Predictors of severe CRS in longitudinal CAR T-cell clinical trial data

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BACKGROUND

- Cytokine release syndrome (CRS) is a life-threatening toxicity of chimeric antigen receptor (CAR) T-cell therapy that limits the widespread use of this life-saving therapy.
- Even though only a portion of patients undergoing CAR T-cell therapy experience CRS, since 2016, no fewer than 15 trials have been put on hold or abandoned due to safety concerns arising out of CRS.
- There is a limited understanding of the risk factors associated with CRS[1]
- Known markers of severe CRS lack specificity or require central lab facilities, making them unsuitable for safety surveillance during trials or for real-time clinical decision-making[2].
- Earlier work by the authors[2] suggests that patterns in longitudinal measurements of common laboratory markers distinguish patients who develop CRS grade 3-5 (sCRS) after CAR-T infusion from those who do not develop CRS[3] grade 3-5.

GOALS

- Using pre-infusion clinical data from the largest pooled repository of anti-CD19 CAR-T treatments from the Medidata Enterprise Data Store (MEDS), derive features that capture **longitudinal patterns in common laboratory markers and vitals before and after the start of lymphodepleting chemotherapy (LDC)**
- Describe these novel features, derived from penalized logistic regression models and their importance in predicting CRS grade 3-5 following CAR-T therapy.

DATA

Summary

The MEDS data comprises 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 2,366 patients (from over 20 trials) that were exposed to the CAR T-cell or other TCR therapy. Patients treated on autologous CD19 CAR-T therapies (both 41BB as well as CD28 stimulated) with no more than 15% missing observations in any predictor variable were included in the analysis.

The dataset consisted of 361 patients: 19.1% B-ALL, 39.9% DLBCL, 21.6% MCL and 19.4% comprising patients with Transformed Follicular Lymphoma, Primary Mediastinal B-cell Lymphoma and High Grade B-cell Lymphoma.

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.

Patients had a mean age 55.8 (SD=14.1) years, 69.5% males. 25.2% had CRS 3+ with a median time-to-event of 4 days. At enrollment, all patients had an ECOG score ≤ 1 with 47.7% patients having an ECOG = 0. During their last therapy prior to CAR-T cell therapy, 51.5% patients had progressive disease and 23.3% patients had a response followed by relapse.

Table 1. Baseline attributes

Age (years)	Overall N = 542	B-ALL N = 131	NHL N = 411
Range	19-85	20-84	19-85
Median	58	46	60
Sex (%)			
Female	30.5	42.0	27.7
Race (%)			
White	83.40	73.90	85.60
Black	3.60	1.45	4.11
Asian	3.60	8.70	2.40
Other	8.86	14.50	7.53
Unknown	0.55	1.45	0.34
Eastern Cooperative Oncology Group (%)			
0	47.60	27.50	52.40
1	52.40	72.50	47.60
Prior stem cell transplant (%)			
	33.2	36.20	32.50
Prior radiotherapy (%)			
	24.90	24.60	25.00
Time from diagnosis to CAR-T therapy in months (median)			
	16.8	15.9	17.1

References

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RESULTS

Predictors of sCRS

Laboratory markers

- Pre-LDC, the levels of leukocyte count, hemoglobin, aspartate aminotransferase and the change in alanine aminotransfersase, albumin, and platelets were the strongest predictors of developing grade 3+ CRS.
- Post-LDC but pre-CAR-T therapy, the levels of alanine aminotransferase, alkaline phosphatase, hemoglobin, platelets and albumin and the change in platelets, albumin, and creatinine were the strongest predictors.
- High levels of Chloride, both pre and post LDC correlate with lower risk of grade 3+ CRS.

Vitals

- Heart rate, temperature and systolic blood pressure, as well as the rate of change in weight post LDC are the strongest predictors of grade 3+ CRS.

Others

- Partial response or disease progression in prior therapy is correlated with grade 3+ CRS

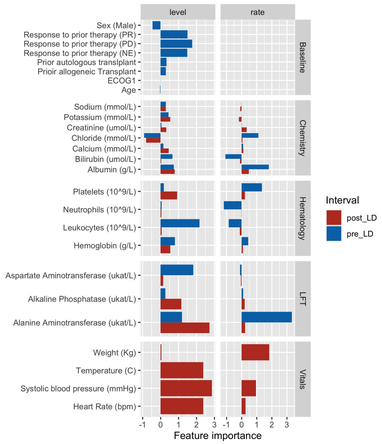

Figure 1. Importance scores for pre and post LDC features

Model performance

Discrimination

- The model with baseline features alone (sex, prior therapy response, prior stem cell transplant, ECOG and age at enrollment) performed worst on the test partition for both the L2 regularized and the elastic net models..
- Adding predictors based on laboratory markers and vital signs, results in about 7-12% improvement in the AUROC over the baseline models (Table 2).

Table 2. Performance in CRS 3+ discrimination from pre-infusion data

Model	Features	5 fold CV Mean AUROC (SD)	Test AUROC
L2LR	Baseline	0.60 (0.03)	0.58
L2LR	Baseline + Laboratory markers	0.66 (0.03)	0.61
L2LR	Baseline + Laboratory markers + vitals	0.68 (0.02)	0.65
Elastic Net	Baseline	0.59 (0.04)	0.57
Elastic Net	Baseline + Laboratory markers	0.69 (0.04)	0.64
Elastic Net	Baseline + Laboratory markers + vitals	0.68 (0.03)	0.69

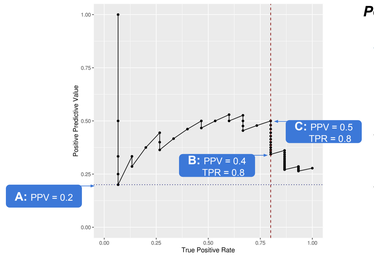

Figure 2. PPV vs TPR for Elastic Net (Baseline + Labs + Vitals)

Post-test probability

- The positive predictive value (PPV) for a naive prediction model (random guessing) is 0.2, equal to the pre-test probability of CRS grade 3+
  (A on Figure 2)
- A prediction model based on tumor burden alone may provide a PPV = 0.4 with a true positive rate (TPR) = 0.8 (B on Figure 2)
- In comparison, the Elastic Net prediction algorithm based on pre-infusion clinical data (baseline + laboratory markers + vitals) provides a PPV = 0.5 with a TPR = 0.8 (C on Figure 2)

METHODS

Feature construction

For each laboratory marker and vital sign, features describing the longitudinal variation were constructed.

- A piecewise linear spline was fit to the values of laboratory or vitals measurement over time with a knot placed at the starting day of LDC
- A 4-tuple consisting of the Intercept and slope for the pre and post LDC segment of the spline was computed as illustrated (Figure 3).
- All values were normalized to have zero mean and unit variance, conditional on the visit day.

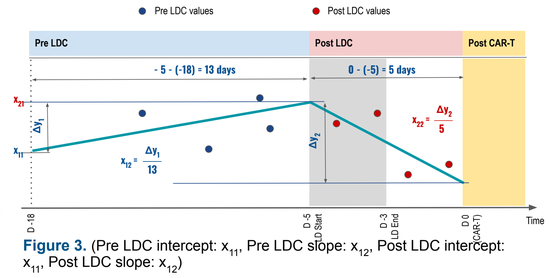

Figure 3. (Pre LDC intercept: x_{11}, Pre LDC slope: x_{12}, Post LDC intercept: x_{11}, Post LDC slope: x_{12})

Response variable

A MedDRA preferred term mention of “Cytokine release syndrome” occurring after CAR-T therapy was used to label a CRS episode in a patient. A maximum CRS grade (maxCRS) was assigned to each patient based on the CTCAE 4.0 grades for each CRS episode within 28 days of CAR-T therapy recorded in the source data. An indicator response variable sCRS was defined as 1 if the value of a maxCRS for a patient was 3 or higher and 0 otherwise.

Model training and tuning

- The model matrix comprising the features and the response variable was split into training (80%) and test (20%) partitions by stratifying on grade 3+ CRS per each study.
- L2 Penalized logistic regression and Elastic net models were fit on the training partition by successively adding laboratory and vitals features to baseline model with only sex, prior therapy response, prior stem cell transplant, ECOG and age at enrollment.
- The penalty hyperparameters of the L2 and Elastic net models were tuned by cross validating over a search grid.

DISCUSSION

- **Risk adapted preemptive strategies for managing severe CRS.** Early treatment with Tocilizumab has been shown to reduce rates of grade 3-5 CRS[4,5]. To balance these gains against the risk of higher neurotoxicity[6], a risk stratification approach based only on tumor burden assessment has been taken shown to be effective[7]. Multivariate algorithms based on pre-infusion laboratory, vitals, treatment history and other clinical assessments can predict grade 3-5 CRS with higher precision without compromising recall, thereby enabling improved patient safety.
- **Temporal patterns in pre-treatment clinical data.** The foregoing results are consistent with our earlier work on modeling commonly measured laboratory markers and vitals data in CAR-T studies[2] – showing that temporal patterns in these variables encode information about future grade 3-5 CRS events.

Limitations

- The results presented herein follow from an observational analysis of historical clinical trials data. The associations between pre & post LDC patterns in the predictors and grade 3-5 CRS require further study to evaluate potential sources of confounding and to understand underlying pathways.
- The linear pattern mining methods described above enable a first order summarization of temporal patterns, without overfitting the data. A larger dataset on CAR-T treatments and outcomes will allow improved longitudinal modeling of the time varying covariates, as well a more robust validation of model performance.

CONCLUSIONS & FUTURE DIRECTIONS

- Absolute levels as well as the rate of change in commonly measured laboratory markers and vitals may indicate immune pathway activity that correlates with a future grade 3-5 CRS event.
  - ***Impact.*** Modeling the pre and post LDC kinetics can enable safer risk adapted management strategies for patients undergoing CAR-T therapy
- The association between pre-infusion temporal patterns in clinical variables and grade 3+ CRS implies that dynamic tracking of patient status will be key to effective mitigation of grade 3-5 CRS.
  - ***Impact.*** Temporal patterns that are associated with grade 3-5 CRS can inform the design of trial protocols and schedule of assessments to enable dynamic risk assessment across CAR-T trials, making them safer for patients.