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Evaluation of PET/clinical parameters to predict toxicity in chimeric antigen receptor T-cell therapy patients with relapsed/refractory non-Hodgkin lymphoma

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INTRODUCTION

T-cell clinical trial with chimeric antigen receptor (CAR) T-cell therapy is an emerging method of treating cancer using the immune system rather than chemotherapy. The early results of this therapy in relapsed/refractory non-Hodgkin lymphoma suggest potential cures in otherwise incurable patients. However, CAR T-cell therapy is associated with significant side effects, namely cytokine release syndrome (CRS) and neurotoxicity. We report the results of predictive models developed to determine the association between 18F-FDG-PET/CT quantitative parameters that predict for CAR T-cell toxicities using the two available commercial CAR T-cell products.

AIM

To determine the correlation between baseline tumor-burden and adverse effects after CAR-T therapy using.:

PET/CT parameters such as volume of metabolically active tumor and total lesion glycolysis

clinical factors, including CART product-type and age.

METHOD

Thirty-one patients who received CAR T-cell therapy in our institution between 2018 and 2019 were enrolled in this study. CRS and neurotoxicity were graded according to our institutional framework, and the Deauville five-point scale was used to determine post-CART PET response. The prognostic PET/CT parameters were metabolic tumor volume (MTV) and total lesion glycolysis (TLG). MTV was defined as the sum of metabolic volumes with an uptake ≥ 1.5 × SUV_{mean} + 2 standard deviations of the liver uptake. TLG was computed as the SUV_{mean} of all active tumor voxels multiplied by the total MTV. Clinical parameters include CAR T-cell product-type and age. A machine learning (RUSEnsemble) model was developed on MATLAB framework to test the parameters as predictors for CRS and neurotoxicity. In our modelling, an ensemble of classifiers was trained on this model using a randomly under-sampled subset of the data. The weights of properly classified samples were increased in each iteration, and the weights of misclassified samples were reduced, enabling the misclassified samples to be correctly classified in subsequent iterations. The final classification was a weighted combination of all classifier results within the ensemble. The model was validated by ten-fold cross-validation to ensure stability of the results. The prognostic abilities of the parameters were analyzed using ROC curves and several classification metrics.

RESULTS

We used several measures to evaluate the effectiveness of our predictive model using sensitivity, specificity and ROC curves as shown in Table 1 and Figure 1. Because CRS often occurs as early toxicity of CAR T-cell therapy, it was included as a predictor for neurotoxicity outcome. In Table 1, the univariate risk analysis showed that the predicting features, product-type, TLG and MTV were statistically correlated to CRS. However, the combination of all these predicting features in multivariate study did not improved the predictive ability of the model for CRS outcome. Looking at the AUC values for example, we identified that product-type (AUC = 0.74) and MTV (AUC = 0.86) were correlated to CRS on univariate analysis; whereas the occurrence of CAR T-cell therapy toxicity, CRS (AUC = 0.59), age (AUC = 0.65) and product-type (AUC = 0.63) were moderately correlated with neurotoxicity. On multivariate analysis, the combination of all predictive parameters showed a clear relationship with CRS (AUC = 0.70), but no relationship with neurotoxicity (AUC = 0.39). This key finding implies that physicians should keep an eye on these parameters for possible CRS toxicity when attending to patients. The relatively low AUC values of age, product-type and CRS with neurotoxicity indicates a weak possibility of occurrence that must be validated with a larger patient cohort for definitive conclusion.

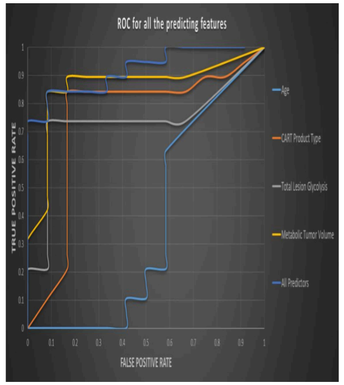

Figure 1a: ROCs of all predicting features for CRS

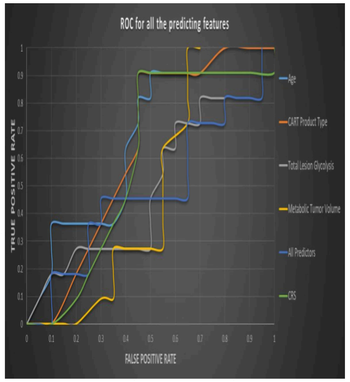

Figure 1b: ROCs of all predicting features for neurotoxicity

Predictor	CRS			Neurotoxicity		
	AUC	Sensitivity	Specificity	AUC	Sensitivity	Specificity
Age	0.37	36	38	0.65	60	56
Product-type	0.74	83	84	0.63	65	75
TLG	0.74	75	74	0.50	51	50
MTV	0.86	78	87	0.48	38	43
CRS	***	***	***	0.59	67	86
All predictors	0.70	67	68	0.39	38	43

Table 1: AUCs of all predicting parameters for CRS and neurotoxicity

CONCLUSIONS

This study demonstrates the promise of PET/CT and clinical parameters to predict CAR T-cell therapy-related toxicities.

Future work should be undertaken to confirm our findings in a larger patient cohort, to further characterize the incidence and management of toxicities.

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