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INFECTIOUS COMPLICATIONS IN RECIPIENTS OF CAR T CELLS: EPIDEMIOLOGY AND PREVENTION

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DISCLOSURE

- Research Support: Merck
- Consultant: Merck
- Ad board: Merck, Janssen, Clinigen
- Investigator: Merck, Gilead, Ansun, AiCuris, Shire/Takeda, Chimerix,

CAR T cellular therapy

- Promising and a novel therapeutic modality

- 2 FDA approved products (anti-CD19 CAR T):

❑ Tisagenlecleucel: Kymriah (Pre B ALL)
❑ Axicabtagene ciloleucel: Yescarta (DLBCL)

- Investigational: AML, solid tumors

  - https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm598029.htm
  - https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm581216.htm

Effects

- CD19-specific CAR T cells lyse CD19 + targets: thus eliminating the malignant B cell targets – also, impacts normal lineage B cells.

- Activation of innate and adaptive immune systems: cause for various toxicities

- B cell aplasia and prolonged hypogammaglobulinemia, and at times neutropenia (Macrophage activation syndrome)

Toxicities

- **Non-infectious**

 - Cytokine release syndrome: difficult to differentiate from infection

 - Neurotoxicity

 - Cardiotoxicity

- **<u>Infectious</u>**

 - related to underlying pre-existing risk

 - Or risk related to post CAR-T effects (hypogammaglobulinemia, neutropenia, lymphopenia)

Major toxicities

- **CRS: cytokine release syndrome:**
- Standardized definitions are in place for grading severity
  - Challenge is differentiating from infection: presents with fever, hypotension, tachycardia, cardiac dysfunction, etc..
  - Biomarkers: IL-6, IFN-gamma, TNFα, IL-2, IL-2R-alpha, IL-8, and IL-10 are elevated. Ferritin and CRP are elevated too (latter being acute phase reactants – often elevated with infection).

Brudno J, Kochenderfer. Blood 2016;127(26):3321-3330

Infectious complications – available literature

- To date - only 2 review papers of ID complications after CAR T cells[1,2] (from single centers)
- Outside of the above reports, minimal literature on infectious complications
- Few case reports in literature[3]
- Most of the clinical trials published make a passing reference to infectious complications[4]

1. Hill J, et al. Blood. 2018;131(1):121-130
2. Park JH et al. Clin Infect Dis. 2018. 67(4):533-40
3. Zahid U, et al. Immunotherapy. 2017; 9(13): 1061-66, and McGraw BI. Pediatrc Blood Cancer. 2018;65:e26739
4. Nellapu SS et al. NEJM. 2017;377(26):2531-44

Infectious complications

- **Risk related to:**

- Underlying hematologic malignancy
- Prior therapies for the hematologic malignancy:
  # of prior treatment regimens, HCT
- Lymphodepletion regimen
- CAR T cell dose
- CRS grade
- Treatment used for managing CRS

Hill J et al. Blood 2018

- 133 patients (47 ALL, 24 CLL, 62 NHL)
- **Baseline features:**
- Median age 54 yr
- Prior antitumor regimens; median 4 (range 1-11)
- Prior autologous or allogeneic HCT: 50 pts
- Pre-lymphodepletion (select features):
  - IgG<400: 34
  - ALC <200: 106
  - ANC<500: 16

Treatment

- Cyclophosphamide/Fludarabine - LD regimen: 104

- CAR-T-cell dose:

  Level 1: $2x10^5$: 35

  Level 2: $2x10^6$: 86

  Level 3: $2x10^7$: 12

Post CAR-T-cell characteristics

- Time to neutrophil recovery: median 6 days (range 1,25)
- CRS grade: gr 0: 40, gr 1-3: 83, gr 4-5: 10
- Neurotoxicity grade: gr 0: 80, gr 1-2: 25, gr 3-5: 28
- Corticosteroids and/ or Tocilizumab use: 28

Infections in 1st 28 days post CART-I

- 3615 pt-days at risk were analyzed
- First infection occurred at median of 6 days (range,1-27 d)
- 80% of first infections occurred in first 10 days.
- Infection density – 1.19 infections/100 days at risk

Infections in 1st 28 days

- 43 infections in 30/133 pts (23%)
- Most common: bacterial – 24 events in 22 pts
- 12 bacteremia (4 GNR; FQ-R)
- Viral infections: 13 events in 11pts; 10 had CRV, 2 developed LRTI
- 1 EBV: plasma and CSF: gr 4 CRS, CMV+ plasma – gr 4 CRS – none had end-organ disease

Infections in 1st 28 days

- Invasive fungal infections (IFI):
- 6 events in 4 pts: all had severe CRS or neurotoxicity that required tocilizumab and/or corticosteroids
- 3 previously had previous autologous or allogeneic HCT
- 2 had invasive mold infections

Infections in the 1st 28 days

- 28 pts had both CRS and infection
- Onset of CRS prior to infection: median of 2 days
- Only 3 patients developed infection prior to CRS onset (suggesting pre-existing infection)
- Median time to CRS and first infection: 1.9 and 6 days respectively (p=0.02)
- Pts with grade 4 CRS: 8/11 infections occurred after the peak of CRS

Infections between 29 and 90 days after CART-I

- One of the risk for infection is B-cell depletion - 98% (116/118 evaluable pts) by day 28
- By day 90, only 17/82 evaluated pts had recovery of B cells
- Hypogammaglobulinemia with IgG <400: developed in 35%, 27% and 46% of evaluable pts between days 15-30, 31-60, 61-90 respectively

Infections between 29 and 90 days

- 119 pts evaluable; 3431 days at risk for infection
- Estimated infection density 0.67, significantly lower than first 28 days (RR 0.56, 95% CI, 0.33-0.93; p=0.02)
- 23 infections in 17/119 pts (9%)

Infections between 29 and 90 days

- Viral: most common. 13 in 11 pts: 9 had URI (1 of them LRTI) – reflective of community exposure
- 3 non-HCT pts developed non-CRV infections:1 with BK cystitis, 1 with CMV pneumonia and 1 CMV viremia
- Bacterial: 8 events in 7 pts (6%), 4 bacteremias(2GNR, FQ-R)
- IFI's – 2 events in 2 pts (both had prior allogeneic HCT)
- Late infections: persistent disease and neutropenia found in 48% and 22% respectively

Severity of infection after CART- Infusion

- **Between day 0 and 90:**

- Mild to moderate infections: 33/66 events (50%) in 23 pts (17%)

- Severe infections; 27/66 events (41%) in 19 pts (14%)

- Life-threatening infections: 4 events in 3 pts

- Infection as primary cause of death: CLL pt without neutropenia with invasive aspergillosis at D90, and a ALL patient with neutropenia, severe CRS and CDI

Severity of infection – relationship to Pre-LD and CRS

- 3/27 (1 bacterial sinusitis and 2 peri-rectal abscess) with severe infection had infection pre-LD, that progressed post CART-I

- 1/4 with life-threatening infection: infection pre-LD (invasive fungal sinusitis), and 2/4 had gr >4 CRS.

Pre CAR-T- Infusion: factors associated with infection

- In multivariable model features associated with higher risk of infection:

- Diagnosis of ALL
- >4 prior antitumor regimens
- Level 3 CAR T cell load

Post CAR-T-I factors associated with infection

- Only factor associated with increased risk for infection in MV model was:

- The “severity of CRS”

- Increased hazard for infection - 3.4 ($p<0.001$) for each increase in CRS severity category

  (grades 0 vs. 1-3 vs. 4-5)

Conclusions from the study

- Majority of infections occurred in the first 28 days
- Increased risk in Pre-B ALL pts, >4 treatment regimens, high CAR-T cell load, and severity of CRS
- Distribution of specific infection categories in the early and late periods after CAR-T-I similar to those observed with UR-HCT
- All pts with IFI had prior HCT or had severe CRS requiring treatment
- Hypogammaglobulinemia is an issue that can be protracted

Park JH et al. CID 2018

- 53 pts – phase 1 trial in relapsed Pre-B ALL pts
- CD19 CAR T cell therapy

- LD regimen:
- 42/53 = Cyclophosphamide
- 10/53 = Cyclophosphamide + fludarabine
- 1/53 = Cyclophosphamide + clofarabine

- 57% lymphopenic and 43% neutropenic prior to LD

Park JH et al. Clin Infect Disease 2018

Table 3. Comparison of Early Versus Late Infections After Chimeric antigen receptor T-cell infusion

	Early[a] (Day 0–30) (n = 53)		Late (Day 31–180) (n = 32)[b]	
	Infections, No.	Patients, No. (%)	Infections, No.	Patients, No. (%)
Any infection	26	22 (42)[c]	15	10 (31)[d]
Bacterial				
Bloodstream[e]	8	7 (13)	1	1 (3)
Bacterial site[f]	9	9 (17)	4	4 (13)
Fungal				
Yeast[g]	1	1 (2)	0	0 (0)
Mold[h]	3	3 (6)	1	1 (3)
Viral				
Respiratory virus[i]	3	3 (6)	8	8 (25)
Other virus[j]	2	2 (4)	1	1 (3)

[a]Day 0 was the day of Chimeric antigen receptor T-cell infusion (CTI).

[b]Patients with complete remission after CTI.

[c]Two patients had >1 infection.

[d]Three patients had >1 infection.

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Risk factors/ Predictors of infection

Table 4. Univariate and Multivariate Cox Models for Predictors of Infection and Bloodstream Infection

	Predictors of Infection				Predictors of Bloodstream Infection			
Variable	Univariate HR (95% CI)	*P* Value	Multivariate HR (95% CI)	*P* Value	Univariate HR (95% CI)	*P* Value	Multivariate HR (95% CI)	*P* Value
Age ≥50 y	1.04 (.43–2.39)	.92	…	…	0.64 (.12–2.51)	.54	…	…
Female sex	1.29 (.51–3.00)	.57	…	…	2.76 (.71–10.69)	.14	2.63 (.67–10.37)	.16
Prior chemotherapy (≥3 lines)	0.86 (.38–2.03)	.72	…	…	1.66 (.42–9.04)	.48	…	…
Prior allogeneic HSCT	0.77 (.30–1.79)	.55	…	…	1.07 (.25–4.03)	.92	…	…
Conditioning regimen								
Cy 1.5 g/m^2	1.00 (—)	…	1.00 (—)	…	1.00 (—)	…	…	…
Cy 3.0 g/m^2	0.47 (.18–1.36)	.16	0.35 (.12–1.05)	.06	1.12 (.21–11.16)	.9	…	…
Cy/Flu or Cy/Clo	1.41 (.49–4.21)	.52	0.83 (.23–3.02)	.77	2.58 (.42–26.63)	.31	…	…
Morphologic disease (≥5% blasts or extramedullary disease)	1.76 (.74–4.72)	.21	0.65 (.18–2.25)	.50	1.72 (.44–9.35)	.45	…	…
CAR T-cell dose (3 × 10^6/kg vs 1 × 10^6/kg)	0.44 (.19–1.01)	.05	0.47 (.16–1.35)	.16	0.72 (.19–2.78)	.62	…	…
Hypogammaglobulinemia (IgG <600 mg/dL)	1.10 (.32–5.66)	.89	…	…	2.21 (.24–292.76)	.56	…	…
CRS grade ≥3[a]	2.64 (1.11–6.03)	.03	2.67 (1.00–7.34)	.05	20.21 (4.40–192.13)	<.001	19.97 (4.32–190.31)	<.001

Abbreviations: CAR, chimeric antigen receptor; CI, confidence interval; Clo, clofarabine; CRS, cytokine release syndrome; Cy, cyclophosphamide; Flu, fludarabine; HR, hazard ratio; HSCT, hematopoietic stem cell transplantation; IgG, immunoglobulin G.

[a]Analyzed as a time-dependent predictor. All the analysis time was CRS grade 3–4.

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CI of infections vs. CRS grade

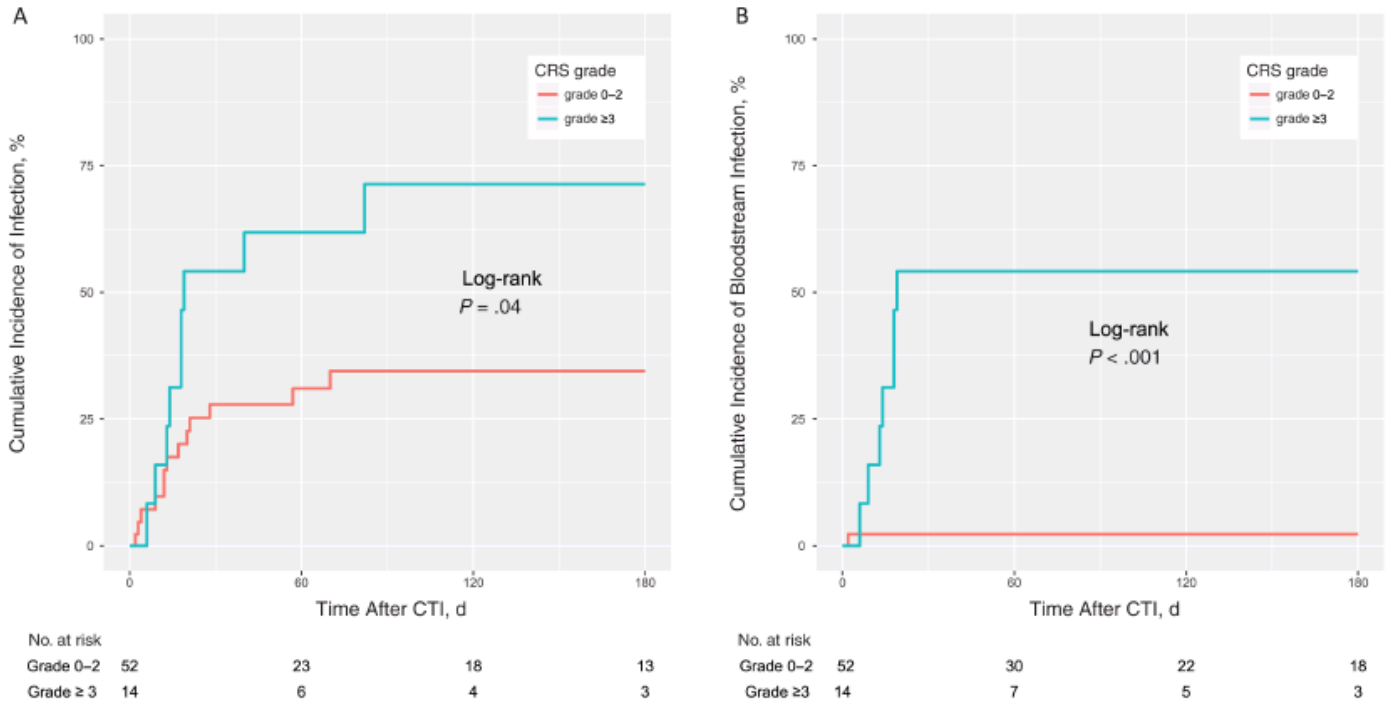

Figure 2. Cumulative incidence of infection after chimeric antigen receptor T-cell infusion (CTI) and cytokine release syndrome (CRS). *A*, Cumulative incidence of any infection in patients by CRS grade. *B*, Cumulative incidence of bloodstream infection by CRS grade. Note that all the analysis time was CRS grade 3–4.

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Cytokine profile assessment

- Cytokine profile using IFN-ɣ, IL6, IL10, IL15 and TNFα
- No difference in the profile in patients with CRS who had infection versus those who did not have infection

Issues

- CRS vs. sepsis due to infection: cytokine profile may not be help in differentiating between the two entities.
- CRS: possibly by causing endothelial dysfunction lead to translocation of bacteria; especially in the context of bacterial infection early after CART-I
- Treatment for CRS: potentially increases risk of opportunistic infection

Cases

Case	Risk factors	Ref
1. 66 yr old with NHL with disseminated coccidioidiomycosis 3 mth after CAR-T	Prior auto and allo HCT Then CAR-T B cell lymphopenia – low IgG (and subclasses)	Zahid U et al. Immunotherapy 2017;9(13):1061-66
2. 10 yr old with recurrent UTI after CAR-T	Multiple lines of chemo Allo HCT Then CAR-T Low salivary and low urinary sIgA	McGraw BI, et al. Pediatrc Blood Cancer. 2018;65:e26739
3. COH patient – Scedosporium infection Influenza A – severe	Prior allo HCT Chemotherapy CAR-T	unpublished
4. COH patients: 2 with CMV disease (1 colitis and 1 pneumonia)		unpublished

Tocilizumab

- **IL-6 inhibition**

- FDA approved for RA/ JRA
- Most of the infections reported are opportunistic - has been with prolonged use of this agent
- Pts with IL-6 antibodies – higher risk for bacterial infections
- Post treatment – symptoms of infection could be muted and atypical

Rose-John S. Nature reviews Rheumatology. 2017;13:399-409, Atsumi T. Modern Rheumatology. 2017, Moots RJ. Rheumatology. 2017;56:541-549

Tocilizumab

- Most of the OI's reported in the rheumatologic literature. Often other immunosuppressive agents are used in conjunction.
- Candida, cryptococcus, pneumocystis, and mycobacterial infections (M.Tb, M. kansasii) have been reported
- With one or 2 doses of Tocilizumab; ? Risk for reactivation of TB or similar diseases. The risk for TB reactivation probably not the same as with chronic use of tocilizumab in rheumatology patients
- Concern for HBV reactivation has been raised by few cases (only with low level chronic HBV)

Nishioka H. J Infect and Chemotherapy. 2018; 24:138-41, Saleem N. The Am J Med Sci. 2017;353(4): 394-397, Chen LF. Int J of Rheum Dis. 2017; 20:859-869

Preventive measures

- Not enough data to base recommendations that are evidence based

- Recommendations - mostly expert opinion

- However, based on the observations from the 2 studies:
  - ❑ Majority of infections occur early in the first 30 days after CAR-T therapy
    - Most of these are bacterial followed by fungal and viral causes
    - CRS is a major risk factor (especially higher grades)

Preventive measures

- **First 30 days post CAR-T infusion**
- Based on MSKCC & FHCRC studies –

- Routine antibacterial prophylaxis perhaps not beneficial as majority of the bacteremias' were due to quinolone resistant/ multidrug resistant pathogens and VRE.

- Antifungal prophylaxis – needs to be tailored based on patient risk factors; underlying hematologic disorder, prior HCT, pre-existing neutropenia, prior h/o IFI, etc. Echinocandin or posaconazole would be appropriate

- Antiviral prophylaxis: is recommended for prevention of HSV and VZV

- PJP prophylaxis: is recommended

Preventive measures

- **Beyond day 30 after CAR-T infusion:**

- **Most of the burden is from CRV's whereas bacterial and fungal infections in the context of neutropenia and lymphopenia**
- Antifungal prophylaxis
- Antiviral prophylaxis
- PJP prophylaxis
- IVIg replacement: IgG monitoring
- Immunizations: perhaps not beneficial if B cell depleted/ hypogammaglobulinemia – no data to make recommendations

Ending remarks

- From the available studies, rates of infection are not higher than salvage chemotherapy or HCT
- Risk adapted approach suggested; for antimicrobial prophylaxis based on local institutional epidemiology and patient characteristics
- Monitoring of IgG recommended