Phosphorus disruption is associated with the incidence and severity of neurotoxicity symptoms in CD19-targeted CAR T-cell therapy: a pooled clinical trial analysis

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Background

- A significant complication of CAR T-cell therapy is immune effector cell-associated neurotoxicity syndrome (ICANS), which presents as confusion, inattention, word-finding difficulties, aphasia, impaired motor skills, somnolence, and in severe cases, neurological weakness, seizures, and coma [1].
- This presentation is similar to the neurological manifestations of clinical hypophosphatemia, which is a well-documented complication of CAR T-cell and other adoptive cell therapies.
- An association between hypophosphatemia and ICANS has been previously reported in smaller clinical cohorts [2-4].
- Given the need for reliable biomarkers and interventions for ICANS, and the inexpensive, accessible nature of electrolyte repletion, we investigated the relationship between electrolyte derangements and ICANS in a large pooled cohort of CD19-directed CAR T-cell clinical trial patients.
- We also explored the association between electrolyte repletion and ICANS, as well as the association between electrolyte derangements and the various neurological manifestations of ICANS.

Methods

- We analyzed 589 patients with relapsed/refractory B-cell acute lymphoblastic leukemia or non-Hodgkin's lymphoma treated with CD19-directed CAR T-cell therapy across pooled clinical trial data from the Medidata Enterprise Data Store.
- Patients were grouped by ICANS status. Variables of interest included baseline patient characteristics (age, sex, indication), ICANS status, and laboratory values including nadir and time to nadir for phosphorus, potassium, magnesium, calcium, as well as peak C-reactive protein and creatinine at time of infusion. Fisher exact test was performed for categorical variables. Mann-Whitney *U* test was performed for numerical variables.
- Hypophosphatemia, hypokalemia, hypomagnesemia, and hypocalcemia were defined as 2.5mg/dL, 3.5mmol/L, 1.3mg/dL, and 8mg/dL respectively.
- For Kaplan Meier curves the log rank test was performed for time to ICANS for patients with serum hypophosphatemia, hypokalemia, hypomagnesemia, and hypocalcemia.
- Spearman's rank correlation coefficients were plotted to show associations between ICANS severity, CRS severity, nadir electrolyte values, and electrolyte derangements with the various neurological manifestations observed in anti-CD19 CAR T-cell recipients.
- For electrolyte repletion analysis, we defined preemptive use as any electrolyte product given to patients with the corresponding electrolyte derangement before the occurrence of ICANS

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Results

		No ICANS (n=267)	ICANS (n=322)	p-value
Age (median, years)		59	57	0.416905118
Sex	F	82	109	0.427589055
	M	185	213	
Indication	ALL	57	79	0.378056271
	NHL	210	243	
CRS		77.9% (208/267)	94.7% (305/322)	0.00000000108
Hypophosphatemia		60.5% (135/223)	73.5% (205/279)	0.002840323
Hypokalemia		5.2% (14/267)	5.9% (18/304)	1
Hypomagnesemia		2.6% (7/267)	4.5% (14/307)	0.275436398
Hypocalcemia		9.9% (24/242)	11.5% (37/321)	0.34427316
Nadir Phosphorus (median, mg/dL)		2.2	2	0.010621167
Nadir Potassium (median, mmol/L)		3.5	3.4	0.003647243
Nadir Magnesium (median, mg/dL)		1.7	1.7	0.002360823
Nadir Calcium (median, mg/dL)		8.6	8.6	0.371309372
Baseline creatinine (mg/dL)		0.70	0.76	0.149256549
Peak CRP (mg/L)		100	118.5	0.073602224

Table 1: Demographics and selected laboratory values for 593 patients treated with anti-CD19 CAR T-cell therapy across pooled clinical trial data from the Medidata Enterprise Data Store.
Abbreviations: F: female; M: male; ALL: acute lymphoblastic leukemia; NHL: non-hodgkin's lymphoma; CRS: cytokine release syndrome; CRP: C-reactive protein

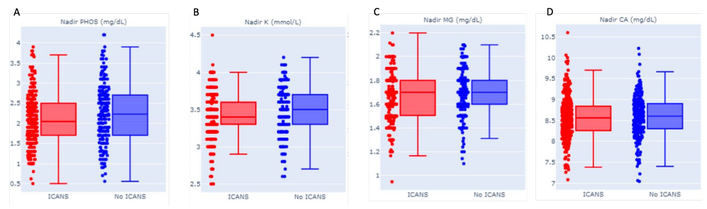

Figure 1: Nadir serum electrolyte values differ in CAR T-cell recipients who developed ICANS. Nadir serum electrolyte values represented as box and whisker plots showing median and range. **(A)** Median nadir serum phosphorus values were lower in patients who developed ICANS compared to those who did not (2.0mg/dL vs 2.2mg/dL, p=0.0028, Mann-Whitney *U* test). **(B)** Median nadir serum potassium levels and **(C)** magnesium levels were also significantly different between patients with ICANS compared to those without (p=0.0036 and p=0.0024, Mann-Whitney *U test*). **(D)** No significant differences were observed in the nadir values for corrected calcium levels between patients with or without ICANS.

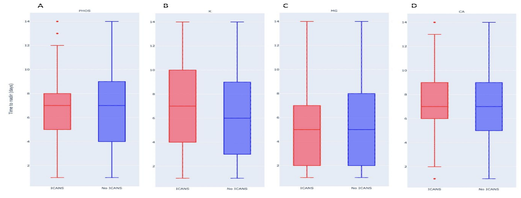

Figure 2: Time to nadir electrolyte value. Median time to nadir serum electrolyte value measured from days post-CAR T-cell infusion represented as a box and whisker plot showing median and range for **(A)** phosphorus, **(B)** potassium, **(C)** magnesium, and **(D)** calcium grouped by ICANS status. Only time to nadir potassium was significantly different between patients who developed ICANS compared to those who did not (p=0.02, Mann-Whitney *U* test)

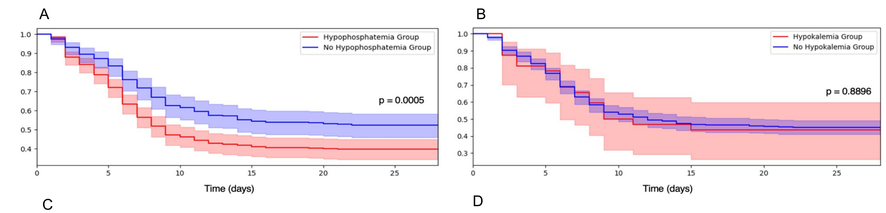

Figure 3: Serum hypophosphatemia is associated with higher cumulative incidence of ICANS. Kaplan Meier curves showing time to ICANS for patients with **(A)** hypophosphatemia (p=0.0005, log-rank test), **(B)** hypokalemia (ns), **(C)** hypomagnesemia (ns), and **(D)** hypocalcemia (ns) compared to those without.

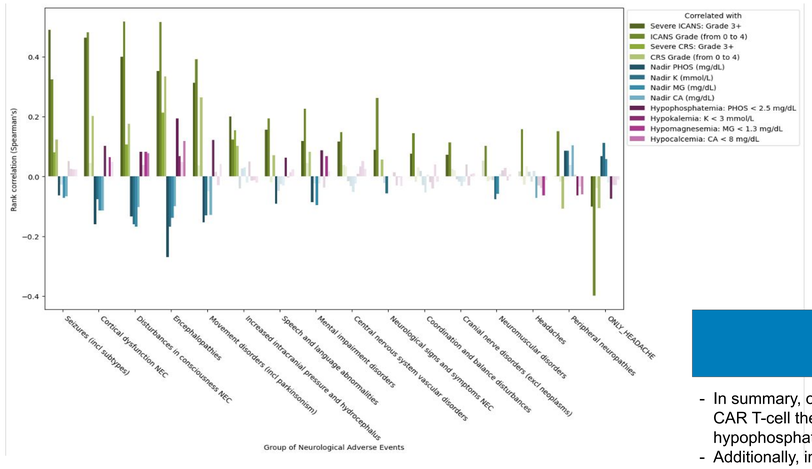

Figure 4: Electrolyte derangements are more closely associated with certain neurological manifestations compared to others. Spearman's rank coefficients were plotted comparing the association between ICANS severity, CRS severity, nadir electrolyte values, and electrolyte derangements with various categories of neurological manifestations observed in anti-CD19 CAR T-cell recipients. Solid bars represent a p-value ≤0.05. Encephalopathies, cortical dysfunction, movement disorders, speech and language disturbances, disturbances in consciousness, and mental impairment disorders were found to be significantly associated with serum hypophosphatemia.

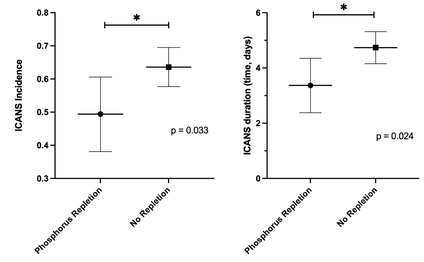

Figure 5: Patients with serum hypophosphatemia who received supplementation with phosphate had a lower incidence of ICANS and experienced decreased duration of ICANS symptoms. (A) Mean incidence of ICANS was lower (0.49 vs 0.64, p=0.033) and **(B)** mean duration of ICANS symptoms was lower (3.37 days vs 4.74 days, p=0.024) in anti-CD19 CAR T-cell recipients with serum hypophosphatemia who received electrolyte repletion containing phosphate prior to onset of ICANS, represented as mean with higher and lower bounds of the 95% confidence interval.

Conclusions

- In summary, our data demonstrates that in the setting of CD19-directed CAR T-cell therapy, ICANS incidence is associated with serum hypophosphatemia.
- Additionally, in those who received electrolyte repletion regimens that contain phosphorus, there is a significantly decreased incidence and duration of ICANS.
- Moreover, certain neurological manifestations of CAR T-cell associated neurotoxicity may be more associated with electrolyte derangements compared to others.
- Thus, serum phosphorus levels may be a useful biomarker for ICANS and phosphorus supplementation may be an inexpensive and widely accessible means to treat or prevent ICANS. However, prospective studies with goal-directed phosphorus repletion are necessary to further study the therapeutic impact on ICANS incidence and severity.

References

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