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Treatment strategies for progressive immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome: case series

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Data sharing beyond what is included in the manuscript will not be made available due to restrictions on sharing of data on individual cases. For additional information please reach out to the corresponding authors.

Immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome (IEC-HS)[1] is an emergent toxicity, recently defined by the American Society of Transplantation and Cellular Therapy (ASTCT), to describe the presentation of hemophagocytic lymphohistiocytosis (HLH)-like manifestations following chimeric antigen receptor (CAR) T-cell infusion.[1] In patients experiencing IEC-HS, typical manifestations include cytopenias, hyperferritinemia, coagulopathy, and/or transaminitis in the days to weeks following CAR T-cell infusion. To be distinguished from cytokine release syndrome (CRS) which, when severe, may often have features of HLH, IEC-HS typically develops as a secondary inflammatory phase as CRS is resolved/resolving and replaces other terms including CAR-T associated MAS or HLH, or variant CRS that have been used to describe this manifestation.

IEC-HS is observed across a host of CAR T-cell constructs; therefore, recent consensus guidelines for IEC-HS establish a foundation for identification of this toxicity and provide insights into initial management strategies.[1] Given the risk of poor outcomes, including fatal complications, developing effective therapeutic approaches is critical. Little is known regrading optimal management of more challenging cases, particularly those refractory to corticosteroids and anakinra.[1] In this report, we discuss 3 unique approaches to refractory IEC-HS across 3 different CAR T-cell constructs to provide insights into management strategies with this difficult toxicity.

Case 1: Use of emapalumab

A 16-year-old male with relapsed chemotherapy- and blinatumomab-refractory Ph-like B-cell acute lymphoblastic leukemia (B-ALL) received tisagenlecleucel following standard lymphodepletion. He was admitted with fever on Day +1 (D+1) and received tocilizumab on D+2 for febrile hypotension with same-day resolution.

Febrile hypotension recurred on D+8, necessitating three doses of tocilizumab and ICU transfer. Although hypotension resolved, he developed profound coagulopathy requiring cryoprecipitate and fresh frozen plasma. By D+10 he had hypofibrinogenemia, hepatic transaminitis, and hyperferritinemia, meeting the criteria for IEC-HS[1] and was started on anakinra and dexamethasone. Despite this, symptoms were progressive leading to life-threatening refractory thrombocytopenia, worsening coagulopathy, and severe hypertension requiring continuous IV nicardipine (Table 1, Fig 1A).

Based on previous reports using interferon-γ (IFNγ) blockade,[2-4] a single dose of emapalumab 100 mg IV (approximately 0.81 mg/kg), an IFNγ-directed antibody, was given on D+11. By 3 hours post-emapalumab, fevers resolved and coagulopathy and hypertension rapidly improved. Steroids, nicardipine, and anakinra were weaned and despite transient elevations in ferritin as steroids were tapered, his clinical manifestations of IEC-HS continued to improve, and he was transferred from the ICU on D+16. He was discharged on D+37 in excellent condition, with improving counts and without infectious complications.

Restaging on D+30 demonstrated a morphologic complete remission (CR) with minimal residual disease (MRD) positivity. Although repeat assessment on D+44 was MRD-negative, disease progressed to 2.0% of mononuclear cells (MNC) by D+65 despite ongoing B-cell aplasia and proceeded to alternate therapy.

Case 2: Use of ruxolitinib

A 58-year-old female with stage IVB high-grade B-cell lymphoma received standard-of-care axicabtagene ciloleucel (axi-cel) following lymphodepletion after progressing from R-CHOP (x 4) and R-DHAP (x 2). She developed persistent fevers starting on D+1, consistent with Grade 1 CRS, and subsequently Grade 1 immune effector cell-associated neurotoxicity syndrome (ICANS) on D+3. Despite tocilizumab and dexamethasone, symptoms progressed, requiring ICU transfer for hypotension necessitating pressors and additional interventions with tocilizumab, anakinra, and high-dose corticosteroids. As symptoms worsened on D+6 to Grade 4 CRS (refractory hypotension) and Grade 4 ICANS (non-responsiveness requiring intubation), siltuximab was incorporated. At this point, on D+7, rapid increases in ferritin and lactate dehydrogenase (LDH), worsening cytopenias, decreasing fibrinogen, and increasing hepatic transaminases were observed, raising concern for either HLH-like manifestations presenting as severe CRS or an evolution to IEC-HS,[1] for which treatment approaches overlap—particularly when refractory to standard CRS management.

As symptoms progressed, ruxolitinib, a janus kinsase (JAK) 1/2 inhibitor with pan-cytokine suppressive properties and efficacy in HLH,[5, 6] was started at 5 mg twice daily on D+8. Within 24 hours, the patient was weaned off pressors. Steroids and anakinra were weaned with steady improvement in ICANS facilitating ICU discharge on D+13. Ruxolitinib was reduced to 5 mg daily on D+14 and stopped on D+16. She remained on antimicrobial prophylaxis

(*Pneumocystis jiroveci* pneumonia, viral and fungal) without signs of infection. A D+28 PET-CT scan demonstrated partial response (Figure 1C) and she was discharged on D+32. D+90, D+260 and D+365 PET-CT scans demonstrated CR. CAR T-cells remained detectable through 28 dayspost-infusion (Figures 1D-1E).

Case 3: Use of low-dose etoposide

A 38-year-old female with post-transplant, post-tisagenlecleucel, relapsed B-ALL with central nervous system (CNS) disease was treated with investigational CD22 CAR T-cells (NCT02315612) following standard lymphodepletion. On D+12 she developed Grade 2 CRS with fevers and hypotension that responded to fluid resuscitation and self-resolved without tocilizumab. She was subsequently discharged on D+18.

Routine outpatient assessment at D+20 revealed rapidly rising ferritin, hepatic transaminitis, lymphocytosis, and worsening cytopenias in all lineages. She was admitted with concern for IEC-HS and started on anakinra and methylprednisolone on D+22, the latter converted to dexamethasone to offset rising lymphocyte counts.

Despite 3 days of anakinra (200 mg twice daily) and corticosteroids, both the rapid rise in ferritin, and the lymphocytosis steadily worsened (Table 1, Figure 1F). This was predominantly driven by CAR T-cell expansion (88% of T-cells were CAR T-cell positive at peak expansion on D+25). Ultimately, low-dose etoposide (50 mg/m^2)—a topoisomerase II inhibitor, was given on D+25 because of its proven efficacy in the treatment of primary[7, 8] and secondary[9] HLH to specifically target the lymphocytosis by inducing T-cell apoptosis and decreasing the inflammatory response.[10] With a single dose, the absolute lymphocyte count (ALC) decreased from 38,870/mcL to 1,190/mcL and the ferritin levels rapidly decreased from over 70,000 ng/mL to less than 20,000 ng/mL, with concurrent improvement in inflammatory markers, and steroids and anakinra were weaned. D+30 restaging reveled a CR, which was maintained at 3 months. Importantly, despite the use of low-dose etoposide, CAR T-cells continued to be detected at high levels and were detectable through the last available timepoint (D+87) (Figure 1G).

First-line approaches for treatment of IEC-HS incorporate the use of corticosteroids and/or anakinra,[1] an IL-1 receptor antagonist based on early experience with these agents in this setting.[11] In cases of progressive or refractory inflammation, this may be insufficient. There is,

however, little guidance in choosing the next, and most effective line of therapy in these challenging cases. Prospective studies, while warranted, are particularly difficult to conduct when testing second or third line agents in refractory settings. Thus, optimal decision making is, by necessity, based on unique patient specific considerations and the toxicities that they are experiencing, aligned with knowledge about the various therapeutics that could be considered and how they have been used in similar circumstances. A particularly unique consideration in the context of CAR T-cells often hinges on the understandable desire to mitigate the toxicity without abrogating the efficacy of the CAR T-cells themselves—especially critical considering the curative potential that these therapies can endow. To this effect, our case series serves to illustrate the utilization of various agents in the treatment of refractory toxicities, including IEC-HS. This series is also amongst the first to clearly demonstrate the therapeutic potential of these agents in treating inflammatory toxicities (Table 2) without complete eradication of CAR T-cells—which may make utilization of such agents more appealing as we strive to improve overall outcomes.

In case 1, IFNγ blockade rapidly resolved life-threatening IEC-HS refractory to multiple other therapies, while still achieving B-cell aplasia and (briefly) MRD negative CR. Based on similar cases available at the time of treatment,[2, 3] its use in primary[12] and secondary[13] HLH, additional experience in CAR T-cells,[14] and comprehensive *in vitro* and animal model investigations suggesting that IFNγ blockade can mitigate CAR T-cell toxicities without compromising efficacy against hematologic malignancies,[4, 15] prospective studies using emapalumab are warranted. While the remission in this emapalumab-treated patient was not durable, patients with high-disease burden and blinatumomab non-responders (like this patient) remain at risk for early relapse independent of emapalumab.

In case 2, the patient had refractory toxicities that ultimately culminated with IEC-HS in the setting of severe CRS and ICANS. Ruxolitinib, a JAK1/2 inhibitor, was administered due to its ability in inhibiting the JAK-STAT pathway responsible for the production of many cytokines involved with these toxicities, including IL-1Ra, IL-2, and IL-6[16] The rapid improvement with use of this agent, in the setting of CR and persistence of CAR T-cells, warrants further investigation of this agent for refractory toxicities.

Lastly, in case 3, low-dose etoposide was specifically chosen to target steroid refractory hyperleukocytosis—a prominent feature of this case, which was associated with a pronounced hyperferritinemia—a sign of hyperinflammation. Given the presentation, an anti-

cytokine directed agent causing increased immunosuppression was not desirable and a single low-dose etoposide led to an immediate decrease in hyperleukocytosis and ferritin levels without eradication of CAR T-cells—highlighting for the first time that low-dose etoposide does not fully eliminate CAR T-cells. The critical observation that low-dose etoposide may rapidly but not permanently target CAR T-cell expansion is particularly relevant when trying to balance toxicity against efficacy.

As HLH-like toxicities independently predict poor survival, for instance after tisagenlecleucel,[1, 17] effective treatment is urgently needed. Since guidance regarding the most appropriate second- and third-line agents is lacking, and systematic study may not be feasible, these cases highlight 3 different approaches for the treatment of IEC-HS. Although variable in their unique mechanisms of action, the agent chosen for each scenario led to dramatic improvement—warranting further study and providing insights into selection of the best agent for an individual patient.

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Tables

Table 1. Overview of patient cases, treatment approach and outcomes

Table 1. Case Presentations			
Definition of IEC-HS (as defined in Hines et al.): Life-threatening syndrome that 1) emerges after IEC therapy, 2) presents with features of macrophage activation/HLH, and 3) occurs with the exacerbation or onset of cytopenias, hyperferritinemia, coagulopathy with hypofibrinogenemia, and/or transaminitis.[1]			
	Case 1	**Case 2**	**Case 3**
CAR T-cell construct	Tisagenlecleucel	Axicabtagene ciloleucel	Investigational CD22 CAR T-cells (ClinicalTrials.gov NCT02315612)
Disease indication	r/r B-ALL	r/r large B-cell lymphoma	r/r B-ALL
Brief patient description	16 yo M with relapsed Ph-like ALL. CNS negative.	58 yo F with progressive disease following 4 cycles of R-CHOP and 2 cycles of R-DHAP.	38 yo F with post-tisagenlecleucel and post-HSCT relapsed CD19/CD22+ CNS (CNS3 at relapse) and EMD B-ALL.
Pre-CAR T-cell disease burden	9.7% of mononuclear cells in bone marrow consistent with B-ALL (D-35 prior to CAR T-cell infusion).	Stage 4B, IPI 4, triple hit. Persistent peritoneal disease and mediastinal adenopathy.	Bone marrow evaluation was negative for disease. Tibial bone marrow biopsy with 45% ALL by flow cytometry. CNS negative.
Presentation of IEC-HS	New onset coagulopathy D+9 with rising INR, falling fibrinogen and by D+10 hyperferritinemia, worsened transaminitis $\geq$ 5x ULN.	On D+7, cytopenia, dramatic increase in AST and ferritin, and a significant decrease in fibrinogen levels observed.	New onset transaminitis and worsening cytopenias on D+20 in the context of hyperferritinemia that was increasing.
Indication for IEC-HS directed therapy	Therapy for life-threatening combination of refractory hypertension and coagulopathy.	Therapy initiated for shock requiring multiple pressors, rising ferritin levels, low fibrinogen, and elevated AST.	Therapy initiated for worsening inflammatory parameters.
Rationale for treatment choice	Emapalumab as no response to dexamethasone, anakinra and continued fevers to 40^{o}C with life-threatening refractory coagulopathy and hypertension.	Anakinra given for concurrent Grade 4 CRS, ICANS, and IEC-HS. Tocilizumab and dexamethasone given for treatment of CRS and ICANS. Ruxolitinib and siltuximab given due to life-threatening IEC-HS.	Low-dose etoposide 50 mg/m2 x 1 dose for hyperleukocytosis and hyperferritinemia that was progressive despite prior interventions.

IEC-HS treatment response	Full resolution of fever in 3 hours, rapid improvement in coagulopathy, weaned off dexamethasone by D+16.	Rapid improvement of hypotension, ferritin levels, and LFTs. By D+15, all laboratory values within normal ranges.	Full resolution of manifestations with a single dose of etoposide. Facilitated rapid wean of systemic immunosuppression. No additional interventions needed.
CAR T-cell outcomes	Complete B-cell aplasia at all timepoints. BM flow D+30 0.33% MRD+ (COG), D+44 MRD negative PB NGS sequencing D+58 ~ 0.05% PB MRD signal BM flow D+65 2.0% MRD positive.	Partial response at D+28, and complete response at D+90, with continued remission at D+260.	MRD negative complete remission by 3 months post CAR T-cell infusion. Isolated CNS relapse at 6 months post infusion.
Data on CAR T-cell persistence	CAR T-cell quantitation not available at center. Peripheral CD19 count remained zero through D+65.	CAR-T cell persistence seen through D+28 despite use of immunosuppressive agents.	CAR T-cell persistence seen through D+87 despite use of etoposide. Additional timepoints not available.

Abbreviations: AST: Aspartate aminotransferase; B-ALL: B-cell acute lymphoblastic leukemia; BID: twice daily; BM: Bone marrow; CAR: Chimeric antigen receptor; CNS: Central nervous system; COG: Children's Oncology Group; CRS: Cytokine release syndrome; CTCAE: common terminology criteria for adverse events; DHAP: dexamethasone, high dose Ara C, cisplatin; EMD; Extramedullary disease; hrs: hours; HSCT: Hematopoietic stem-cell transplantation; ICANS: Immune effector cell-associated neurotoxicity syndrome; IEC-HS: Immune effector cell associated HLH-like syndrome; IPI: International Prognostic Index; LFTs: liver function tests; MRD: minimal residual disease; N/A: not applicable; PB: Peripheral blood; qd: daily; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; r/r: relapsed/refractory.

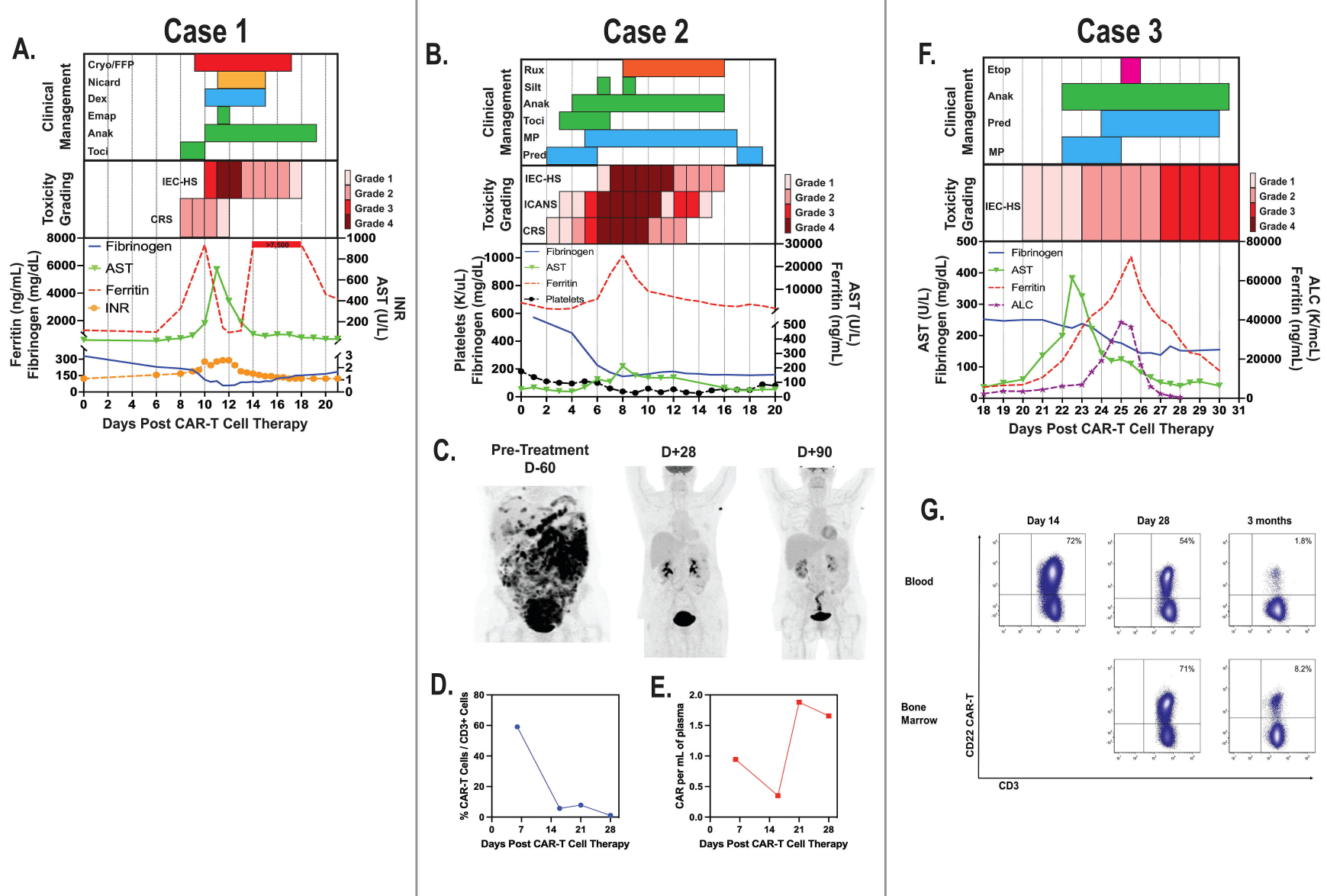
Table 2. Summary of Agents Used in the Management of CAR T-cell Associated Toxicities			
Agent	**Potential Use for CAR T-cell Toxicities (including IEC-HS)**	**Mechanism of Action**	**Experience with Use in HLH or IEC-HS**
Emapalumab (Case 1)	Insufficient response to anakinra and steroids (particularly after 48 hours).[1] Elevated IFNγ.[3]	IFNγ is a pro-inflammatory cytokine produced by T cells and antigen-presenting cells. IFNγ and IFNγ-inducible genes are elevated in patients with HLH and are thought to be implicated in the mechanism of IEC-HS. Emapalumab is a human IgG1 monoclonal antibody that binds and neutralizes free and receptor-bound IFNγ, preventing its pro-inflammatory effect.	Emapalumab has been used to treat primary HLH in pediatric patients[12] and for the treatment of IEC-HS.[2] There is limited data for use of emapalumab in adults. Monitor dosing of drugs that are CYP450 substrates. Monitor patient for tuberculosis, histoplasmosis, herpes zoster infections, and for viral infections and reactivations broadly.
Ruxolitinib (Case 2)	Insufficient response to anakinra and steroids (particularly after 48 hours).[1] Concurrent CAR T-cell-associated side effects (i.e. CRS, ICANS), resulting in the need for broad pro-inflammatory cytokine inhibition.	Ruxolitinib is a small-molecule inhibitor of the JAK-STAT pathway, which is involved in the production of several pro-inflammatory cytokines, such as IFNγ, IL-2, and IL-6. These cytokines are broadly implicated in IEC-HS and other CAR T-cell-related toxicities.[11]	Ruxolitinib has successfully treated secondary HLH in pediatric and adult patients.[6] Ruxolitinib has successfully treated IEC-HS (previously referred to as CAR-HLH). Avoid strong CYP3A4 inhibitors, as ruxolitinib also inhibits the metabolic activity of this enzyme. May cause cytopenia, particularly with longer term use. May cause increased risk for bacterial infections. Monitor patient for tuberculosis, herpes zoster, esophageal candidiasis, PJP, CMV, cryptococcal infections, and for viral infections and reactivations broadly.[1]
Low-Dose Etoposide	Insufficient response to anakinra and steroids	Etoposide is a topoisomerase II	Etoposide is well-studied and highly effective for the treatment of primary

(Case 3)	(particularly after 48 hours).[1] Steroid-refractory hyperleukocytosis (particularly after 48 hours).	inhibitor, which induces double-stranded DNA breaks and inhibits proliferation by preventing T cell from completing mitosis.[16] The therapeutic mechanism involves potent selective deletion of activated T cells and efficient suppression of inflammatory cytokine production. Etoposide promotes programmed cell death (apoptosis) rather than proinflammatory lytic cell death (pyroptosis), conceivably decreasing subsequent systemic inflammation – and the severity of cytokine storm.	HLH in children[7] and secondary HLH in pediatric and adult patients.[9] Because etoposide is mainly cleared by the kidneys, dose reduction is recommended if renal function is impaired; obstructive jaundice may further impair clearance, but only in the context of impaired renal function (for guidance on initial dosing see Ehi et al.) Monitor patient for bacterial infections in the setting of neutropenia.[1]

Figures

Figure 1: Timelines capturing key laboratory findings, relevant toxicity grading(s), and pharmacological interventions on a daily basis for each case. Figure 1A: Case 1; Figure 1B: Case 2; Figure 1C. FDG-PET CT scan at pre, Day+28 and Day +90 timepoints, showing complete resolution of extensive disease for Case 2. 1D and E. Evaluation of CAR T-cells over time, shown as the percentage (D) or absolute number (E) of CAR+ T-cells per microliter of blood detected via flow cytometry (Case 2). 1F. Case 3. 1G. Evaluation of CAR T-cells as detected by flow cytometry at D+14, D+28 and 3 months post CAR T-cell infusion (Case 3)

Abbreviations: ALC: Absolute lymphocyte count; Anak: Anakinra; AST: Aspartate aminotransferase; CRS: Cytokine release syndrome; Emap: Emapalumab; Etop: Etoposide; ICANS: Immune effector cell-associated neurotoxicity syndrome; IEC-HS: Immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome; INR: international normalized ratio; MP: Methylprednisone; Nicard: Nicardipine; Pred: Prednisone; Rux: Ruxolitinib; Toci: Tocilizumab; Silt: Siltuximab


A.
Case 1
Clinical Management
Cryo/FFP
Nicard
Dex
Emap
Anak
Toci
Toxicity Grading
IEC-HS
CRS
Grade 1
Grade 2
Grade 3
Grade 4
Fibrinogen
AST
Ferritin
INR
>7,500
Ferritin (ng/mL)
Fibrinogen (mg/dL)
AST (U/L)
INR
Days Post CAR-T Cell Therapy
B.
Case 2
Clinical Management
Rux
Silt
Anak
Toci
MP
Pred
Toxicity Grading
IEC-HS
ICANS
CRS
Grade 1
Grade 2
Grade 3
Grade 4
Fibrinogen
AST
Ferritin
Platelets
Platelets (K/uL)
Fibrinogen (mg/dL)
AST (U/L)
Ferritin (ng/mL)
C.
Pre-Treatment
D-60
D+28
D+90
D.
% CAR-T Cells / CD3+ Cells
Days Post CAR-T Cell Therapy
E.
CAR per mL of plasma
Days Post CAR-T Cell Therapy
F.
Case 3
Clinical Management
Etop
Anak
Pred
MP
Toxicity Grading
IEC-HS
Grade 1
Grade 2
Grade 3
Grade 4
Fibrinogen
AST
Ferritin
ALC
AST (U/L)
Fibrinogen (mg/dL)
ALC (K/mcL)
Ferritin (ng/mL)
Days Post CAR-T Cell Therapy
G.
Day 14
Day 28
3 months
Blood
Bone Marrow
72%
54%
1.8%
71%
8.2%
CD22 CAR-T
CD3