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Pegcrisantaspase (PegC) induces an increase in plasma threonine in patients with acute myeloid leukemia (AML)

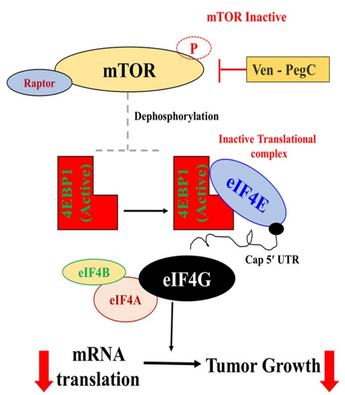
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INTRODUCTION

- Glutamine depletion is a therapeutic vulnerability in AML through inhibition of mTOR[1].
- Recently completed a phase 1 of Pegcrisantaspase (PegC) and Venetoclax (Ven) [VenPegC] in relapsed/refractory AML (NCT0466649)[2].
- Exploratory analysis included alterations in alternative amino acids following glutamine depletion.
- Patients received oral Ven daily on Days 1-28 and IV PegC on Days 1 and 15 of 28-day cycles.



METHOD

- 25 total patients were enrolled in this phase 1 clinical trial with 20 patients with available amino acid data.
- Plasma samples were collected at enrollment, baseline, and Days 1 (PegC trough), 8, 15 (PegC trough), 22 of each 28-day cycle while on study.
- Amino acids were analyzed with cation-exchange chromatography and ninhydrin.

RESULTS

- Both asparagine and glutamine were depleted in all patients with an increase in plasma aspartate and glutamate.
- Baseline mean threonine levels was 85.6 µM (range 28–188).

Positive correlation between asparaginase activity and threonine

Correlation	Amino Acid	Asparaginase Activity	Asparagine	Glutamine	Glutamate
r	Threonine	0.57 (<0.001)	-0.47 (<0.001)	-0.37 (<0.001)	0.67 (<0.001)
r_{rm}	Threonine	0.52 (<0.001)	-0.47 (<0.001)	-0.20 (0.0123)	0.67 (<0.001)

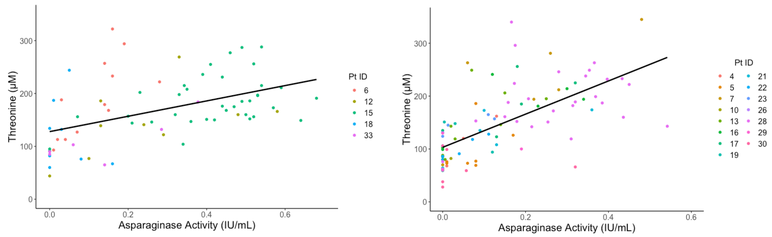
Pearson correlation coefficient (r) and repeated measures correlation (r_{rm}) of threonine with asparaginase activity, asparagine, glutamate, and glutamine.

Threonine increases with increase in asparaginase activity

Threonine	Coef.	Std. Err	Z	P> |z|	95% Conf. interval
Asparaginase Activity	237.69	28.88	8.23	<0.001	181.09-294.30
CR	-7.34	16.01	-0.46	0.647	-38.71-24.03
Constant	113.14	9.31	12.15	<0.001	94.88-131.39

Multivariate linear regression adjusting for asparaginase activity and for patients achieving CR/CRi/CRh.

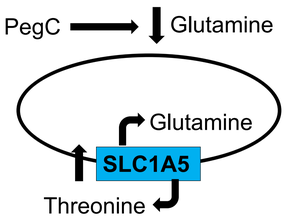
Threonine levels segregated by CR and non-CR patients



Scatterplots of threonine vs asparaginase activity segregated by patients who achieved CR/CRi/CRh and those who did not.

CONCLUSIONS

- A significant increase in threonine
- following PegC treatment was observed.
- This may be a compensatory change due to glutamine depletion.
- This may suggest increase in activity of the glutamine/threonine antiporter SLC1A5.



REFERENCES

1. Emadi, A., et al., *Venetoclax and pegcrisantaspase for complex karyotype acute myeloid leukemia.* Leukemia, 2021. **35**(7): p. 1907-1924.
2. Liu, Y., et al., *Overcoming Venetoclax (Ven) Resistance through Glutamine (Gln) Depletion: Final Analysis of the Phase 1 Trial of Ven and Pegcrisantaspase (PegC) Combination in Relapsed and Refractory (R/R) Acute Myeloid Leukemia (AML).* Blood, 2023. **142**(Supplement 1): p. 60-60.

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