Co-occurrence patterns of CRS and ICANS in patients undergoing autologous CD19-targeted CAR T-cell treatments

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BACKGROUND AND GOALS

- Immune Effector Cell Associated Neurotoxicity Syndrome (ICANS) remains a key challenge for safe use of Chimeric Antigen Receptor T-cell (CAR-T) therapies[1, 2, 3, 4].
- We study the association of ICANS with CRS in the largest cohort of patients on CD19-targeted CAR-T therapies studied to date.
- We evaluate the associations of the maximum ICANS grade assigned to each patient with maximum CRS grade assigned to each patient and demographic variables, prior treatments, medical history, CAR-T cell dose

DATA

The dataset comes from the MEDS data and consists of **582 patients**: 23.9% B-ALL, 44.8% DLBCL, 14.1% MCL and 17.2% comprising patients with Transformed Follicular Lymphoma, Primary Mediastinal B-cell Lymphoma and High Grade B-cell Lymphoma.Patients treated on autologous CD19 CAR-T therapies (both 41BB as well as CD28 stimulated) were included in the analysis.

Patient level variables related to demographics, concomitant medications, medical history, laboratory, exposure, vitals and adverse events were standardized to the CDISC Analysis data Model (ADaM) version 1.1. Medications were coded using WHODRUG (201919) and adverse events and medical history coded using (Medical Dictionary for Regulatory Activities) MedDRA v 22.1.

Using adverse events occurring within 28d of CAR-T therapy, we assigned to each patients: a maximum ICANS grade (**maxICANS**), using a neurologist-led review of adverse events from MedDRA's nervous system disorders class, and a maximum CRS grade (**maxCRS**), based on the CTCAE v4.03.

METHODS

ICANS and CRS events occurring within 28d of treatment were considered.The results for patients who received prophylactic IL6R blockade and/or corticosteroid prior to CRS/ICANS within 28d of treatment are reported in the preemptive group (vs. nonpreemptive).

- Associations of maxICANS with maxCRS, demographic variables, prior treatments, medical history, CAR-T cell dose were tested (Mann Whitney, Chi squared or Fisher's exact test). Additionally, incidence of maxICANS(3-5), the incidence of maxICANS(3-5) with maxCRS(0-2), the overall and grade-wise incidence of maxCRS, conditional on maxCRS=0 and the Spearman rank correlation coefficient between maxICANS and maxCRS were calculated.
- The timing of ICANS in patients who developed maxCRS(3-5) was compared with patients who developed only maxCRS(0-2) via a time-to-event analysis, using Kaplan-Meier curves.

RESULTS

Associations of maxICANS(3-5) with demographic variables, prior treatments, medical history, CAR-T cell dose and maxCRS

- The incidence of maxCRS(3-5) is significantly lower in the preemptive group (-6.5%, $p < 0.0001$) and the incidence of maxICANS(3-5) is higher in the preemptive group (4.5%, $p = 0.105$), though not significant (Fig1A).
- The incidence of maxICANS(3-5) with maxCRS(0-2) is higher in the preemptive group(6.8%, $p = 0.064$) though not significant (Fig1B).

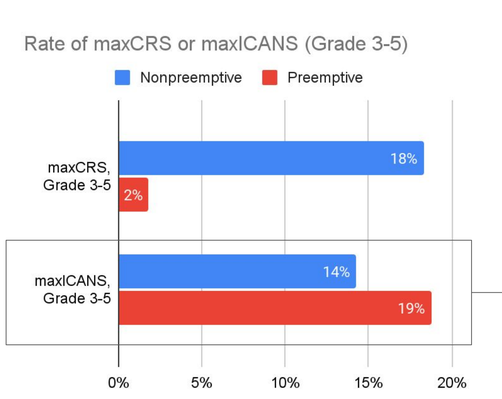

Figure 1A.

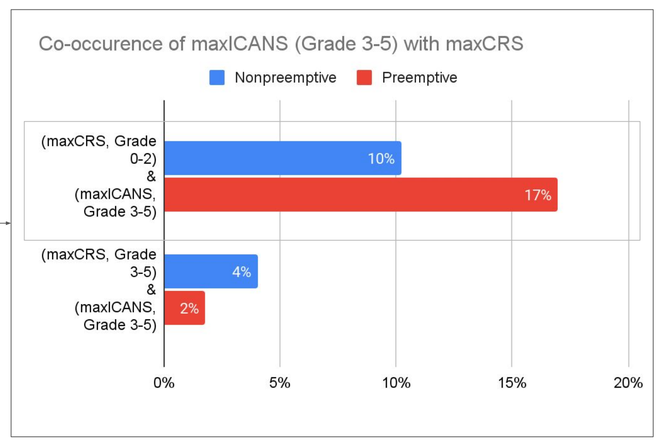

Figure 1B.

- Conditional on maxCRS=0, the overall and grade-wise incidence of maxICANS are not different in the two groups (Cochran Mantel Haenszel test, $p = 0.083$).
- Spearman's correlation between maxICANS and maxCRS in the nonpreemptive group is 0.28 ($p < 0.0001$), and weaker in the preemptive group (Spearman rho = 0.17, $p < 0.0001$) (Fig1C).

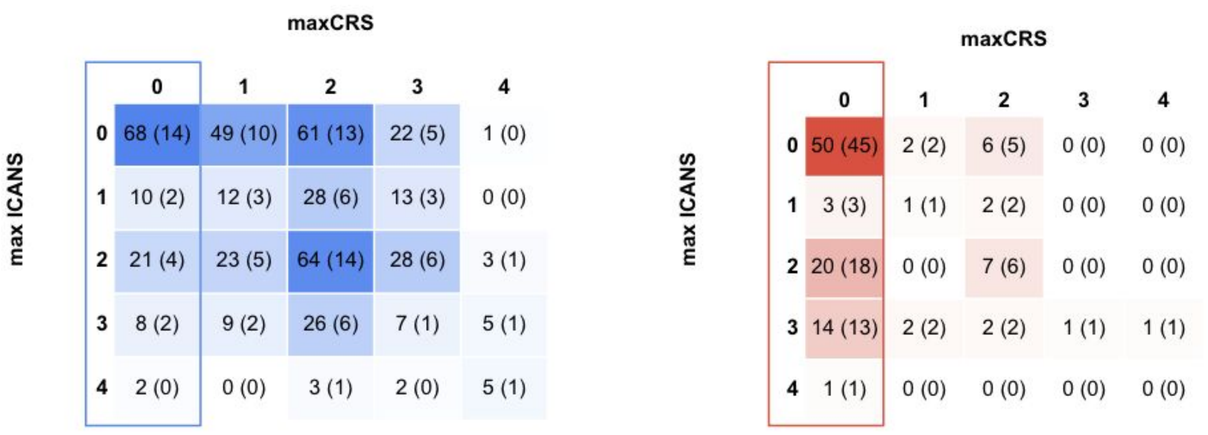

Figure 1C. Count (%) of subjects by maxCRS and maxICANS grade in the nonpreemptive group (left) and in the preemptive group (right)

- The average preconditioning cyclophosphamide dose for patients with maxICANS(3-5) was higher in the nonpreemptive vs. preemptive group[1, 2.]
- Time from diagnosis was associated with maxICANS(3-5) in the preemptive group only. In both groups, the average preconditioning fludarabine dose was higher in patients with maxICANS(0-2), though not clinically significant.

		Nonpreemptive treatment (n = 470)			Preemptive treatment (n = 112)		
Grade		**0-2**	**3-5**	**p**	**0-2**	**3-5**	**p**
	Overall	403 (85.74)	67 (14.26)		91 (81.25)	21 (18.75)	
Age, n (%)	**18-30**	24 (5.96)	13 (19.4)		13 (14.29)	6 (28.57)	
	30-60	183 (45.41)	30 (44.78)		39 (42.86)	9 (42.86)	
	> 60	196 (48.64)	24 (35.82)	**0.0005**	39 (42.86)	6 (28.57)	0.2323
Weight (kg)	**mean**	80.21	85.55		81.99	74.63	
	median	78.65	82		77.2	72.1	
	min	38.4	44.5		49	47.8	
	max	166.3	138.7	**0.015**	200.9	151	0.0941
Body Mass Index (BMI) (kg/m^2)	**mean**	27.51	29.36		28.2	26.81	
	median	26.59	27.68		25.34	25.08	
	min	14.25	16.51		17.55	17.87	
	max	54.76	53.25	**0.0189**	57.98	60.01	0.1332
Months from diagnosis	**mean**	30.68	33.03		29.83	12.45	
	median	16.15	25.2		16.65	12.5	
	min	2.8	2.6		3.1	5	
	max	311.7	126.6	0.3868	170.3	22	**0.026**
Fludarabine dose in in the conditioning chemotherapy (mg/m^2)	**count**	372	50		87	20	
	median	90	90	**< 0.0001**	90	75	**< 0.0001**
Cyclophosphamide dose in the conditioning chemotherapy (mg/m^2)	**count**	392	60		88	20	
	median	1,500.00	1,500.00	**< 0.0001**	1,200.00	900	**< 0.0001**
CRS grade, n (%)	**0**	99 (24.6)	10 (14.9)		73 (80.2)	15 (71.4)	
	1-2	237 (58.8)	38 (56.7)		18 (19.8)	4 (19.0)	
	3-5	67 (16.6)	19 (28.4)	**< 0.0001**	0 (0.0)	2 (9.5)	**0.0578**

Table 1: Associations of maxICANS(3-5) with demographic variables, prior treatments, medical history, CAR-T cell dose and maxCRS, including only the significant variables.

Time to event analysis

- In the nonpreemptive group, median time-to-ICANS (any grade) for maxCRS(0-2) and maxCRS(3-5) was 6d days and 5d days, respectively (Fig1D). In the preemptive group, the median time-to-ICANS for maxCRS(0-2) was 7d.

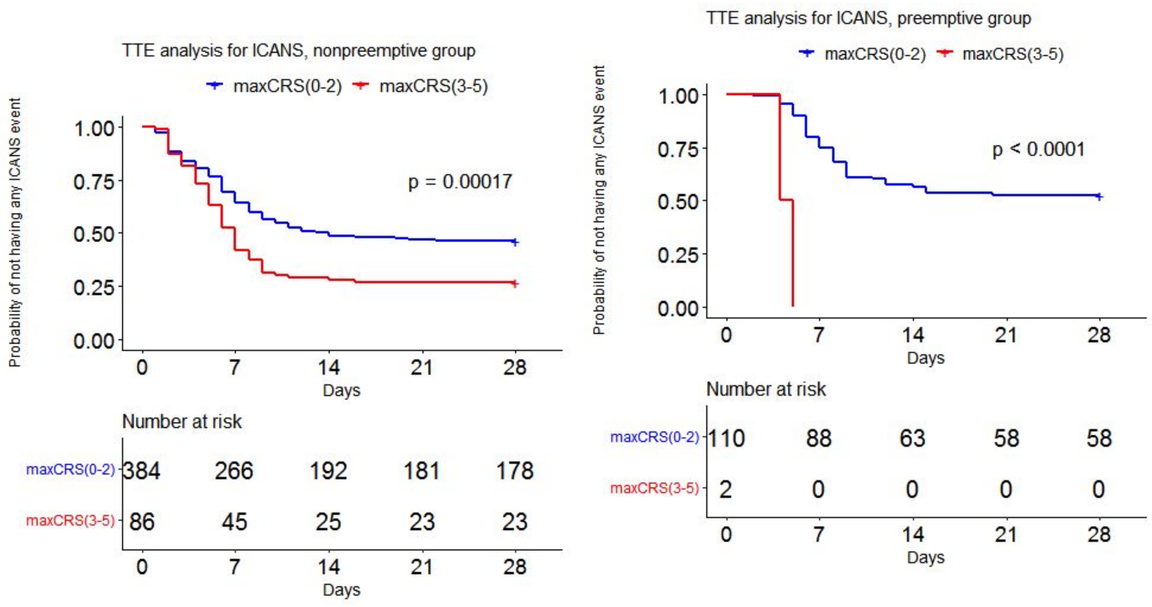

Figure 1D. Probability of remaining ICANS-free post CAR-T cell therapy in the nonpreemptive group (left) and in the preemptive group (right)

CONCLUSIONS

- **Preemptive treatment with IL6R blockade or corticosteroids** decreased the overall incidence of CRS but not ICANS[2].
- Since ICANS occurrence and severity appears to be driven by CRS occurrence, **a reduction in CRS incidence in the preemptive group decouples its association with ICANS. Higher grade CRS also portends earlier ICANS**.
- The evidence of conditional independence with preemptive treatment suggests that **IL6R blockade or corticosteroid given prior to onset does not directly target pathways underlying ICANS.**

References

1. Santomasso BD, Park JH, Salloum D, et al. Clinical and Biological Correlates of Neurotoxicity Associated with CAR T-cell Therapy in Patients with B-cell Acute Lymphoblastic Leukemia. Cancer Discov. 2018;8(8):958-971. doi:10.1158/2159-8290.CD-17-1319
2. Sheth VS, Gauthier J. Taming the beast: CRS and ICANS after CAR T-cell therapy for ALL. Bone Marrow Transplant. 2021;56(3):552-566. doi:10.1038/s41409-020-01134-4
3. Schuster SJ, Bishop MR, Tam CS, et al. Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma. N Engl J Med. 2019;380(1):45-56. doi:10.1056/NEJMoa1804980
4. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. N Engl J Med. 2017;377(26):2531-2544. doi:10.1056/NEJMoa1707447

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