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Chimeric antigen receptor T-cell therapy associated hemophagocytic lymphohistiocytosis syndrome: clinical presentation, outcomes, and management

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Dear Editor,

Hemophagocytic lymphohistiocytosis (HLH) is a rare complication of chimeric antigen receptor T-cell (CAR-T) therapy [1–3]. With the increasing use of CAR-T therapy in treating hematological malignancies, the unique phenomenon of CAR-T-associated HLH (carHLH) is increasingly recognized. Albeit rare, reported rates vary from 1–3% to 35% depending on the underlying disease, patient population and the CAR-T product [1–3]. Recently ASTCT has published guidelines recognizing HLH in the setting of CAR-T as immune effector cell-associated HLH-like syndrome (IEC-HS) [4]. The most extensive series to date that comprehensively described manifestations, along with patient and CAR-T specific factors associated with the development of carHLH, is that of anti-CD22 CAR-T in 21 pediatric patients with B-ALL [2]. We herein provide a detailed description of clinical presentation, treatment strategies, and outcomes in adult patients who developed carHLH across three sites at Mayo Clinic.

A chart review to summarize patient and CAR-T characteristics for carHLH was conducted. It included adult patients undergoing CAR-T for non-Hodgkin lymphoma (NHL) and multiple myeloma (MM) receiving B-cell maturation antigen (BCMA) CAR-T. Baseline characteristics were determined at the time of lymphodepletion (LD). CAR-T-related toxicities were graded based on the ASTCT 2019 guidelines [5]. CarHLH was identified based on the combination of laboratory and clinical criteria adapted from HLH diagnostic criteria, and previously reported series for HLH after CAR-T cell therapy [3]. These criteria were reviewed and approved by the cell therapy group at Mayo Clinic and included a peak ferritin level of >10,000 ng/L and at least 2 of the following criteria: [1] impaired hepatic function including bilirubin > 3 x upper limit of normal (ULN) or baseline, or transaminases >5 x ULN or baseline; [2] impaired renal function including oliguria or creatinine >3 x ULN or baseline, [3] grade ≥3 pulmonary edema or hypoxia [4] presence of hemophagocytosis by morphology and/or CD68 immunohistochemistry in organs, [5] new or unexplained grade ≥3 cytopenia, and [6] new-onset grade ≥3 acidemia requiring intervention and not attributable to other causes. This study was conducted according to the Declaration of Helsinki and was approved by the institutional board review at Mayo Clinic.

A total of 3% of patients (13/436) receiving CAR-T therapy between 1/1/2018 and 5/31/2022 met the criteria for carHLH. Table 1 describes individual-level baseline patient characteristics, toxicities, interventions, and outcomes. The median age of patients at the time of CAR-T infusion was 61 years (39–89 years). Underlying diseases included high-grade B-cell (HGBL) with *MYC* and *BCL2* rearrangements (4), HGBL, not otherwise specified [NOS] (1), diffuse large B-cell lymphoma (4), mantle cell lymphoma (1), CLL (1), and MM (2). Of the NHL patients (CLL not included), 90% (9/10) had advanced-stage disease, elevated LDH at the time of LD, and 70% (7/10) had high-risk IPI (Table 2). Eight of the 10 NHL patients required bridging therapy, of which 75% (6/8) required chemotherapy. Within the NHL cohort, CAR-T products included axicabtagene ciloleucel (5), lisocabtagene maraleucel (4), and brexucabtagene autoleucel (1). The two patients with MM both had IgG kappa type, high-risk disease based on cytogenetics, and >90% bone marrow involvement at the time of LD. One MM patient received idecabtagene vicleucel (6 prior lines of treatment), and the other was treated with an anti-BCMA CAR-T on a clinical trial.

All patients experienced CRS with 39% (5/13) experiencing grade ≥3. The median time to onset of CRS from CAR-T was 2 days (0–7). ICANS was seen in 10 (77%) patients, with a grade ≥ 3 in 9 patients. The median time to onset of ICANS from CAR-T was 7 days (4–10). The median time to carHLH onset from CAR-T was 8 days (4–32). CarHLH resolved in 7 patients (54%). The median time to resolution was 8 days (5–62). CarHLH was a continuum of CRS in 8 (53%) of the 13 patients, whereas there was a clear resolution of CRS before carHLH development in the other 5 patients.

Tocilizumab was used in 92% (12/13) of patients after carHLH onset. The median number of tocilizumab doses were 3 (1–4). All patients received steroids with a median duration of 14 days (5-56). Anakinra was used in 92% (12/13) of the patients with a median duration of 7 days (3-74). Chemotherapy was used in 2 patients one each with etoposide and cyclophosphamide. Siltuximab, an anti-IL6 monoclonal antibody, in seven patients. Anti-thymocyte globulin and JAK2 inhibitor ruxolitinib were utilized in 2 patients. Basiliximab, an IL-2 receptor-blocking antibody, was used in 2 patients. Dialysis was initiated as continuous venovenous hemodialysis (CVVH) in 54% (7/13) patients for new onset acidemia and/or removal of cytokines. The median duration of CVVH was 4 days (1–6). One patient was started on an extracorporeal cytokine adsorber (CytoSorb®). Three of the 7 patients needing CVVH had resolution of carHLH. Vasopressor support was needed in 5 patients (38%), and the median duration of use was 4 days (2–5). Eight patients (62%) developed infectious complications after developing carHLH, none before carHLH onset. Only 2 of the seven patients had infection resolution and were alive at the last follow-up (Table 2). Ten carHLH patients (77%) had died at the time of data cut-off. The causes of death included carHLH (5), progressive lymphoma (1), neurotoxicity-related aspiration event (1), bowel perforation resulting in septic shock (1), COVID infection (1) and unknown

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Table 1. Individual patient demographics, disease characteristics, baseline laboratory values, toxicities and clinical outcomes.

Patient number	1	2	3	4	5	6	7	8	9	10	11	12	13
Baseline characteristics at day -5 before initiation of conditioning													
Age/sex	53/M	57/M	58/M	65/M	59/M	61/F	89/M	39/F	77/F	68/M	71/M	58/M	62/F
Complication type	HLH	HLH	HLH	HLH	HLH	HLH	HLH	HLH	HLH	HLH	HLH	HLH	HLH
CAR-T type	Commercial	Trial	Commercial	Trial	Trial	Commercial	Commercial	Commercial	Trial	Commercial	Commercial	Commercial	Commercial
Disease type	HGBL	HGBL	DLBCL	DLBCL	IgG Kappa MM	HGBL	MCL	HGBL	CLL/SLL	HGBCL	T–cell rich LBCL	DLBCL	IgG Kappa MM
Stage	IV	II	IV	IV	R-ISS III	IV	III	IV	NA	IV	IV	IV	R ISS III
IPI	2	2	3	3	NA	4	3	4	NA	4	5	1	NA
BM inv. (%)	No	No	No	Yes (>90%)	Yes (>95%)	Yes (20%)	Yes (>95%)	Yes (30%)	yes	Yes (>90%)	Yes	Yes	Yes (80%)
Elevated LDH	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	yes	Yes	Yes	No	No
CNS involvement	No	No	No	No	No	No	No	No	No	Yes	No	No	No
FISH	*MYC, BCL2 and BCL6* rearrangements	*MYC, BCL2 and BCL6* rearrangements	None	None	Del 1q, Del 17p	*MYC* and *BCL2* rearrangements	Del 17p, complex cytogenetics	*MYC* and *BCL2*rearrangements	Del 13q, trisomy 12	None	None	None	Del 17p, Del 1p
Prior lines	2	1	2	5	4	2	3	2	6	2	2	3	6
Prior Auto transplant	No	No	No	No	Yes	No	No	No	No	No	No	No	Yes
Prior CD19 or BCMA directed treatment	No	No	No	No	No	No	No	No	yes, CD 19	No	Yes, CD 19	Yes, CD 19	No
Bridging therapy/type	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes		Yes		Yes	Yes
	Chemo+ steroids	Chemo	Steroids + RT		Chemo + steroids	Chemo	Monoclonal antibody + steroids	Chemo	No	Monoclonal antibody + steroids	No	Chemo	Chemo
Refractory disease	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes
Toxicities													
CRS	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Time to Onset	Day (D) 6	D 2	D 2	D 0	D 1	D 5	D 7	D 0	D1	D3	D3	D3	D0
Peak grade	G4	G2	G2	G2	G1	G4	G2	G3	G1	G3	G2	G1	G3
Duration	8 days	9 days	8 days	14 days	4 days	Not resolved	2 days	7 days	1 day	Not resolved	3 days	2 days	4 days
ICANS	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Time to Onset	D 10	D 7	D 7			D 8	D 10	D 6		D4	D7	D4	D4
Peak grade	G3	G3	G4			G1	G3	G3		G3	G3	G4	G3
Duration	14 days	7 days	13 days			Died before resolution	Died before resolution	6 days		Died before resolution	5 days	16 days	13 days
HLH													
Time to onset	D 9	D 7	D 7	D 10	D 24	D 8	D 16	D 4	D8	D8	D17	D32	D4
Duration	5 days	5 days	6 days	62 days	Died before resolution	Died before resolution	Died before resolution	Died before resolution	8 days	Died before resolution	12 days	Died before resolution	16 days
Bone marrow	Positive	Not obtained	Not obtained	Negative	Negative	Not obtained	Negative	Negative	Not obtained	Not obtained	Equivocal	Not obtained	Positive
Laboratory markers, peak value (baseline value at LD chemo)													
Ferritin (normal11-307 mcg/L)	9990 (496)	8028 (81)	>100,000 (997)	76,530 (382)	>120,000 (1315)	67,200 (443)	13,208 (1465)	74,230 (4586)	106,677 (1780)	24,420 (1846)	3854 (635)	15,209 (N/A)	29,455 (896)
CRP (normal ≤8.0 mg/L)	277.6 (8.0)	97.4 (49.2)	98.9 (82.9)	89 (13.5)	< 3.0 (3.9)	165.2 (6.4)	3.8 (63.8)	22 (106.3)	131.4 (4.1)	240.9 (39.4)	90 (19.3)	137 (N/A)	21.7 (8.6)
D-Dimer (normal < 500 ng/mL)	6436 (not available)	5442 (1642)	>42,000 (8291)	>42,000 (1375)	>42,000 (5551)	22,000 (749)	7920 (1913)	5755 (1394)	>42,000 (1122)	16,451 (5715)	30,650 (7076)	20,578 (N/A)	5784 (2001)
Soluble IL-2α (normal <960 pg/mL), peak only	7793	11,911	Not available	Not available	5860	61288	Not available	>4000	>4000	>4000	2213	3361	>4000

Table 1. continued

Patient number	1	2	3	4	5	6	7	8	9	10	11	12	13
LDH (normal 122-222 U/L)	>2375 (842)	>2375 (488)	>2375 (> 2375)	7570 (1854)	>9000 (232)	>9000 (479)	252 (133)	1799 (2020)	849 (196)	1246 (811)	1147 (206)	1106 (N/A)	1573 (215)
Circulating malignant cells	No	No	No	Yes	Yes	No	Yes	No	Yes	No	No	No	No
Hepatic dysfunction (CTCAE ver 5.0)	G2	G3	G3	G2	G4	G4	G3	G3	G3	G2	G4	G3	G3
Fibrinogen (lowest, normal 200-393 mg/dL)	74	61	93	72	70	121	82	54	95	90	79	151	93
Toxicity management													
Tocilizumab (doses)	4	3	4	3	2	3	3	2	1	2	3	None	2
Steroids (duration)	14 days	7 days	13 days	56 days	49 days	6 days	14 days	15 days	5 days	12 days	26 days	43 days	19 days
Anakinra (duration)	7 days	7 days	7 days	74 days	54 days	3 days	8 days	13 days	None	6 days	7 days	4 days	25 days
Dialysis (days)	Yes (6)	No	Yes (3)	No	Yes (6)	Yes (3)	No	Yes (4)	No	yes (1)	No	No	yes (6)
Vasopressor support (duration)	Yes (3)	No	No	No	Yes (4)	Yes (5)	No	Yes (2)	No	Yes(4)	No	No	No
Chemotherapy	No	No	No	No	Yes, cyclophosphamide	No	No	Yes, etoposide x 2 doses	No	No	No	No	No
Other interventions	Cytosorb		Siltuximab x 1 dose		Siltuximab x 1 dose, ruxolitinib 25 days	Siltuximab x 1 dose, ATG		Siltuximab x 1 dose, ATG		siltuximabx2, basiliximabx1, ruxolitinib x5 days.	Siltuximab x 1 dose		basiliximab x 1, siltuximab x 1
Outcomes													
HLH/MAS-L resolution	Yes	Yes	Yes	Yes	No	No	No	No	Yes	No	Yes	No	Yes
Infection (organism)	No	No	No	Fungal (sinusitis; fusarium)	Bacterial (bloodstream, line; E. coli, MRSE)	No	Bacterial (bloodstream, line; MRSE, streptococcus)	Bacterial (bloodstream; streptococcus, enterococcus faecium, MRSE)	Bacterial(blood stream;Ecoli)	No	No	Bacterial(diverticulitis; Enterococcus fecium)	Bacterial(blood stream, line; enterococcus) CMV viremia
Best response of underlying malignancy	PR	CR	CR	CR	CR	Died before evaluation	PR	Died before evaluation	CR	Died before evaluation	Died before evaluation	CR	CR
Post CAR-T relapse	Yes	No	No	No	No		Died before evaluation		No			No	No
Vital status (last follow up/ cause of death)	Dead (D 330)	Dead (D 347)	Alive (D 41)	Alive (D 280)	Dead (D 46, infection)	Dead (D 11; HLH)	Dead (D 22; HLH)	Dead (D 15; HLH, infection)	Alive (D 43)	Dead (D 17; HLH)	Dead(D 31;Unknown)	Dead(D 46;HLH,iCANS G4)	Dead(D 49;other)

Table 2. Baseline characteristics, biomarker data, toxicities, interventions and outcomes in CAR-T-associated HLH syndrome.

Characteristics (at the time of lymphodepletion)	***N* = 13**
Median age at the time of CAR-T infusion	61 years (range 39–89 years)
Disease subtypes	
High-grade B-cell (HGBL) with *MYC* and *BCL2* rearrangements	4
HGBL, not otherwise specified [NOS]	1
DLBCL, NOS	4
Mantle cell lymphoma	1
Multiple myeloma	2
CLL	1
NHL patients excluding CLL	***N* = 10**
Stage III/IV	9
Elevated LDH	9
IPI ≥ 3	7
Bone marrow involvement	7
Prior autologous stem cell transplant	0
Media prior lines of treatment	2 (1–6)
CAR-T product	***N* = 13**
Axicabtagene ciloleucel	5
Lisocabtagene maraleucel	5 (4 – clinical, 1 – trial [now approved])
Brexucabtagene autoleucel	1
Idecabtagene vicleucel	1
BCMA CAR-T on trial	1 trial
Biomarker data (at the time of lymphodepletion)	***N* = 13**
Elevated ferritin > 500 µ/L	10 (77%)
Elevated C-reactive protein (CRP)	8 (62%)
Fibrinogen < 150 mg/dL	0
Elevated D-dimer	13 (100%)
Neutropenia with ANC $<1.0 \times 10^9$/L	5 (38%)
Biomarker data (at the time of CarHLH)	***N* = 13**
Elevated ferritin > 500 µ/L	13 (100%)
Elevated C-reactive protein (CRP)	11 (85%)
Fibrinogen < 150 mg/dL	12 (92%)
Elevated D-dimer	13 (100%)
Elevated triglyceride > 265 mg/dL	10 (77%)
Bone marrow biopsy with hemophagocytosis (obtained in 7 patients)	3
Toxicities	***N* = 13**
Any grade CRS	13 (100%)
Grade ≥ 3 CRS	5 (39%)
Median time to onset of CRS	2 days (range 0–7 days)
Any grade ICANS	10 (77%)
Grade ≥ 3 ICANS	9 (69%)
Median time to onset of ICANS	7 days (range 4–10 days)
Median time to carHLH onset	8 days (range 4–32 days)
CarHLH resolved	7 (54%)
Median time to CarHLH resolution	8 days (range 5–62 days)

Table 2. continued

Interventions after CarHLH development	***N* = 13**
Tocilizumab	12 (92%)
Steroids	13 (100%)
Anakinra	12 (92%)
Chemotherapy	
Etoposide	1
Cyclophosphamide	1
Siltuximab	7 (54%)
Basiliximab	2 (15%)
Ruxolitinib	2 (15%)
Anti-thymocyte globulin	2 (15%)
Dialysis	7 (54%)
Complications	***N* = 13**
Infections	8 (62%)
Bacterial	6
Fungal	1
COVID	1
Intestinal perforation	2
CMV re-activation	1
Causes of death	***N* = 13**
Deaths	10
Car HLH	5 (50%)
Disease progression (lymphoma)	1
Aspiration in the setting of ICANS	1
Bowel perforation	1
COVID infection	1
Unknown cause	1

DLBCL diffuse large B cell lymphoma, *CLL* chronic lymphocytic leukemia, *LDH* lactate dehydrogenase, *IPI* international prognostic index, *CRS* cytokine release syndrome, *ICANS* Immune effector cell associated neurotoxicity syndrome.

cause (1). For those who died due to carHLH, the median time from CAR-T to death was 27 days (11-49). Day 30 response was available in 9/13 patients. There were seven (54%) complete responses (CR) and 2 (15%) partial responses (PR). The rest of the patients had died before day 30 evaluation.

This report represents the most extensive published series of adult patients with NHL or MM receiving CAR-T therapy. The prior two reports have been in the pediatric population with CD22- and CD19-directed CAR-T in B-ALL [2, 3, 6]. In our series, carHLH was rare (3%), which is similar to that noted in the report by Ahmad et al. (6/105 patients) but significantly lower than that reported by Shah et al. (36%) [1, 3]. These variable numbers are likely an effect of both the patient as well as CAR product characteristics. The timing of CRS and carHLH also varied from prior series in B-ALL. The median time to onset to CRS was 2 days and carHLH was 8 days, which was shorter than Shah et al. (8 days and 15 days, respectively) and Hines et al. (5 days and 11.5 days, respectively). Different patterns of carHLH were noted with 8/13 carHLH occurring as a continuum of CRS and the rest after CRS resolution [7]. The diagnosis of carHLH remains challenging due to overlapping symptoms and laboratory abnormalities with CRS or pre-existing laboratory derangements due to the disease itself and prior treatments [4, 8]. The recently developed IEC-HS guidelines are based on expert opinion due to paucity of data, and our criteria did overlap with the report [4]. The management of CRS and carHLH

beyond tocilizumab and steroids have not been well outlined. Anakinra was the most common intervention (12/13 patients) [9]. Chemotherapy is recommended as the mainstay of treatment in patients with primary HLH but is not commonly used in the carHLH reports [10]. The two patients treated with etoposide and cyclophosphamide did not have carHLH resolution. Both patients receiving chemotherapy subsequently developed infections. We also described the use of siltuximab (7/13 patients) and ruxolitinib (2 patients). Siltuximab was used in patients with persistent elevation of IL-6 levels despite tocilizumab. Three of these 7 patients had carHLH resolution. One reason for the increased use of siltuximab was the national tocilizumab shortage during the study period. Our report is also the first one to describe the use of basiliximab, an IL-2 receptor blocking antibody, in 2 patients. One of the 2 patients had resolution of HLH while the other did not. Extracorporeal blood purification therapies have recently gained some interest in severe CRS and carHLH [11]. In addition continuous renal replacement therapy can help correct electrolyte, acid-base and fluid derangements encountered during severe CRS and carHLH, promoting renal recovery and preventing life-threatening complications. Early utilization of CVVH can help mitigate manifestation and complications related to carHLH and decrease the duration of immunosuppression [12]. In our series, 7/13 patients were initiated on CVVH, including one with CytoSorb® device. Three of these 7 patients had carHLH resolution. A considerable increase in infectious complications was noted in our series. We hypothesize this to be related to iatrogenic immune suppression. While infection itself can be a driver for secondary HLH, especially viral infections such as EBV or CMV, none of our patients had infections diagnosed before the onset of carHLH.

In conclusion, carHLH is a rare but life-threatening complication of CAR-T. We present the most extensive real-world series of carHLH in patients with NHL, MM and CLL receiving anti-CD19 or BCMA CAR-T. Early recognition and prompt interventions are paramount for the resolution of carHLH and to prevent fatal outcomes. Larger studies are required for the development of evidence-based guidelines. Multidisciplinary teams with expertise in managing such critically ill patients will be needed for optimal management.

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AUTHOR CONTRIBUTIONS

AK and YL conceived and designed the study. AK, ACR, RM, MG, RB, MAH, and MI collected and assembled the data. AK, MAH, RB, and MG, analyzed and verified the data. AK, ACR, RM, MG, RB, MAH, MI, UD, and YL verified and interpreted the data. AK, ACR, UD, ANN, MI, YW, JP, JCV, DD, TK, NL, HA, MWR, AGM, PV, JH, SSK, NNB, PBJ, SMA, and YL were involved closely in patient care and contributed cases to the series. All authors wrote and approved of the article and are accountable for publication.

COMPETING INTERESTS

J.P. received research funding from Karyopharm. Y.W. received funding from Incyte, LOXO Oncology, Novartis, Genetech, and Morphosys; also had Incyte, LOXO Oncology, Eli Lilly, TG Therapeutics membership on advisory committee. Y.L. received research funding from Kite, Janssen, Celgene, Bluebird Bio, Merck, and Takeda; also received consulting fees from Janssen, Novartis, Celgene, Bluebird Bio, Juno, Legend, Sorrento, Gamida Cell, and Vineti. Also, LOXO Oncolgy, Incyte, Eli Lilly, and TG Therapeutics were taking part on an advisory committee. Stephen Ansell received from Bristol Myers Squibb, ADC Therapeutics, Seattle Genetics, Regeneron, Affimed, AITherapeutics, Pfizer, Trillium and Takeda.

ADDITIONAL INFORMATION

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