SIGNIFICANT CYTOKINE RELEASE SYNDROME RISK MODEL WITH T-CELL ENGAGING THERAPIES

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BACKGROUND

- T-cell engaging (TCE) immuno-oncology therapies such as bispecific T-cell engager [BiTE], dual-affinity re-targeting proteins [DART], and chimeric antigen receptor T cells [CAR-T], show antitumor efficacy in solid tumors and hematologic malignancies such as acute lymphoblastic leukemia (ALL) and non-Hodgkin lymphoma (NHL).[1,2]
- Antitumor immunity response of TCE therapies can lead to the adverse event of cytokine release syndrome (CRS).[3,4]
- Data describing risk factors associated with CRS in patients treated with non-CAR-T TCE therapies are limited.

OBJECTIVES

- To develop a model to predict the pre-infusion risk of significant CRS (sCRS) for patients treated with non-CAR-T TCE therapies.

METHODS

Data source and patients

- TCE dataset sourced from the Medidata Enterprise Data Store, an anonymized data repository from completed clinical trials evaluating non-CAR-T TCE therapies.

Outcome of interest

- First sCRS (grade ≥2 by CTCAE v4.0 scale) occurring within 10 days of TCE therapy.

Selection of features

- Potential predictive features for assessing sCRS risk factors (identified from the research literature and preliminary data analysis) measured before or at the time of the first TCE infusion.
- Patients included if they had a fill rate of >70% for the key features.
- Features pruned by assessing multicollinearity across features.
- To compare different TCE therapies, first treatment doses normalized by dividing patients' first dose by the mean of the first dose of the TCE administered in each study.
- Tumor burden not selected for the final model.

Model selection

- Logistic regression and tree-based models were trained.
- Average area under the receiver-operator characteristic (AUROC) curve calculated for each model type; random forest model selected.
  - Best model to predict sCRS had a mean AUROC of 0.69 (95% confidence interval, 0.66–0.72) on the test set.
- Normalization for variables applied immediately after the train-test split; categorical variables handled with one hot encoding.
- Missing data was imputed by using the mean value for numerical variables and the median value for categorical variables

Statistical methods

- Correlation/collinearity between variables evaluated via Pearson correlation; *P* values <0.05 considered statistically significant.

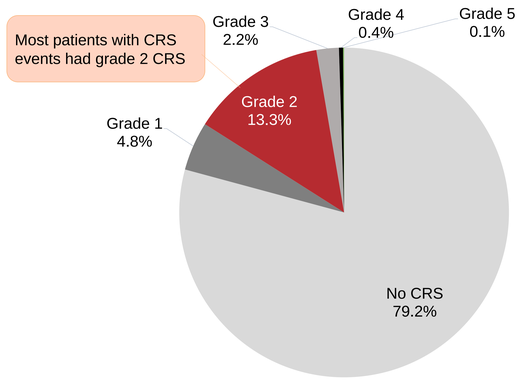
RESULTS

Table 1. Baseline characteristics based on sCRS outcome (N=715 from 13 trials)

	CRS <2 (n=600)	CRS ≥2 (n=115)	*P* value
Age (years)[a]	34.00 (16.75–55.00)	36.00 (23.00–54.50)	0.229
Sex, male, n (%)	328 (54.7)	62 (53.9)	0.963
Race, n (%)			
American Indian or Alaska Native	5 (0.8)	0 (0)	**<0.001**
Asian	127 (21.2)	67 (58.3)	
Black or African American	15 (2.5)	1 (0.9)	
White	433 (72.2)	46 (40.0)	
Other/Unknown/Missing	20 (3.3)	1 (0.9)	
Geographic Region, n (%)			
Asia	99 (16.5)	65 (56.5)	**<0.001**
Europe, Middle East, Africa	11 (1.8)	0 (0)	
North America	61 (10.2)	9 (7.8)	
Unknown/Missing	429 (71.5)	41 (35.7)	
Baseline ECOG Score, n (%)			
0	160 (26.7)	40 (34.8)	0.906
1	211 (35.2)	49 (42.6)	
2	51 (8.5)	13 (11.3)	
Unknown/Missing	178 (29.7)	13 (11.3)	
Indication, n (%)			
ALL	478 (79.7)	104 (90.4)	**0.00966**
Solid Tumors and NHL	122 (20.3)	11 (9.6)	
Infections, n (%)	166 (27.7)	44 (38.3)	**0.0298**
Time since diagnosis (years)[a]	1.50 (0.75–2.75)	1.29 (0.50–2.62)	0.139
First dose[a]	1.00 (0.89–1.00)	1.00 (1.00–1.00)	**<0.001**
Bilirubin (mg/dL)[a]	0.47 (0.30–0.60)	0.49 (0.40–0.69)	**0.045**
White blood cell count (10^9/L)[a]	4.52 (2.33–7.60)	5.21 (2.02–10.54)	0.351
Hemoglobin (g/dL)[a]	10.10 (9.00–11.90)	10.40 (8.75–11.85)	0.929
Alkaline phosphatase (U/L)[a]	126 (77–228)	92 (63–172)	**0.006**
Lactate dehydrogenase (U/L)[a]	399 (235–799)	318 (188–890)	0.16
Alanine aminotransferase (U/L)[a]	33 (19–62)	28 (18–46)	0.17
Serum creatinine (mg/dL)[a]	0.64 (0.42–0.87)	0.69 (0.48–0.84)	0.239

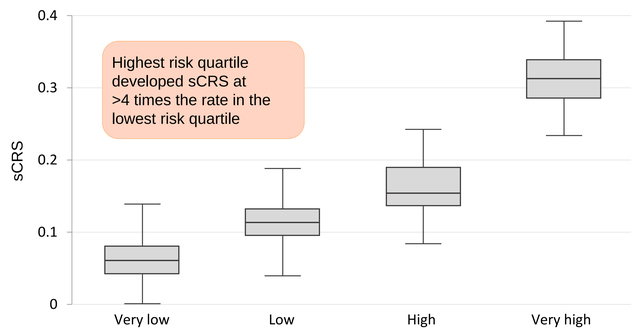
[a]Data are presented as median (IQR).
ALL, acute lymphoblastic leukemia; CRS, cytokine release syndrome; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; NHL, non-Hodgkin lymphoma; sCRS, significant CRS.

Figure 1. Highest grade of CRS event within 10 days of the start of TCE therapy



The number of unique individuals who had a CRS event at a given grade. No CRS, n=566; grade 1, n=34; grade 2, n=95; grade 3, n=16; grade 4, n=3; grade 5, n=1. CRS event is defined as the highest CRS that happened within 10 days of the start of TCE treatment.
CRS, cytokine release syndrome; TCE, T-cell engaging.

Figure 2. Proportion of sCRS for each risk quartile (test set over 100 iterations)



sCRS, significant cytokine release syndrome.

Table 2. Predictive model features between very low and very high CRS risk quartiles (defined by predictive risk score)

Feature/Test	Very low CRS risk quartile	Very high CRS risk quartile	*P* value
First dose (normalized by study)[a,b]	0.61 (0.50–0.87)	1.00 (1.00–1.00)	**<0.001**
Bilirubin,[b] mg/dL	0.35 (0.24–0.50)	0.51 (0.42–0.71)	**<0.001**
White blood cells, 10^9/L	4.20 (2.42–6.39)	3.40 (1.84–6.88)	0.182
Hemoglobin, g/dL	10.50 (9.59–12.0)	10.20 (8.70–11.6)	0.074
Serum creatinine,[b] mg/dL	0.38 (0.27–0.73)	0.66 (0.52–0.81)	**<0.001**
Lactate dehydrogenase,[b] U/L	446 (290–666)	197 (155–425)	**<0.001**
Alanine aminotransferase,[b] U/L	39 (24–73)	25 (14–45)	**<0.001**
Time since diagnosis,[b] years	2.00 (1.42–2.92)	0.92 (0.42–2.25)	**<0.001**
Baseline ECOG score			0.150
0	25%	46%	
1	80%	41%	
2	4%	13%	
Infections	12%	49%	**<0.001**
Disease type: ALL	67%	99%	**<0.001**

Categorical data presented as %. Numerical data presented as median (IQR). Chi-square test for categorical variables. Kruskal-Wallis for continuous variables. Wilcoxon-Mann-Whitney test for ordinal variables.
[a]The first dose was used for these calculations, as most CRS events have been described to occur after the first dose of TCE therapy.[5] [b]Important risk factors associated with sCRS.
ALL, acute lymphoblastic leukemia; CRS, cytokine release syndrome; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range.

LIMITATIONS

- Most patients had ALL, limiting generalizability of the present findings to patients with other tumor types.
- CRS grade ≥2 used as the cutoff for sCRS as CRS grade ≥3 is uncommon with TCE therapies[6,7] and current TCE dataset had very few patients with high-grade CRS.

CONCLUSIONS

- Patients with the highest risk quartile developed sCRS at >4 times the rate in the lowest risk quartile.
- CRS risk stratification may facilitate patient selection for TCE therapy and tailored pre-treatment and monitoring of CRS, with potential to maximize treatment efficacy, patient safety, and resource allocation.
- Validation of the model is necessary prior to implementation in clinical practice.
- Tumor burden can be a critical determinant of sCRS risk in other clinical settings[6,8,9]; therefore, future research should evaluate the impact of tumor burden on sCRS across different indications.

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