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POSTER ABSTRACTS

801.GENE THERAPIES

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

Hypophosphatemia due to increased cell metabolic activity as seen in refeeding syndrome and sepsis, has a similar neurologic presentation to immune effector cell-associated neurotoxicity syndrome (ICANS), an associated risk of CAR-T cell therapy. CAR-T patients who develop ICANS are observed to have a higher incidence and more severe degrees of hypophosphatemia (Tang et al, 2022). We further explored the association of hypophosphatemia and other electrolyte disturbances with ICANS incidence across pooled CAR-T clinical trial patients to assess how serum electrolytes correlated with risk of ICANS.

Methods

We analyzed 593 patients with relapsed/refractory B-cell acute lymphoblastic leukemia or non Hodgkin's lymphoma, with ICANS (n=325), and without ICANS (n=268) treated with CD19-targeted CAR-T cell therapy across pooled clinical trial data from the Medidata Enterprise Data Store.

Patients were grouped by ICANS status. A Fisher exact test was performed for categorical variables. A Mann-Whitney was performed for numerical variables. Variables of interest were baseline patients characteristics (age, gender, indication) and ICANS status. Common lab values investigated were nadir values and time to nadir for phosphate (Phos), magnesium (Mg), calcium (Ca), and potassium (K), peak value for C-reactive protein (CRP), and creatinine (Cr) at the time of infusion. To assign a hypo- phosphatemia, -kalemia, -magnesemia and -calcemia status to each patient, we used thresholds of <2 mg/dL, 3.5 mmol/L, 1.5 mg/dL and 2.0 mmol/L respectively. We performed a univariable logistic regression with ICANS status as the outcome variable and the following:

- Baseline value at infusion for Mg, K, Phos, Ca, Cr
- Nadir values between day 0 and 14 for Mg, K, Phos, Ca, Cr
- Slope (between baseline and nadir) for Mg, K, Phos, Ca, Cr
- Peak CRP, Cr and Urate between day 0 and 14

The odds ratios were calculated.

Kaplan Meier curves were plotted. The log rank test was performed for time to event of ICANS, grouped by hypo- phosphatemia, -kalemia, -magnesemia and -calcemia status.

We performed an analysis on the effect of the preemptive use of electrolyte replacement. We defined preemptive use as any electrolyte replacement given to patients either before the occurrence of ICANS or if patients did not get ICANS. For those with hypophosphatemia, we examined the preemptive use of electrolyte replacements for any electrolyte excluding Phos and any electrolyte with Phos. For those 2 groups we compared the rates of ICANS.

Results

CRS, and hypo- phosphatemia, -kalemia, -magnesemia and -calcemia status were statistically significantly different between ICANS and no ICANS groups. When looking at the nadir values, these 4 electrolyte disturbances were also statistically significant, with lower values associated with ICANS. For the time to nadir, only K was significant and higher for the ICANS group. Peak CRP was also higher for patients with ICANS, but did not meet the 0.05 threshold to be statistically significant.

For the univariate logistic regression, variables positively associated with ICANS and significant were peak values for creatinine and CRP, OR of 3.8 (1.6-9.2) and 2.1 (0.9 - 5.0) respectively. Variables negatively associated with ICANS and significant were

nadir values for Phos (OR 0.3 (0.1 - 0.8)), K (OR 0.2 (0.1-0.7)), Ca (OR 0.2 (0.1-0.6)), Mg (OR 0.17(0.1-0.5)) and urate (0.3(0.1-1)), and slope for Mg (OR 0.0 (0.0-0.2)).

When plotting the Kaplan Meier curves, ICANS seems to develop sooner for patients with either hypo- phosphatemia, -kalemia, -magnesium or -calcemia and the log rank test showed to be statistically significant (Figure 1).

Among the patients with hypophosphatemia, the use of Phos as part of electrolyte replacement reduces the ICANS rate: 52% (0.39-0.65) versus 71% (0.58-0.84) for the electrolyte replacement without Phos.

Conclusion

Our data demonstrate that ICANS incidence is associated with disruptions in serum phosphorus levels, and that supplementation of phosphorus is able to mitigate the incidence of ICANS as well. Monitoring phosphorus may serve as a useful biomarker for ICANS, while goal directed phosphorus supplementation may serve as an inexpensive and readily available means to treat or prevent ICANS. Prospective studies with goal-directed phosphorus repletion are necessary to further study the therapeutic impact of electrolyte supplementation on ICANS incidence and severity.

Disclosures Lafeuille: Medidata, a Dassault Systèmes company: Current Employment. **Diamond:** Medidata, a Dassault Systèmes company: Current Employment. **Socolov:** Medidata, a Dassault Systèmes company: Current Employment. **Aptekar:** Medidata, a Dassault Systèmes company: Current Employment. **Nowicki:** Medidata, a Dassault Systèmes company: Consultancy.

Table 1. Patients characteristics grouped by ICANS / no ICANS status

		FALSE	TRUE	p
Patients count	count	267	322	
	median	59	57	0.417
AGE	25%	47	45	
	75%	66	66	
	F	82	109	0.428
SEX	M	185	213	
AINDTYPE	ACUTE LYMPHOBLASTIC LEUKEMIA	57	79	0.378
	NON-HODGKIN'S LYMPHOMA	210	243	
CRS	FALSE	59	17	0.000
	TRUE	208	305	
Hypophosphatemia	FALSE	140	151	0.056
	TRUE	83	128	
Hypokalemia	FALSE	153	146	0.005
	TRUE	114	176	
Hypomagnesemia	FALSE	178	178	0.007
	TRUE	89	143	
Hypocalcemia	FALSE	66	51	0.009
	TRUE	201	270	
Nadir PHOS (mg/dL)	median	2.2	2	0.011
	25%	1.7	1.7	
	75%	2.7	2.5	
Nadir K (mmol/L)	median	3.5	3.4	0.004
	25%	3.3	3.2	
	75%	3.7	3.6	
Nadir MG (mg/dL)	median	1.7	1.7	0.002
	25%	1.6	1.5	
	75%	1.8	1.8	
Nadir CA (mmol/L)	median	2	1.9	0.001
	25%	1.8	1.8	
	75%	2.1	2	
Time to Nadir PHOS	median	7	7	0.822
	25%	4	5	
	75%	9	8	
Time to Nadir K	median	6	7	0.017
	25%	3	4	
	75%	9	10	
Time to Nadir MG	median	5	5	0.188
	25%	2	2	
	75%	8	7	
Time to Nadir CA	median	7	7	0.294
	25%	5	6	
	75%	9	9	
Peak CRP (mg/L)	median	100	118.5	0.074
	25%	53.4	65.7	
	75%	144	154.3	
Baseline CREAT (umol/L)	median	61.9	67.2	0.149
	25%	53	53	
	75%	76.9	79.6	

Figure 1: Kaplan-Meier curve for the Time to Event for ICANS, grouped by Hypophosphatemia status. The 2 group are compared using a log-rank test

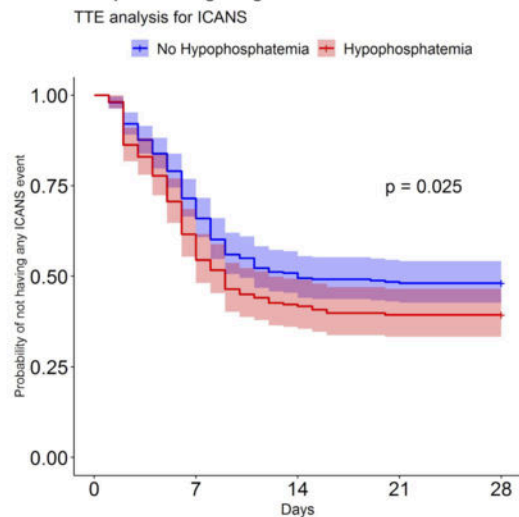


Figure 1

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