Evaluation of early risk of moderate-to-severe Cytokine Release Syndrome (CRS) induced by CAR T-cell therapy using pooled clinical trial data

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BACKGROUND

- Chimeric antigen receptor (CAR) T-cell therapy is a novel targeted immunotherapy to treat several hematological tumors that is commonly associated with cytokine release syndrome (CRS), a life-threatening event involving immune hyperactivation and cytokine driven organ dysfunction.[1,2]
- Early risk monitoring is imperative as CRS typically occurs within 7 days of CAR T-cell infusion, where initial fever and flu-like symptoms can quickly evolve into life-threatening multi-organ dysfunction.[3]
- There is a need for a greater understanding of risk factors associated with CRS, especially for moderate-to-severe CRS where a therapeutic intervention to suppress the immune response and support organ systems is warranted.[4]
- Past studies to identify CRS risk factors were conducted on relatively small cohorts with limited real-world evidence repositories available, indicating a need for further exploration on a broader patient population.

OBJECTIVE

- To explore early risk factors associated with moderate-to-severe CRS (CRS grade 2+) within 7 days of CAR T-cell therapy using a large patient population captured in the pooled clinical trial data.

METHODS

Data source

- The pooled CT data was sourced from Medidata Enterprise Data Store, comprising more than 25,000 historical clinical trials with 6.3 million patients from approximately 1,400 customers in around 100 countries over 20 years.
- The study database comprised 6,013 patients in the CAR T-cell or other T-cell receptor (TCR) therapy trials. Of these, 2,366 patients (spanning over 20 trials) were exposed to the CAR T-cell or other TCR therapy.
- This database includes phase I-III trials on several indications including Leukemias, Lymphomas, and Myeloma and has information on patients with early and advanced stage as well as relapsed refractory cancers. More than one CAR T-cell types and doses were captured in the data with extremely rich data points around the first week of therapy, where CRS risk was the highest.
- Data was converted into an analysis-ready Study Data Tabulation Model (SDTM) format.

Study population

- Patients who met the following criteria were included in the analysis:
  - Patients with Acute Lymphocytic Leukemia (ALL) or Other liquid tumors were required to be in the experimental CAR T-cell therapy (e.g., CAR-19 and CAR-BCMA) arm to be included in the study.
  - Patients were excluded if the first CRS occurrence within 7 days of CAR T-cell infusion was CRS grade 1, according to Common Terminology Criteria for Adverse Events (CTCAE) 4.03.
    - Since CRS grade 1 patients were likely to be preemptively exposed to immunosuppressive agents, affecting their likelihood of progressing to CRS grade 2+, excluding these patients from the analysis may reduce potential confounding by treatment use.
- Follow-Up:
  - Patients were followed from the day of CAR T-cell treatment for 7 days or until the first occurrence of CRS grade 2+, whichever came first.

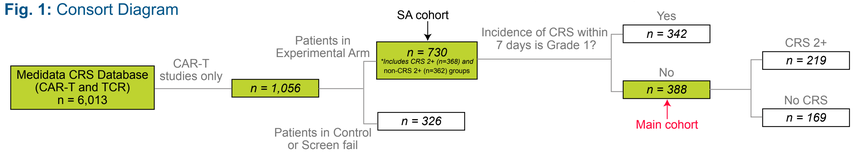
Sensitivity analysis (SA Cohort)

- To provide a more comprehensive exploration of CRS risk within 7 days, we conducted a sensitivity analysis in which patients whose first CRS occurrence within 7 days of CAR T-cell infusion was grade 1 (who got excluded in the main analysis) were retained and analyzed.

Statistical analysis

- Outcome of interest was incidence of CRS grade 2+ within 7 days of CAR T-cell infusion.
- All demographics and baseline clinical characteristics were described for all patients and stratified by CRS status. Appropriate statistical tests were used to compare the characteristics by CRS status. A conventional alpha of 0.05 and a two-tailed level of significance was used. No statistical comparison was made between the main and the SA cohorts.
- Kaplan-Meier method was employed to estimate the risk of CRS grade 2+ occurrence within 7 days following CAR-T cell infusion.
- P-values were estimated using log-rank tests with a demographic or baseline characteristic evaluated as the only covariate.
- All statistical analyses were performed using R version 4.0.3 and Medidata Analytics Workbench platform.

Fig. 1: Consort Diagram



RESULTS

- A total of 388 patients met all the inclusion and exclusion criteria in the main analysis (**Fig. 1**). Average age was 55 (SD=14, median=58) years, 67% males, 81% White, 83% Non-Hispanic or Latino, and 20% with ALL indication (**Tab. 1**).
- Within the ALL subgroup, no difference in high tumor burden was observed between CRS 2+ relative to the non-CRS 2+ group (**Tab. 1**).
- Within the Other liquid tumor subgroup, there were significantly different proportions of patients with Stage I/II and Stage III/IV between the CRS 2+ and the non-CRS 2+ groups (p=0.02, **Tab. 1**) with CRS 2+ patients having more advanced disease.
- There was a significantly higher baseline ferritin levels in the CRS 2+ group than non-CRS 2+ group in the main cohort (p = 0.010).
- Similar trends were observed in the SA cohort (data not shown). For example, there was a trend towards higher baseline ferritin levels in the CRS 2+ group than non-CRS 2+ group (p = 0.140).

Medidata's CRS pooled clinical database enables robust assessment of factors independently associated with the development of CRS 2+ as presented in this study. Future addition of more CAR T-cell trials in this database will allow more granular assessments by specific pre-CRS parameters and factors.

Baseline characteristics

Tab. 1: Main Cohort - Demographics and Baseline Characteristics

	Total (N=388)	CRS 2+ (N=219)	No CRS (N=169)	*p*
Age				
Mean (SD)	55.0 (14.4)	54.7 (14.6)	55.3 (14.1)	0.684
Median	58	58	58	
Gender, N (%)				
Male	259 (66.8)	151 (68.9)	108 (63.9)	0.349
Race, N (%)				
White	313 (80.7)	172 (78.5)	141 (83.4)	
Black or African American	12 (3.1)	8 (3.7)	4 (2.4)	
Asian	17 (4.4)	10 (4.6)	7 (4.1)	0.699
Other	35 (9.0)	21 (9.6)	14 (8.3)	
Unknown	11 (2.8)	8 (3.7)	3 (1.8)	
Ethnicity, N (%)				
Non-Hispanic or Latino	323 (83.2)	178 (81.3)	145 (85.8)	
Hispanic or Latino	53 (13.7)	35 (16.0)	18 (10.7)	0.298
Unknown	12 (3.1)	6 (2.7)	6 (3.6)	
Acute Lymphoblastic Leukemia (ALL) indication, N (%)	79 (20.4)	44 (20.1)	35 (20.7)	0.982
Baseline ECOG 1+, N (%)	220 (56.7)	122 (55.7)	98 (58.0)	0.229
Prior stem cell transplant, N (%)	122 (31.4)	63 (28.8)	59 (34.9)	0.237
Severe baseline thrombocytopenia[1], N (%)	89 (22.9)	49 (22.4)	40 (23.7)	0.858
High baseline ferritin[2], N (%)	87 (22.4)	48 (21.9)	39 (23.1)	0.010
High tumor burden[3], N (%)	37 (9.5)	23 (10.5)	14 (8.3)	0.714
Cancer stage (Other liquid tumor indication only), N (%)				
Stage I/II	63 (16.2)	26 (11.9)	37 (21.9)	
Stage III/IV	235 (60.6)	143 (65.3)	92 (54.4)	0.020
ALL indication/Unknown stage information	90 (23.2)	50 (22.8)	40 (23.7)	

[1]Defined as baseline platelet count <50,000/µL
[2]Defined as baseline ferritin value >1500 ug/L
[3]Defined as ≥60% marrow involvement

Outcome

- The Kaplan-Meier curve (**Fig. 2**) showed median time to CRS 2+ occurrence in the main cohort was 5 days. The median time was 7 days in the SA cohort (combined CRS 1 and 2+).
- Similar 7-day risk of CRS 2+ between ALL and Other liquid tumor indications was observed in both cohorts (**Fig. 3**). The Other liquid tumor group in the main cohort had a nominally higher proportion of patients experiencing CRS 2+ at days 2, 3, 4, and 5 than the ALL group though the percentage of CRS-free subjects on Day 5 (48.5% vs. 62.0%, p=0.49) was not significant (**Fig. 3**).
- Within the Other liquid tumor subgroup in the main cohort, patients with a higher cancer stage (III/IV) had a higher risk of developing CRS 2+ relative to patients with stage I/II (p=0.03, **Fig. 4**). A similar result was observed in the SA cohort (p=0.0094, 75% CRS-free subjects: 3 vs. 4 days, **Fig. 4**).
- Within the ALL subgroup in the main cohort, high tumor burden had a nominally higher proportion of patients experiencing CRS 2+ at days 2, 3, 4, and 5 than patients with a lower tumor burden but the percentage of CRS-free subjects on Day 5 (51.4% vs. 79.4%, p=0.32) was not significant (**Fig. 5**). A similar trend was observed at days 2, 3, 4, and 5 in the SA cohort, and there was no difference in median time between the two strata (**Fig. 5**).
- No statistically significant difference in 7-day risk of CRS 2+ was observed by age, gender, baseline ECOG score, baseline ferritin levels, severe thrombocytopenia, or prior stem cell transplant in either cohort (data not shown).

RESULTS

Fig. 2: Time to CRS 2+ from CAR T-cell Treatment

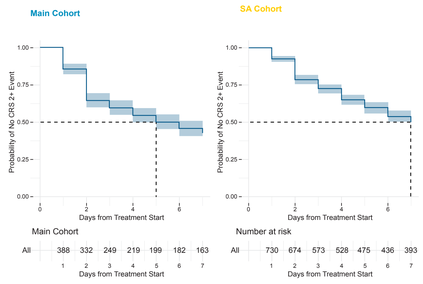


Fig. 3: Time to CRS 2+ from CAR T-cell Treatment, stratified by indication

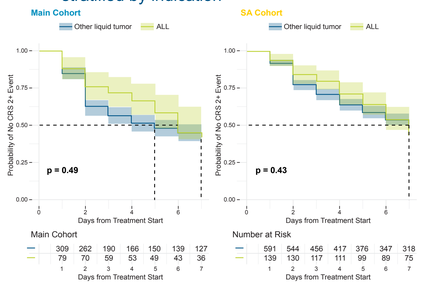


Fig. 4: Time to CRS 2+ from CAR T-cell Treatment, stratified by cancer stage (Other liquid tumor indication only)

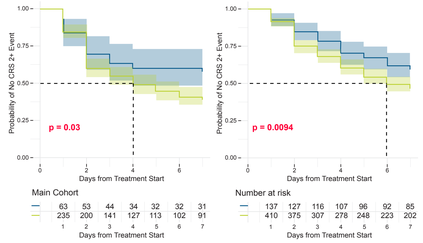
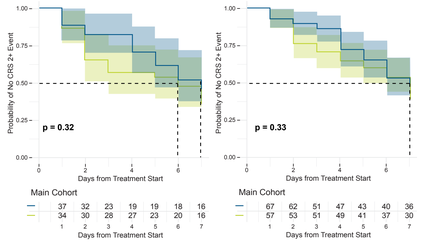


Fig. 5: Time to CRS 2+ from CAR T-cell Treatment, stratified by tumor burden (ALL indication only)



DISCUSSION & CONCLUSION

- This study demonstrates how pooled CT data enables robust assessment of factors independently associated with the development of CRS 2+ within 7 days of CAR T-cell therapy that is not preceded by CRS grade 1.
- Our study found that slightly over half of the patients had CRS Grade 2+ within 7 days in the main analysis, which was lower than the finding in Yan et al. (2021)[3].The difference in the observations could be due to exclusion of CRS grade 1 incident patients, the time period within which CRS was observed, differences in the definition of CRS grades, and potential use of prophylactic immunosuppressive agents in some trials included in this study.
- While other liquid tumor patients appeared to have an increased proportion of CRS 2+ earlier in the disease course compared to ALL (**Fig. 3**), similar trends were observed across both sub-groups where patients with high tumor burden (ALL) and advanced stage (liquid) tended to have CRS 2+ earlier than patients with lower tumor burden or less advanced stage (**Fig. 4-5**).
- These results may suggest that early and close monitoring for advanced cancer patients receiving CAR T-cell therapy is warranted.
- Future studies will need to assess how pre-CRS parameters can be used to predict responsiveness to various treatments such as anti-IL-6 therapies as well as early indicators that someone is likely to develop CRS or be non-responsive to CRS treatment after CAR-T cell therapy is infused.

Limitations

- Due to privacy concerns, we combined lymphomas and multiple myeloma indications into the Other liquid tumor group. Future addition of more CAR T-cell trials in the database will allow more granular assessment by specific indications.
- We did not separate out the various types of CAR-T cell therapies (e.g., CAR19, CAR-BCMA).
- Assessment of tumor burden was limited to the ALL indication and cancer stage limited to Other liquid tumor group because of data limitation.
- For a small percentage of CRS events (<7%) where the CTCAE scale was not available, the Lee scale was used to ascertain CRS grading.

References

1. NCCN Guidelines for Patients® Immunotherapy Side Effects: CAR T-Cell Therapy https://www.nccn.org/patients/guidelines/content/PDF/immunotherapy-se-car-tcell-patient.pdf
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