CAR T-cell Therapy, the Infectious Diseases Perspective

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Goals and Objectives

- Review general statistics of infections in recipients of CAR T-cell therapy
- Review risk factors for infections post CAR T-cell therapy
- Discuss CMV issues in CAR T-cell recipients
- Commentary about hypogammaglobulinemia post CAR T-cell therapy
- Concluding with recommendations of post CAR T-cell vaccinations

General Statistics (1)

- Large meta-analysis with overall rate of infection 33.8%
  - 16.2% were severe (grade ≥ 3)
  - Pooled attributable mortality was **1.8%** in adults
  - Type of infection and the timing depends on a variety of issues
    - Type of underlying cancer being treated
    - Type of CAR T-cell product

Telli Dizman G, et al, Risk of infection in patients with hematological malignancies receiving CAR T-cell therapy: systemic review and meta-analysis. *Expert Review of Anti-Infective Therapy*. 2022.

General Statistics (2)

Therapy	Modality	Target	Median prior lines	Manufacturing time, days	Infections/ grade ≥ 3, %	CRS/ grade ≥ 3, %	ICANS/grade ≥ 3, %	ORR/CR, %	mPFS, mo	mOS, mo	EMD efficacy
Talquetamab (800 µg Q2W)[1]	BsAb	GPRC5D	5	N/A	34/7	80/0	5/0	73/38.7	11.9	12-mo OS 77.4%	ORR 45%
Teclistamab[2]	BsAb	BCMA	5	N/A	76.4/44.8	72.1/0.6	14.5/0.6	63/39.4	11.3	18.3	ORR 36%
Elranatamab[3]	BsAb	BCMA	5	N/A	73.6/26.4	65.1/1.2	5.8/2.3	61/35	NR; 15-mo PFS 50.9%	NR; 15-mo OS 56.7%	ORR 38%
Idecabtagene vicleucel[4]	CAR T	BCMA	3	49	58/28[a]	88/5	15/3	71/39	13.3	NR	ORR 55.7%; mPFS 7.2 mo
Ciltacabtagene autoleucel[5,6]	CAR T	BCMA	2,[5] 6[6]	44	62/26.9[a]	76.1/1.1[b]	4.5/0.1[b]	84.6,[5] 97[6]/ 73.1	34.9[6]; 12-mo PFS 75.9%[5,c]	NR; 12-mo OS 84.1%	NR

Liu, L et al, CAR T-cell vs bispecific antibody therapy for relapsed / refractory multiple myeloma, ASCO Daily News, July 3, 2024
Mohan, M et al, Charting the course: sequencing immunotherapy for multiple myeloma, Hematologic Malignancies ASCO, April 2024

Risk Factors Associated with Infectious Risk after CAR T-cell Therapy

Host Related Risk Factors	
	Prior lines of pre-CAR T-cell therapy
	Prior history of transplantation
	Underlying malignancy: B-cell ALL and MM
	CAR-Hematotox Score > 2, lymphopenia
	Prior history of infection within 100d
	Performance status at baseline
	Baseline hypogammaglobulinemia
	Older age

CAR T-cell Related Risk Factors	
	High CAR T-cell dose and intensity of lymphodepletion
	Presence and severity of CRS
	Immune effector cell-associated hematotoxicity (ICHAT)
	Corticosteroid use
	Hypogammaglobulinemia post-CAR T-cell therapy
	Immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome (IEC-HS)

Shahid Z et al, Best Practice Considerations by The American Society of Transplant and Cellular Therapy: Infection Prevention and Management after Chimeric Antigen Receptor T Cell Therapy for Hematological Malignancies, *Transplantation and Cellular Therapy*, 2024

Antimicrobial Prophylaxis during CAR T-cell Therapy

- There are no clinical trials discussing this issue
  - Protocols are traditionally based on recommendations from hematopoietic cell transplantation (HCT) and expert recommendations
- Main points
  - Highest risk of infection: in the first 30d
  - Risk likely driven by neutropenia (NP) + issues potentially from CRS +/- ICANS

Prophylaxis				
	Option 1	**Option 2**	**Option 3**	**Timing of D/C**
Antibacterial	Monitor	Fluoroquinolone	3rd gen Cephalosporin	D/C when no longer NP
Antifungal (vs. *Candida sp.*)	Fluconazole	Triazole (for specific risks)		D/C when no longer NP
Antifungal (vs. *Pneumocystis jirovecii / PJP*)	TMP/SMX	Atovaquone	Pentamidine	D/C > 6 mo vs. CD4+ T-cell count
Antiviral	Acyclovir	Valacyclovir		D/C > 6 mo

CMV Issues in CAR T-cell Therapy

- Very individualized question
  - Pre-CAR T-cell, did the patient have issues
  - Prospective post CAR T-cell data
    - Reactivation rate of upwards of 25%
    - Increased risk especially in the BCMA CAR T-cell recipients with > 3d of steroid use
  - If there is the issue and therefore treatment of Immune effector cell-associated Hemophagocytic Lymphohistiocytosis-like Syndrome (IEC-HS)
- Consider in high-risk patients
  - Weekly CMV PCR for 2 to 6 weeks post infusion in those considered high risk

Chen G et al. CMV reactivation after CD19 CAR T-cell therapy is clinically significant. *Haematologica*, 2023.
Kampour E et al. CMV reactivation and CMV-specific cell-mediated immunity after CAR T-cell therapy. Clinical Infectious Diseases. 2023.
Khawaja F et al. CMV Reactivation within the first year after CAR T cell therapy: experience from the first two years at a major cancer center. *Blood*. 2022.

High Prevalence of Hypogammaglobulinemia

- CAR T-cell regimens especially the original ones that were anti CD19 as well as the plasma cell surface antigen BCMA
  - Can result in hypogammaglobulinemia
    - Leads to increased risk of repeated infections
      - Encapsulated infections
      - Respiratory viral infections
- There is a lack of current data specifically in CAR T-cell patients for replacement with IVIG
  - Expert opinion will often recommend IVIG supplementation especially in patients with repeated infections (3 or more) + IgG ≤ 400 mg/dL
    - Consider giving it q 28d for minimum 3 to 6 months

Hill JA et al. CAR T and a side of IgG, to go? Immunoglobulin replacement in patients receiving CAR-T cell therapy. *Blood Rev.* Nov 2019.

Vaccines in CAR T-cell Recipients (1)

- Traditionally it is recommended to re-vaccinate post CAR T-cell
  - Based on recommendations from ACIP and other expert guidance
    - Influenza A/B
    - SARS-CoV-2
    - Pneumococcal vaccination (PCV20)
    - Diphtheria Tetanus Pertussis (Dtap / Td / Td)
    - Hepatitis A virus (HAV)
    - Hepatitis B virus (HBV)
    - Varicella zoster virus (VZV)

Hill, JA, Seo SK. How I prevent infections in patients receiving D19-targeted chimeric antigen receptor T cells for B-cell malignancies. *Blood*. 2020.
Hill, JA et al. SARS-CoV-2 vaccination in the first year after hematopoietic cell transplant or CAR T-cell therapy: a prospective, multicenter, observational study, *Clinical Infectious Diseases*, 2024

Vaccines in CAR T-cell Recipients (2)

- Timing is based on these issues
  - If CAR T-cell is the final therapy then ..
  - ≥ 3 months for endemic or seasonal issues
    - Influenza
    - SAR-CoV-2
      - Recommendations = fully revaccinated post CAR T = primary series (3 doses for mRNA vaccine) + booster
  - ≥ 6 months from CAR T-cell therapy then can consider inactivated vaccines
  - ≥ 12 months from CAR T-cell therapy then can consider live and non-live adjuvant vaccines with expert assessment

Hill, JA, Seo SK. How I prevent infections in patients receiving D19-targeted chimeric antigen receptor T cells for B-cell malignancies. *Blood*. 2020.
Hill, JA et al. SARS-CoV-2 vaccination in the first year after hematopoietic cell transplant or CAR T-cell therapy: a prospective, multicenter, observational study, *Clinical Infectious Diseases*, 2024.

Vaccinations in CAR T-cell Recipients (3)

Moffitt Cancer Center

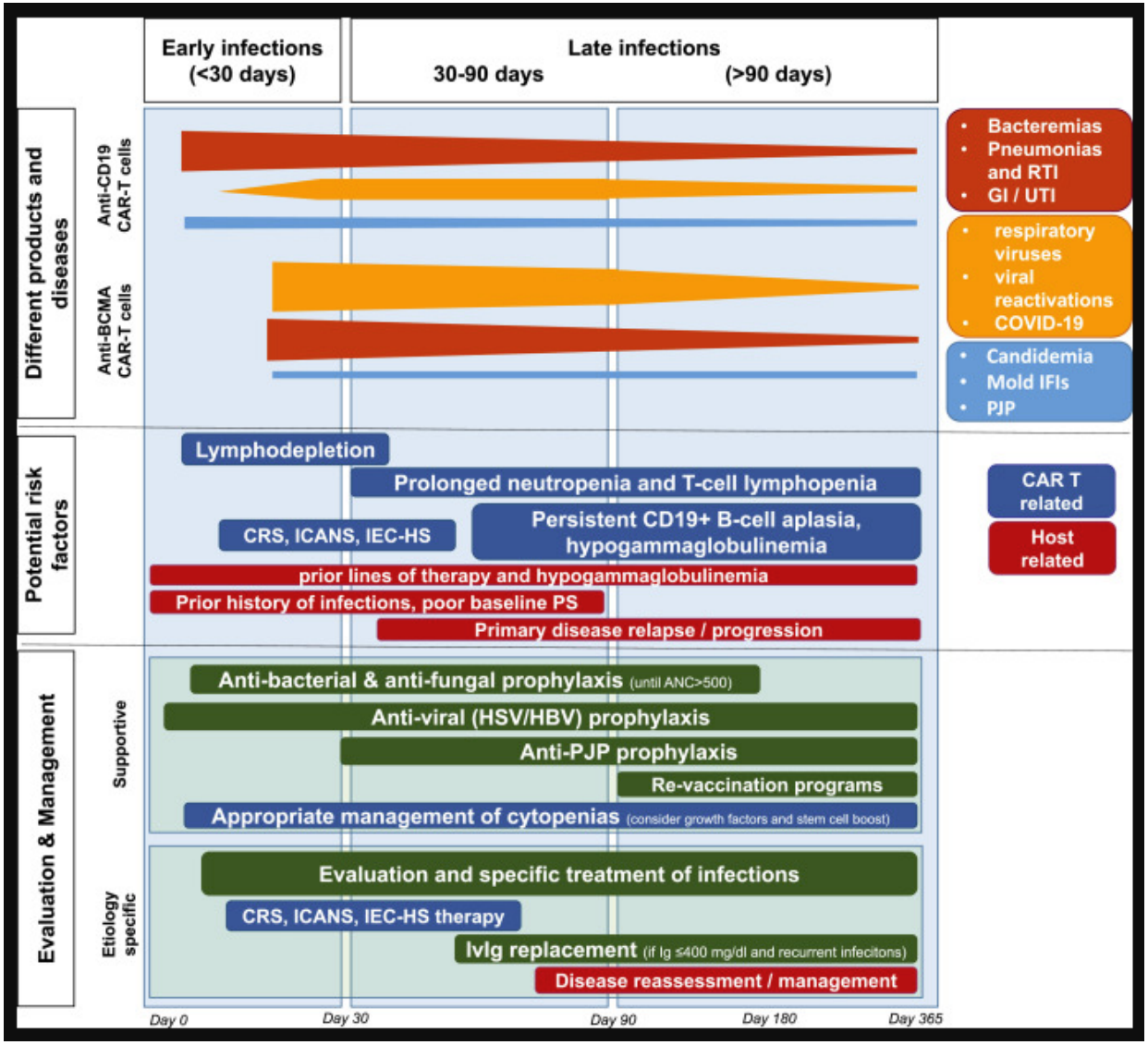
BMT CI PROGRAM GUIDELINE: BMT-G-109 Vaccination Post HCT and Cellular Immunotherapy

Autologous Transplant Recipients / CAR-T Recipients								
Vaccine	**Time after Cellular Therapy (months)**							
	3 months	6 months	7-8 months	12 months	18 months	24 months	25-26 months	78 months[a]
Inactivated vaccines								
Diphtheria, tetanus, pertussis (DTaP/Infanrix)		DTaP #1		DTaP #2	DTaP #3			
Polio, inactivated vaccine (IPV/IPOL)		IPV #1		IPV #2	IPV #3			
Haemophilus influenzae type b conjugate (Hib/ActHIB)		Hib #1		Hib #2	Hib #3			
Pneumococcal conjugate vaccines (PCV20/Prevnar 20)	PCV20 #1	PCV20 #2		PCV20 #3	PCV20 #4			PCV20 #1 if not prior
Hepatitis B (HBV/Engerix B)		HBV #1		HBV #2	HBV #3			
Recombinant herpes zoster (RZV/Shingrix)[b]	RZV #1	RZV #2						
Influenza, seasonal	Administer annually starting 3 months after transplant							
SARS-CoV-19	Restart COVID-19 vaccine series starting 3 months after transplant – refer to CDC guidance[c]							
Special Populations								
Age ≤ 45								
Human papillomavirus (HPV/Gardasil)[d]		HPV #1	HPV #2	HPV #3				
Functional or anatomic asplenia, during outbreaks, sickle cell disease, complement inhibitor (eculizumab or ravulizumab), cGVHD								
Meningococcal A (MCV4/Menveo)[e,f]		MCV4 #1		MCV4 #2				
Meningococcal B (MenB/Bexsero)		MenB #1		MenB #2				
During outbreaks, chronic liver disease, international travelers, HIV+, MSM, dormitory residents								
Hepatitis A (HAV/Havrix)[f]		HAV #1		HAV #2				
Live-attenuated vaccines ONLY IF: immunocompetent and off immunosuppression[g]								
Measles-mumps-rubella (MMR)						MMR #1	MMR #2	

[a] Refer to survivorship guidelines for general vaccine guidance after initial transplant series
[b] Continue acyclovir until 12 months post cellular therapy. Do not interrupt acyclovir for vaccine. If acyclovir stopped early, continue at least 2 weeks after RZV #2.
[c] https://www.cdc.gov/vaccines/covid-19/index.html. Note patients should be given letter explaining need for revaccination to local pharmacy.
[d] HPV - must acquire insurance authorization prior to administration. Enter at prior visit.
[e] If using Menactra for meningococcal vaccination – must separate from PCV by 4 weeks. Formulary option is Menveo.
[f] Reference Florida Department of Health for information regarding local outbreaks
[g] 2 doses recommended only if immunocompetent and at least 8 months after last IVIG and no IVIG for 2 weeks after. MMR is the only live vaccine recommended

Example from Moffitt Cancer Center BMT CI SOP for Vaccines, last accessed on 9/5/2024

In Conclusion via a graphic



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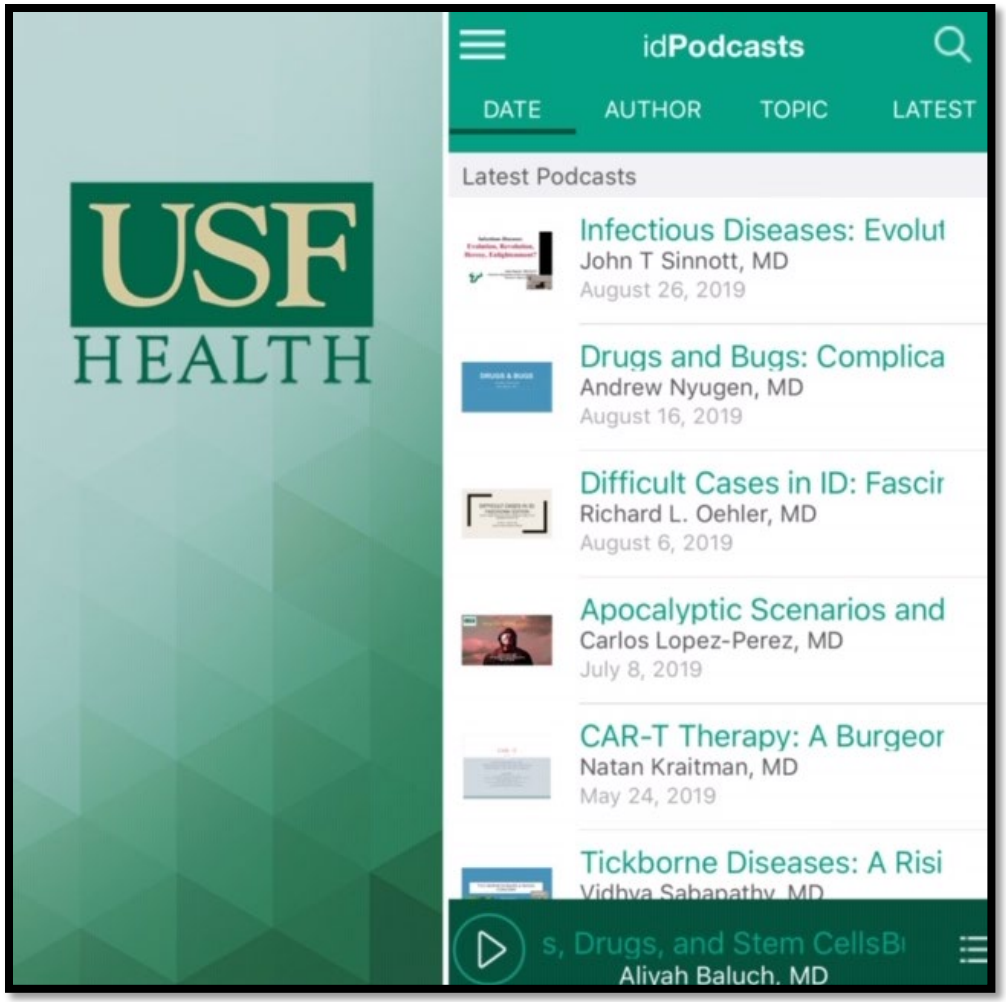
It takes a village to be ‘SMART’!

Circa 3/2024; *SMART = Stewardship at Moffitt for improving Antimicrobial use and Reducing resistance: Team approach

Teaching Resources

AliyahBaluchTID



QUESTIONS

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(**S**tewardship at **M**offitt for Improving **A**ntimicrobial Use and **R**educing Resistance: **T**eam Approach)
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MISSION: To Contribute to the Prevention and Cure of Cancer
VISION: To Transform Cancer Care through Service, Science and Partnership