dose of one pressor, cases that required low oxygen supplement (< 40%), or the development of grade 2 organ toxicity per CTCAE. Grade 3 is referred to cases for which prior interventions were inadequate, requiring more aggressive intervention, including more pressor support (high or multiple doses) and oxygen supplement (> 40%), and these cases typically require admission to intensive care units (ICU) for close attention and management. Grade 3 also includes patients who develop grade 3 organ toxicities or grade 4 transaminases per CTCAE. Grade 4 is limited to life-threatening symptoms, including grade 4 organ toxicities per CTCAE (excluding transaminases) and the requirement of ventilator support [30]. Refer to Table 2 for revised CRS grading and management recommendations. In the updated version of the CTCAE (version 5.0), grading of CRS was revised and now it is more consistent with Lee et al. grading; however, requiring one pressor in version 5.0 classifies CRS as grade 3 rather than grade 2.

Prevention of CRS

Severe CRS was successfully reduced during blinatumomab therapy with the introduction of step-wise dose escalation during the first cycle when patients have active disease [5, 16]. This dose escalation is not needed during subsequent cycles of blinatumomab when the patient is remission or during blinatumomab therapy in the MRD+ setting, since the risk of CRS in these circumstances is negligible [3, 25]. Furthermore, mandating pre-treatment with dexamethasone before starting blinatumomab is another intervention that has also contributed to abrogating the risk of severe CRS [5]. The recommendation for pre-treatment with dexamethasone is also applied before dose escalation and in the event of therapy interruption. Importantly, the concern that dexamethasone leads to impairing effector T cells and reduced blinatumomab efficacy has not been demonstrated [5, 31].

For CAR T cells, disease burden appears to be the key determinant of CRS severity risk. Therefore, efforts were conducted to reduce disease burden by intensifying pre-lymphodepletion salvage regimens, and more elegantly, by tailoring the intensity of lymphodepletion toward disease burden. This tailoring therapy has shown success in reducing severe CRS rates among patients with bulky leukemia at the time of lymphodepletion [32]. Investigators at University of Pennsylvania examined delivering fractionated (split) doses of CAR T cells to allow intra-patient dose modification and the opportunity of holding subsequent doses in case of severe

Table 2 Revised CRS grading and management recommendations

Grade	Definition	Management
1	• Non-life-threatening symptoms that only require symptomatic therapy	• Supportive care • Anti-microbial coverage
2	• Hypotension that is managed with intravenous fluids or a low dose of one pressor • Requirement of low oxygen supplement (< 40%), or • Development of grade 2 organ toxicity per CTCAE	• Supportive care • Oxygen and supplement and pressor support • Tocilizumab for older patients and patients with co-morbidities
3	• Cases for which prior interventions were inadequate, requiring more aggressive intervention, including more pressor support (high or multiple doses) and oxygen supplement (> 40%), • Cases typically require admission to intensive care units (ICU) for close attention and management, • Patients who develop grade 3 organ toxicities, or • Grade 4 transaminases per CTCAE	• Supportive care • Anti-microbial coverage • Oxygen and supplement and pressor support • Tocilizumab • +/− steroid depends on response to tocilizumab and severity of symptoms
4	• Life-threatening symptoms, • Grade 4 organ toxicities per CTCAE (excluding transaminases), or • The requirement of ventilator support	• Supportive care • Anti-microbial coverage • Ventilator support • Tocilizumab • Steroid

toxicities, yet the efficacy of this approach needs to be proven [33]. Another approach to avoid significant CRS was conducted by investigators at MD Anderson Cancer Center (MDACC), where CAR T cells were infused in the postallogeneic HCT setting as pre-emptive therapy to reduce relapse risk in high-risk ALL [26]. The majority of patients had minimal to no detectable disease at the time of infusion, and the study reports no CRS in this setting. However, CAR T cell expansion may be limited because of low or lack of adequate target cells. A similar study was conducted in patients with lymphoma where CAR T cells were infused after autologous HCT, and the approach was reported to be safe with manageable toxicities [34].

Another strategy to reduce severe CRS is early intervention based on surrogate markers predicting the risk of severe CRS. This approach can be done by monitoring baseline levels of cytokines and their dynamic changes upon CAR T cell infusion, and the early administration of anti-cytokine therapy to avoid rapid progression to life-threatening CRS [13•]. Some institutions and studies have proposed algorithms for CRS intervention and incorporated cytokine markers to guide CRS risk and pre-emptive administration of anti-cytokine therapy.

Treatment of CRS

The treatment of CRS during T cell therapy depends on the administered agent and the severity of symptoms. The short half-life of blinatumomab (~2 h) allows CRS manifestations to resolve quickly by interrupting therapy in conjunction with supportive care with or without additional interventions. However, once CAR T cells are infused, the effect cannot be withdrawn, and the infused cells may persist for prolonged durations, depending on CAR properties and platforms. Therefore, expected manifestations and treatment of CRS are different between the two modalities.

For mild and moderate cases, the practice of supportive measures is the principal management of CRS, including administering anti-biotics and anti-pyretics for fever, fluid resuscitation, low-dose pressors for mild-moderate hypotension, and oxygen supplementation when saturation drops. Tocilizumab is usually required in advanced cases such as for resistant hypotension and when more pressor support is required. However, for older patients and patients with co-morbidities, the infusion of tocilizumab may be administered at an earlier stage to avoid detrimental outcomes [30]. For severe cases of CRS, the patient should be admitted to the ICU for close monitoring, and in addition to aggressive supportive care, administration of repeated doses of tocilizumab is required when no improvement is observed. Steroids are usually added for resistant and severe cases to control CRS, and they are given at higher doses to ablate CAR T cells.

Tocilizumab is an anti-IL-6 receptor antibody and functions by blocking cytokines and ameliorating manifestations of CRS rather than eliminating the effector cells. Tocilizumab is used more widely in CAR T cells as opposed to blinatumomab therapy, and the majority CAR T cell protocols have integrated tocilizumab administration as part of CRS management algorithms. The FDA approval of tocilizumab for CRS management was simultaneously granted when the first CAR T cell

therapy for ALL was approved in August 2017. Tocilizumab use is favored over steroid because of the lack of adverse impacts on treatment efficacy [20]. Tocilizumab does not appear to impair sufficient CAR T cell proliferation in vivo or persistence [6]. Other anti-inflammatory agents have been administered for severe CRS in some cases, such as siltuximab, etanercept, infliximab, and anakinra, but clinical experience in this setting is undeveloped [10, 23, 30, 35].

Steroid administration can eliminate effector T cells, and therefore, it has the potential to influence and impair T cell activity. Studies have shown a correlation between prolonged steroid administration and a reduction in circulating CAR T cells as well as an increased risk of treatment failure [20] Therefore, steroids are usually spared for only severe or refractory CRS cases that fail to respond to anti-cytokine therapy. It is worth noting that short-term use of steroids on the other hand has not been shown to negatively impact the CD19CAR efficacy in the ZUMA-1 trial. Steroids are also effective in controlling CRS symptoms during blinatumomab therapy, and steroids have shown no to little impact on blinatumomab activity [5, 31]. We have demonstrated that prolonged administration of steroids (≥ 1 week) was common during the first cycle of blinatumomab therapy for r/r ALL, but use was not different between responders and non-responders (39% vs. 41%, $p = 0.92$) and did not impact survival afterward [31].

CRS usually resolves quickly within 1 to 3 days after administration of tocilizumab and steroids [20]. IL-6 levels may continue to rise temporarily after tocilizumab administration for CRS before it drops, a result of its blocking of the IL-6 receptor [30].

Next-generation CAR T cells have included suicide genes to allow eradicating CAR T cells in the event of uncontrolled toxicity. Investigators have incorporated an inducible caspase-9 enzyme that can be turned on by administering a synthetic dimerizing drug (AP1903) that would lead to rapid T cell death [36]. Others have introduced a truncated EGFR receptor in the CAR product to allow ablation with cetuximab when needed [37].

Conclusions and Future Directions

T cell-based therapy in ALL has emerged as an effective treatment for advanced and chemo-resistant disease, but severe CRS hampers its widespread use outside specialized centers. The future will likely introduce new approaches and products with less severe CRS, allowing safe administration for more patients in need.

Optimizing the timing of T cell-based therapies in ALL may improve the safety of the regimen and ameliorate severe CRS. This approach can be achieved by administering treatment in patients with low disease burden either by utilizing therapy more frequently in patients with only MRD disease, providing cytoreduction before administration of bispecific T cell engagers or CAR T cells, or using therapy as a consolidation for patients in remission or following HCT.

Identifying new biomarkers that are elevated in advance before the onset of severe CRS and that predict more accurately the development of CRS with better reproducibility, sensitivity, and specificity, compared to traditional methods, would be useful to allow early pre-emptive intervention in order to avert progression to severe CRS. Additionally, it would be valuable to identify genetic polymorphisms or susceptible mutations that lead to pronounced cytokine release and severe manifestations of CRS. This strategy can potentially help in tailoring the dose of T cells as well as lymphodepleting agents and other early interventions.

Another important step is developing and investigating novel anti-cytokine agents that have anti-CRS activity in patients failing tocilizumab while having no or little influence on T cell activity and response to therapy. Studies are also needed to examine the activity and safety of suicide genes in blocking CRS progression in vivo and their impact on the activity of CAR T cells.

Compliance with Ethical Standards

Conflict of Interest Ibrahim Aldoss declares that he has no conflict of interest.

Samer K. Khaled has received compensation from Juno Therapeutics for service as a consultant.

Elizabeth Budde declares that she has no conflict of interest.

Anthony S. Stein has received compensation from Amgen and Celgene for service on speakers' bureaus.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

Papers of particular interest, published recently, have been highlighted as:

- Of importance

1. Fielding AK, Richards SM, Chopra R, Lazarus HM, Litzow MR, Buck G, et al. Outcome of 609 adults after relapse of acute lymphoblastic leukemia (ALL); an MRC UKALL12/ECOG 2993 study. Blood. 2007;109(3):944–50. https://doi.org/10.1182/blood-2006-05-018192.
2. Gokbuget N, Kelsh M, Chia V, Advani A, Bassan R, Dombret H, et al. Blinatumomab vs historical standard therapy of adult relapsed/refractory acute lymphoblastic leukemia. Blood Cancer J. 2016;6(9):e473. https://doi.org/10.1038/bcj.2016.84.

3. Gokbuget N, Dombret H, Bonifacio M, Reichle A, Graux C, Faul C, et al. Blinatumomab for minimal residual disease in adults with B-cell precursor acute lymphoblastic leukemia. Blood. 2018;131(14):1522–31. https://doi.org/10.1182/blood-2017-08-798322.
4. Kantarjian H, Stein A, Gokbuget N, Fielding AK, Schuh AC, Ribera JM, et al. Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia. N Engl J Med. 2017;376(9):836–47. https://doi.org/10.1056/NEJMoa1609783.
5. Topp MS, Gokbuget N, Stein AS, Zugmaier G, O'Brien S, Bargou RC, 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.
6. Maude SL, Frey N, Shaw PA, Aplenc R, Barrett DM, Bunin NJ, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. N Engl J Med. 2014;371(16):1507–17. https://doi.org/10.1056/NEJMoa1407222.
7. Park JH, Riviere I, Gonen M, Wang X, Senechal B, Curran KJ, et al. Long-term follow-up of CD19 CAR therapy in acute lymphoblastic leukemia. N Engl J Med. 2018;378(5):449–59. https://doi.org/10.1056/NEJMoa1709919.
8. Lee DW, Kochenderfer JN, Stetler-Stevenson M, Cui YK, Delbrook C, Feldman SA, et al. T cells expressing CD19 chimeric antigen receptors for acute lymphoblastic leukaemia in children and young adults: a phase 1 dose-escalation trial. Lancet. 2015;385(9967):517–28. https://doi.org/10.1016/s0140-6736(14)61403-3.
9. Maude SL, Laetsch TW, Buechner J, Rives S, Boyer M, Bittencourt H, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. N Engl J Med. 2018;378(5):439–48. https://doi.org/10.1056/NEJMoa1709866.
10. Turtle CJ, Hanafi LA, Berger C, Gooley TA, Cherian S, Hudecek M, et al. CD19 CAR-T cells of defined CD4+:CD8+ composition in adult B cell ALL patients. J Clin Invest. 2016;126(6):2123–38. https://doi.org/10.1172/jci85309.
11. Fry TJ, Shah NN, Orentas RJ, Stetler-Stevenson M, Yuan CM, Ramakrishna S, et al. CD22-targeted CAR T cells induce remission in B-ALL that is naive or resistant to CD19-targeted CAR immunotherapy. Nat Med. 2018;24(1):20–8. https://doi.org/10.1038/nm.4441.
12. Obstfeld AE, Frey NV, Mansfield K, Lacey SF, June CH, Porter DL, et al. Cytokine release syndrome associated with chimeric-antigen receptor T-cell therapy: clinicopathological insights. Blood. 2017;130(23):2569–72. https://doi.org/10.1182/blood-2017-08-802413.
13.• Hay KA, Hanafi LA, Li D, Gust J, Liles WC, Wurfel MM, et al. Kinetics and biomarkers of severe cytokine release syndrome after CD19 chimeric antigen receptor-modified T-cell therapy. Blood. 2017;130(21):2295–306. https://doi.org/10.1182/blood-2017-06-793141 **This study characterized the kinetics and identified risk factors for severe CRS, and it showed that severe CRS is associated with increased endothelial activation biomarkers.**
14.• Teachey DT, Lacey SF, Shaw PA, Melenhorst JJ, Maude SL, Frey N, et al. Identification of predictive biomarkers for cytokine release syndrome after chimeric antigen receptor T-cell therapy for acute lymphoblastic leukemia. Cancer Discov. 2016;6(6):664–79. https://doi.org/10.1158/2159-8290.CD-16-0040 **This study developed a model that accurately predicts patients at risk of developing severe CRS early during therapy, and this approach can be translated into tailoring cytokine-directed therapy. The data were validated using an independent cohort.**
15. von Stackelberg A, Locatelli F, Zugmaier G, Handgretinger R, Trippett TM, Rizzari C, et al. Phase I/phase II study of Blinatumomab in pediatric patients with relapsed/refractory acute lymphoblastic leukemia. J Clin Oncol. 2016;34(36):4381–9.
16. Nagele V, Kratzer A, Zugmaier G, Holland C, Hijazi Y, Topp MS, et al. Changes in clinical laboratory parameters and pharmacodynamic markers in response to blinatumomab treatment of patients with relapsed/refractory ALL. Exp Hematol Oncol. 2017;6(14):14. https://doi.org/10.1186/s40164-017-0074-5.
17. Klinger M, Brandl C, Zugmaier G, Hijazi Y, Bargou RC, Topp MS, 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):6226–33. https://doi.org/10.1182/blood-2012-01-400515.
18. Schultz DR, Arnold PI. Properties of four acute phase proteins: C-reactive protein, serum amyloid a protein, alpha 1-acid glycoprotein, and fibrinogen. Semin Arthritis Rheum. 1990;20(3):129–47.
19. Pepys MB, Hirschfield GM. C-reactive protein: a critical update. J Clin Invest. 2003;111(12):1805–12. https://doi.org/10.1172/JCI18921.
20. Davila ML, Riviere I, Wang X, Bartido S, Park J, Curran K, et al. Efficacy and toxicity management of 19-28z CAR T cell therapy in B cell acute lymphoblastic leukemia. Sci Transl Med. 2014;6(224):224ra25. https://doi.org/10.1126/scitranslmed.3008226.
21. Hill JA, Li D, Hay KA, Green ML, Cherian S, Chen X, et al. Infectious complications of CD19-targeted chimeric antigen receptor-modified T-cell immunotherapy. Blood. 2018;131(1):121–30. https://doi.org/10.1182/blood-2017-07-793760.
22. Teachey DT, Rheingold SR, Maude SL, Zugmaier G, Barrett DM, Seif AE, et al. Cytokine release syndrome after blinatumomab treatment related to abnormal macrophage activation and ameliorated with cytokine-directed therapy. Blood. 2013;121(26):5154–7. https://doi.org/10.1182/blood-2013-02-485623.
23. Grupp SA, Kalos M, Barrett D, Aplenc R, Porter DL, Rheingold SR, et al. Chimeric antigen receptor-modified T cells for acute lymphoid leukemia. N Engl J Med. 2013;368(16):1509–18. https://doi.org/10.1056/NEJMoa1215134.
24. Martinelli G, Boissel N, Chevallier P, Ottmann O, Gokbuget N, Topp MS, 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):1795–802. https://doi.org/10.1200/jco.2016.69.3531.
25. Topp MS, Kufer P, Gokbuget N, Goebeler M, Klinger M, Neumann S, et al. Targeted therapy with the T-cell-engaging antibody blinatumomab of chemotherapy-refractory minimal residual disease in B-lineage acute lymphoblastic leukemia patients results in high response rate and prolonged leukemia-free survival. J Clin Oncol. 2011;29(18):2493–8. https://doi.org/10.1200/jco.2010.32.7270.
26. Kebriaei P, Singh H, Huls MH, Figliola MJ, Bassett R, Olivares S, et al. Phase I trials using sleeping beauty to generate CD19-specific CAR T cells. J Clin Invest. 2016;126(9):3363–76. https://doi.org/10.1172/jci86721.
27. Jin Z, Xiang R, Qing K, Li X, Zhang Y, Wang L, et al. The severe cytokine release syndrome in phase I trials of CD19-CAR-T cell therapy: a systematic review. Ann Hematol. 2018;97:1327–35. https://doi.org/10.1007/s00277-018-3368-8.
28.• Neelapu SS, Tummala S, Kebriaei P, Wierda W, Gutierrez C, Locke FL, et al. Chimeric antigen receptor T-cell therapy - assessment and management of toxicities. Nat Rev Clin Oncol. 2018;15(1):47–62. https://doi.org/10.1038/nrclinonc.2017.148 **This article represents consensus recommendations from leaders in CAR T cell therapy proposing algorithms for the monitoring, grading, and management of CRS.**
29. Porter DL, Hwang WT, Frey NV, Lacey SF, Shaw PA, Loren AW, et al. Chimeric antigen receptor T cells persist and induce sustained remissions in relapsed refractory chronic lymphocytic leukemia.

Sci Transl Med. 2015;7(303):303ra139. https://doi.org/10.1126/scitranslmed.aac5415.

30. Lee DW, Gardner R, Porter DL, Louis CU, Ahmed N, Jensen M, et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood. 2014;124(2):188–95. https://doi.org/10.1182/blood-2014-05-552729.
31. Aldoss I, Song J, Stiller T, Nguyen T, Palmer J, O'Donnell M, et al. Correlates of resistance and relapse during blinatumomab therapy for relapsed/refractory acute lymphoblastic leukemia. Am J Hematol. 2017;92(9):858–65. https://doi.org/10.1002/ajh.24783.
32. Lee DW, Stetler-Stevenson M, Yuan CM, Fry TJ, Shah NN, Delbrook C, et al. Safety and Response of Incorporating CD19 Chimeric Antigen Receptor T Cell Therapy in Typical Salvage Regimens for Children and Young Adults with Acute Lymphoblastic Leukemia. Blood. 2015;126:abstract#684.
33. Frey NV, Shaw PA, Hexner EO, Gill S, Marcucci K, Luger SM, et al. Optimizing chimeric antigen receptor (CAR) T cell therapy for adult patients with relapsed or refractory (r/r) acute lymphoblastic leukemia (ALL). J Clin Oncol. 2016;34(15_suppl):7002. https://doi.org/10.1200/JCO.2016.34.15_suppl.7002.
34. Wang X, Popplewell LL, Wagner JR, Naranjo A, Blanchard MS, Mott MR, et al. Phase 1 studies of central memory-derived CD19 CAR T-cell therapy following autologous HSCT in patients with B-cell NHL. Blood. 2016;127(24):2980–90. https://doi.org/10.1182/blood-2015-12-686725.
35. Chen F, Teachey DT, Pequignot E, Frey N, Porter D, Maude SL, et al. Measuring IL-6 and sIL-6R in serum from patients treated with tocilizumab and/or siltuximab following CAR T cell therapy. J Immunol Methods. 2016;434:1–8. https://doi.org/10.1016/j.jim.2016.03.005.
36. Di Stasi A, Tey SK, Dotti G, Fujita Y, Kennedy-Nasser A, Martinez C, et al. Inducible apoptosis as a safety switch for adoptive cell therapy. N Engl J Med. 2011;365(18):1673–83. https://doi.org/10.1056/NEJMoa1106152.
37. Wang X, Chang WC, Wong CW, Colcher D, Sherman M, Ostberg JR, et al. A transgene-encoded cell surface polypeptide for selection, in vivo tracking, and ablation of engineered cells. Blood. 2011;118(5):1255–63. https://doi.org/10.1182/blood-2011-02-337360.