HLH-like toxicity due to CAR T-cell therapy

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knowledge changing life

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Disclosure of Conflicts of Interest

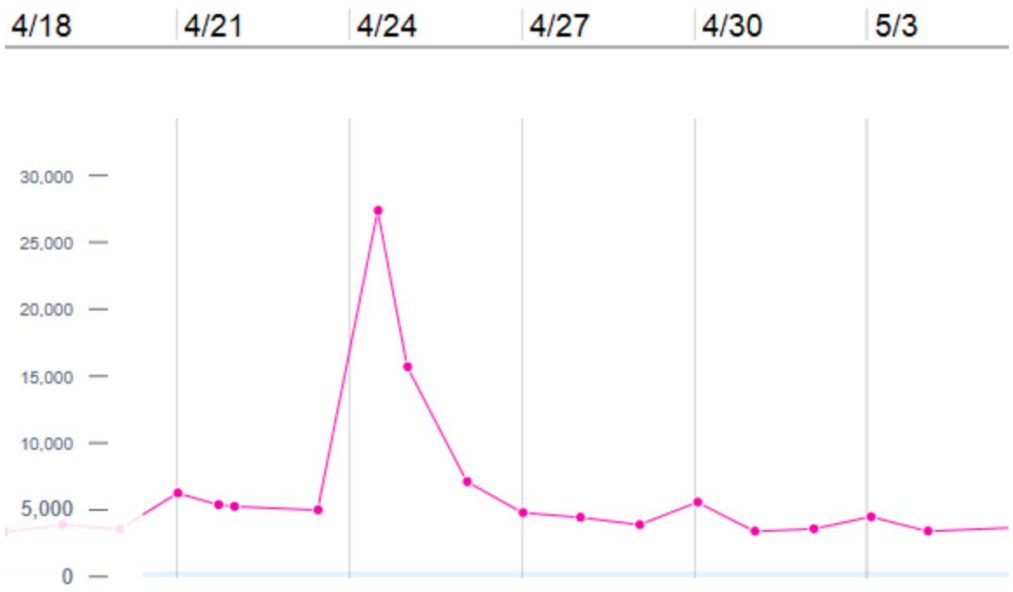
- Fateeha Furqan, MD, has no relevant financial relationships to disclose.

Case

- 60 years old man with relapsed/refractory mantle cell lymphoma was admitted to the hospital for a planned bispecific CD20/CD19 (LV20.19) CAR T-cell therapy for a clinical trial.
- Course was complicated by grade 1 CRS and grade 3 ICANS for which he received 2 doses of tocilizumab, dexamethasone, and IT hydrocortisone
- CRS resolved within 3 days and ICANS within 7days.
- Discharged home with dexamethasone taper with an ICE score of 10/10

Case-continued

- Two days later, he presented again with fatigue, RUQ tenderness and poor PO intake.
- Blood work:
  - Hgb 10.1 g/dL, WBC 2.9x10^3, platelet 23,000.
  - AST 636, ALT 1229, ALP 168, Bilirubin 1.8
  - **Ferritin 27,371 ng/mL**
  - Fibrinogen 84, INR 1.1, aPTT 26.2



Case-continued

- Diagnosed with HLH-like toxicity secondary to CAR T-cell therapy
- Started on high dose steroids
- Anakinra 200 mg TID x 4 days
- Discharged on steroid taper
- Presented again 2 days later, with septic shock secondary to Enterobacter bacteremia
- Unfortunately, he did not improve despite therapy and passed away from infection.

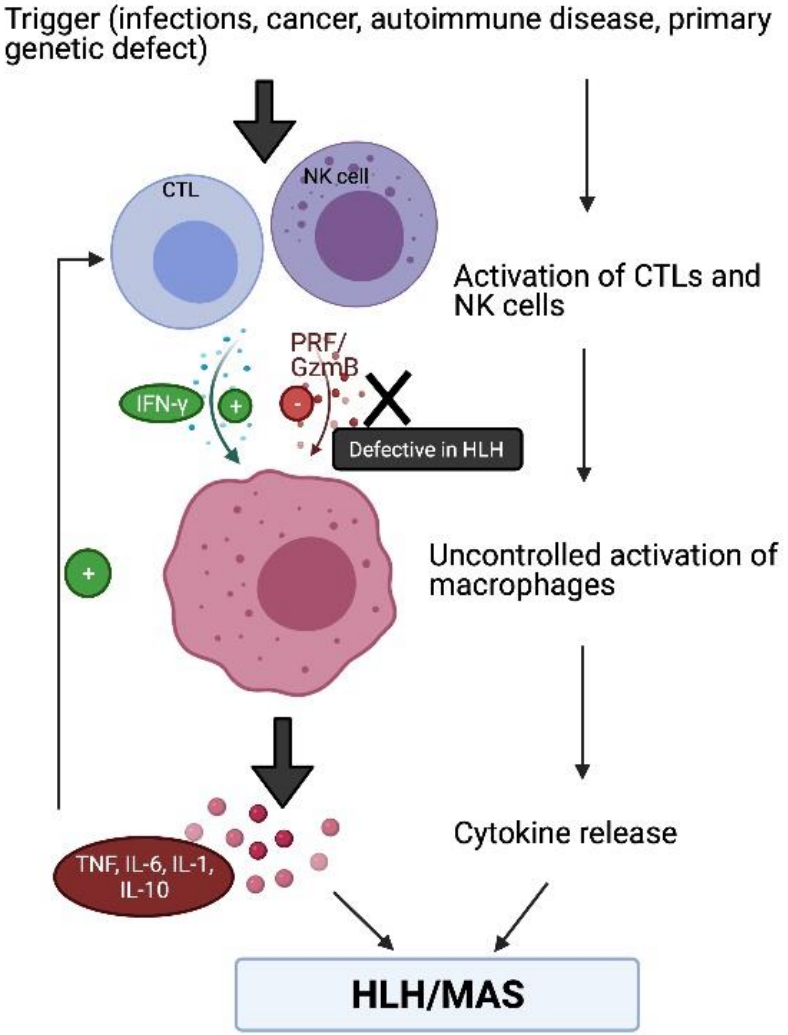
What is HLH?

- Syndrome of excessive immune activation
- Felt to be macrophage driven
- Primary/Familial and Secondary forms of HLH exist
- Diagnosis requires meeting 5 of 8 HLH 2004 criteria

HLH Criteria (5/8)
Fever
Splenomegaly
Cytopenia (2 of 3 lineages)
Ferritin ≥500 mg/L
Hypertriglyceridemia
Hemophagocytosis in bone marrow or spleen or lymph nodes
Soluble CD25 (i.e., soluble IL-2 receptor) ≥2,400 U/ml
Low or absent NK-cell activity

Henter JI et al. *Pediatr Blood Cancer.* 2007;48(2):124-131.

Mechanism of HLH-like toxicity



HLH like toxicity after CAR T-cell therapy

- Incidence:
  - 1-3.5% with CD19 CAR
  - 35-40% with CD22 CAR
- Timing
  - 11-14 days post-infusion
- Risk factors:
  - High tumor burden
  - Marked T-cell expansion
  - Pre-infusion natural killer(NK) cell lymphopenia and higher bone marrow T-cell:NK cell ratio

Neelapu et al. NEJM 2017 2017;377(26):2531-2544
Nirali N. Shah et al. ournal of Clinical Oncology 2020 38:17, 1938-1950
Lichtenstein et. *Cancer Res* 15 August 2020; 80 (16_Supplement)
Hines, et al. Br. J. Haematol., 194: 701-707.

Diagnostic Criteria

- Low utility of H-score and HLH-2004 criteria
- Neelapu Criteria
- Shah criteria
  - Ferritin >100,000 mg/mL

Neelapu criteria
Ferritin >10,000mg/mL + 2 of the below
Hepatic aminotransferases or bilirubin grade ≥ 3
Oliguria/Creatinine grade ≥ 3
Pulmonary edema grade ≥ 3
Evidence of hemophagocytosis on bone marrow aspirate/biopsy

Neelapu SS, et al. *Nat Rev Clin Oncol.* 2018;15(1):47-62.

HLH-toxicities due to CD19 CAR at MCW

- Retrospective analysis of patients who received CD19 CAR T-cell therapy
- Out of 150 patients treated with CAR, 17 patients had HLH-like toxicity
- Criteria:
  - Ferritin>5000 mg/mL
  - Fever
  - Coagulopathy/hypofibrinogenemia
  - Organ dysfunction: renal, liver, pulmonary edema/effusion/hypoxia

Baseline characteristics	Patients (n)
Median Age at CAR-T	61 (20-79)
Female sex	17.6% (3/17)
Histologies	
• DLBCL	17.6% (3/17)
• CLL	23.5% (4/17)
• Richter's	29.5% (5/17)
• ALL	11.7% (2/17)
• MCL	11.7% (2/17)
• Burkitt's	6% (1/17)
Prior lines of therapy	
• Median	
• Prior ASCT	17.6% (3/17)
• Prior Allo-HCT	17.6% (3/17)
Type of CAR	
• IL7/IL15 expanded LV20.19 CAR	10/17
• IL-2 expanded LV20.19 CAR	2/17
• Lisocabtagene	4/17
• Axicabtagene	1/17

HLH-like Toxicities

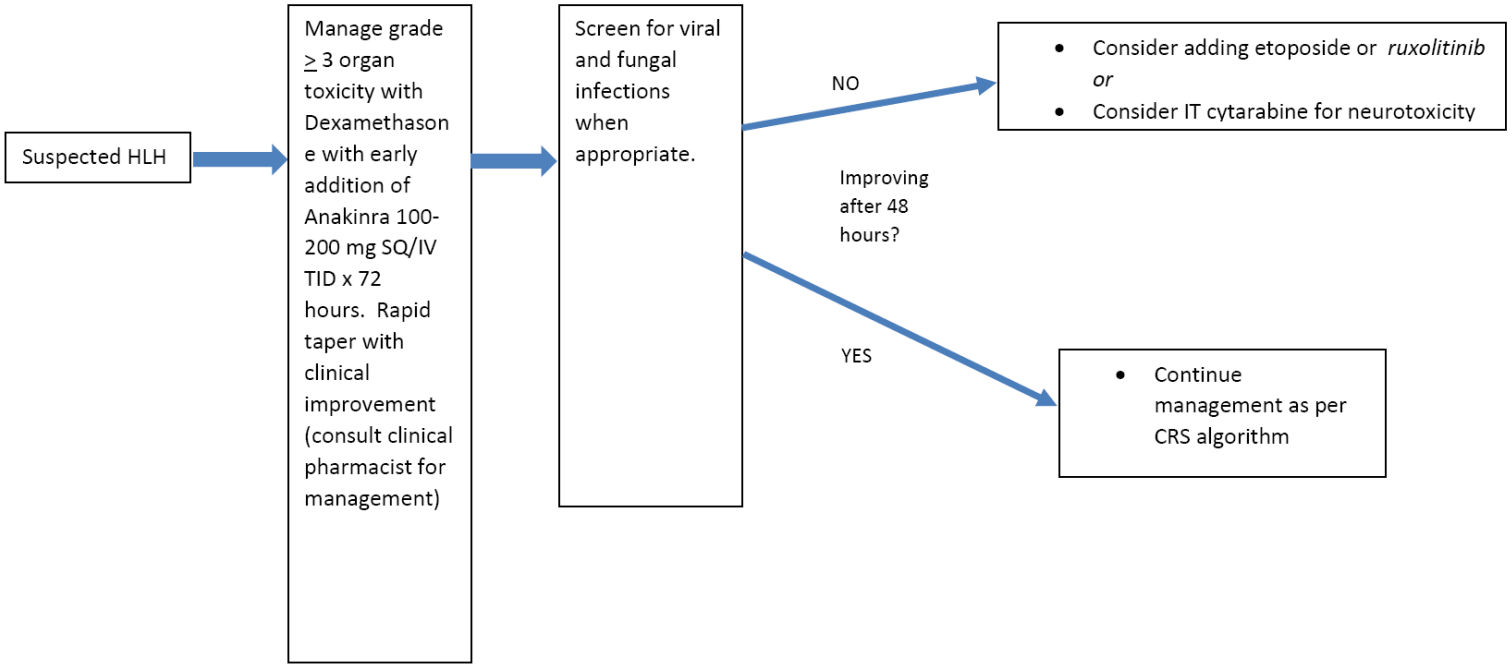
- Median day of onset was day 7
- 16 out of 17 patients had ferritin >10,000
- All patients had LFT elevation while only 40% had renal dysfunction and 47% had hypoxia/pleural effusion/pulmonary edema
- Table 2 shows inflammatory markers

HLH Markers	Day 0 labs	Peak levels
Ferritin (ug/L)	1543	34682
CRP (mg/L)	2.74	12.7
LDH (U/L)	361	1485
D-dimer (mg/L)	1.76	9.99
Fibrinogen (mg/dL)	425	54 (lowest)

Treatment and Outcomes HLH-toxicities

HLH Outcomes	Patients (n)
Steroid use Median dose of steroid	100% (17/17) 292 mg
Anakinra use	59% (10/17)
Other therapies • Etoposide • Ruxolitinib (same patient) • IT steroids	 6% (1/17) 6% (1/17) 29% (5/17)
Death • Bacterial infection • Viral infection • Hemorrhage (intraventricular) • Progressive disease	53% (9/17) 24% (4/17) 11% (2/17) 6% (1/17) 12% (2/17)

MCW Treatment Guidelines

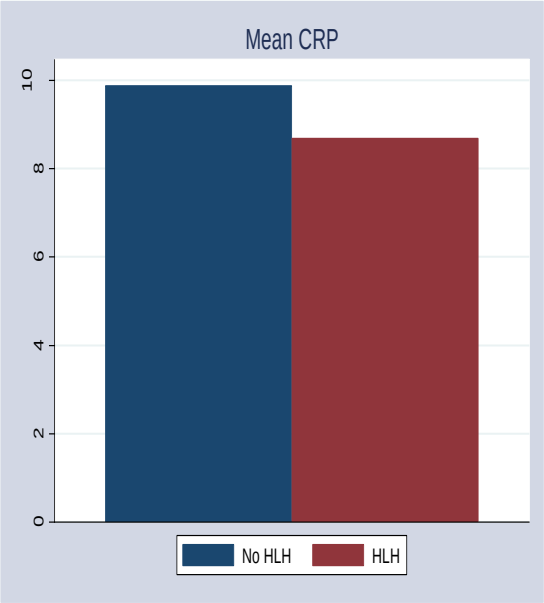


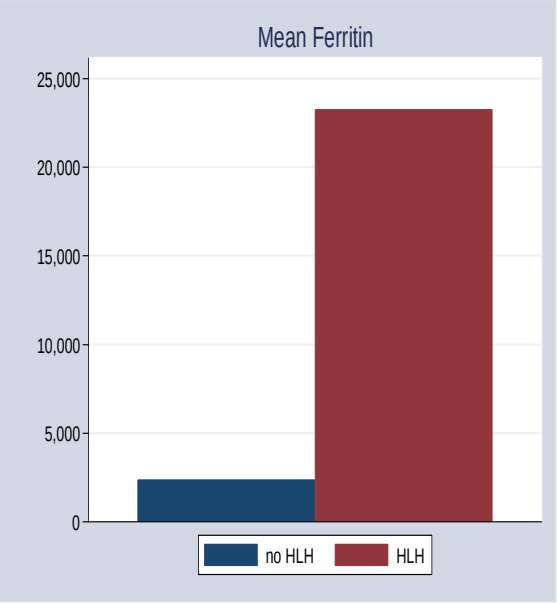
CAR-HLH with LV20.19 CAR T-cells

- This is a bispecific, tandem, anti-CD20, anti-CD19 CAR T-cell therapy for B-cell malignancies
- Approximately 15% of LV20.19 patients had CAR-HLH
- IL-7/IL-15 adult NHL=36 patients, 7 with HLH like manifestations

LV20.19 Adult NHL

- Mean Ferritin HLH group=23218 ng/mL vs Non-HLH group=2356 ng/mL
- No difference in Day 28 response rate
- No difference in peak CRP.



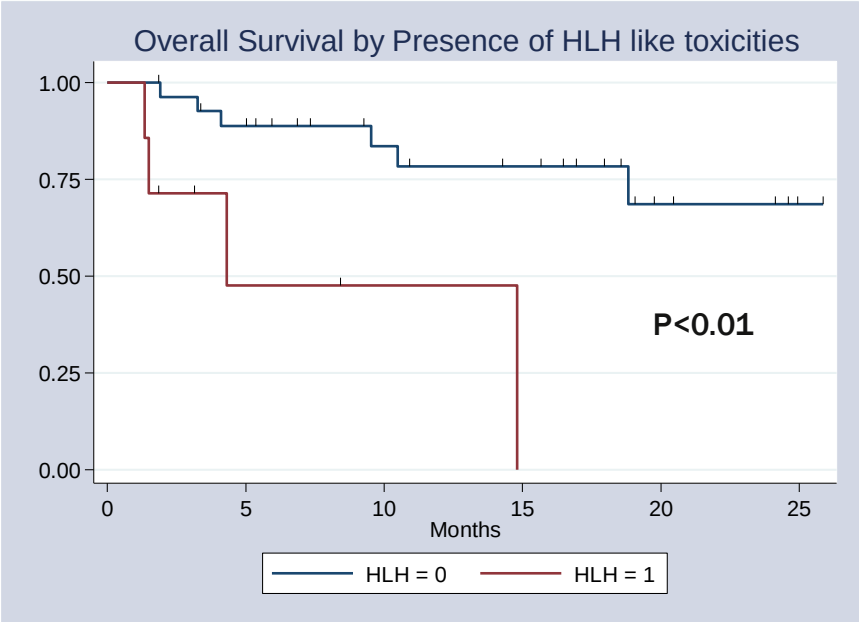


Worse Survival in HLH patients

- **LV20.19 CAR patients in NHL**

Deaths are not due to HLH but infectious complications.

- 2 bacterial sepsis (both received anakinra)
- 1 COVID19 death (late toxicity)
- 1 progressive disease



Conclusions

- Secondary HLH like toxicities post CAR T-cell therapy is an under recognized conditions that impacts patient outcomes
- Mechanisms and treatment algorithms are different than traditional CRS, tocilizumab is not the favored treatment option
- MCW approach involves steroids +/- anakinra, while effective in treating HLH, infectious complications with additional immunosuppression have limited successful outcome
- ASTCT working group is trying to define and develop recommendations on management to better recognize this event and treat complications (TBD)