Technology in Cancer Research & Treatment
Volume 20: 1-2

DOI: 10.1177/15330338211049902
journals.sagepub.com/home/tct
SAGE

Comment on "Correlation of L-asp Activity, Anti-L-asp Antibody, asn and gln with Adverse Events Especially Anaphylaxis Risks in PEG-asp-Contained Regime Treated Pediatric ALL"

Wing H. Tong, MD, PhD, MSc[1,2]

Keywords
pediatric acute lymphoblastic leukemia, asparaginase activity, asparagine, glutamine, anaphylaxis, asparaginase antibodies

Abbreviations
AE, adverse events; ALL, acute lymphoblastic leukemia; Anti-L-asp, anti-native *Escherichia coli* asparaginase; Anti-PEG-ASP, anti-polyethylene glycol asparaginase; Anti-SS-linker, anti-succinimidyl succinate linker; ASN, asparagine; DCOG, Dutch Childhood Oncology Group; *Erwinia* asparaginase, *Erwinia* chrysanthemi asparaginase; GLN, glutamine; L-asp, native *Escherichia coli* asparaginase; PEG, polyethylene glycol; PK/PD, pharmacokinetics/pharmacodynamics; TDM, therapeutic drug monitoring.

Received: August 11, 2021; Revised: August 18, 2021; Accepted: August 25, 2021.

Dear Editor

I have read with great interest the publication by Wu *et al.*[1] In the context of the Chinese Children's Cancer Group (CCCG)-ALL-2015 protocol, they studied the plasma L-asp activity/anti-L-asp antibody/asparagine/glutamine levels of 91 pediatric ALL patients who underwent PEG-asp-contained treatment on the seventh day after drug administration. Very recently, this CCCG-ALL-2015 protocol was used in an open-label, multicenter, randomized, phase 3, non-inferiority trial which involved twenty major medical centers across China.[2] Yang *et al.* concluded that vincristine plus dexamethasone pulses might be omitted beyond one year of treatment for children with low-risk ALL.[2] Wu *et al.* suggested that the measurement of L-asp activity/anti-L-asp antibody/asparagine/glutamine levels might assist the prevention of anaphylaxis-related AEs in pediatric ALL patients who underwent PEG-asp-contained treatment.[1] Although this clinical study is of interest, some important questions can be raised, which I address below.

Wu *et al.* measured the PK/PD parameters during PEG-asp-contained treatment on day seven after administration. At that moment, no trough activity levels were monitored.[3] Trough asparaginase activity levels of 100 U/L or greater appears to be a safe target level to ensure therapeutic benefit.[4] Why did Wu *et al.* choose to use the peak levels on day 7 of PEGasparaginase?

Furthermore, anti-asparaginase antibodies and asparagine measurements are not indicated for clinical decision making outside the context of a clinical trial.[4] Wu *et al.* studied anti-L-asp antibody, however, recent publications showed that not anti-L-asp antibody, but PEG is the major antigen that causes allergic reactions.[5] Liu *et al.* concluded that anti-PEG-ASP has utility in predicting and confirming clinical reactions to PEGasparaginase as well as in identifying patients who are most likely to experience failure with rechallenge.[5] Similar finding was found by the Dutch researchers, namely that anti-asparaginase antibodies were detected in only 11% during induction (of their DCOG ALL-11 protocol), but 94% during

[1] Department of Public Health and Primary Care (PHEG), Leiden University Medical Center, Leiden, the Netherlands
[2] Argos Zorggroep "DrieMaasStede", Center for Specialized Geriatric Care, Schiedam, the Netherlands

Corresponding Author:
Wing H. Tong, MD, PhD, MSc, Department of Public Health and Primary Care (PHEG), Leiden University Medical Center (LUMC), Building 3, Hippocratespad 21, PO Box 9600, 2300 RC, Leiden, The Netherlands.
Email: w.h.tong@lumc.nl

intensification.[6] Wu *et al.* only studied the induction phase.[1] Kloos *et al.* concluded, however, that anti-PEG and anti-SS-linker antibodies predominantly play a role in the immunogenic response to PEGasparaginase during induction.[6] Of interest, these authors suggest that switching to native *Escherichia coli* asparaginase would be an option for adequate treatment. Do Wu and colleagues also have data on anti-PEG-ASP? If not, why did the authors only focus on anti-L-asp antibody?

Previously, it was published that no glutamine depletion was seen during PEGasparaginase therapy.[3] Wu *et al.* suggested, however, that glutamine level might assist the prevention of anaphylaxis-related AEs.[1] It is remarkable that these authors did find glutamine depletion, how could this phenomenon be explained? What was the role and the influence of day 7 post-infusion measurement on the glutamine level in this clinical study?

Finally, Wu *et al.* stated that for patients with plasma drug activity < 100 U/L, it was suggested to switch from PEGasparaginase to *Erwinia* asparaginase.[1] These authors found that seven patients had anaphylaxis. These patients were switched to *Erwinia* asparaginase, were the data available after the switch on these parameters: L-asp activity/anti-L-asp antibody/asparagine/glutamine levels? This is particularly of interest as the number of patients switching to *Erwinia* asparaginase is currently limited.[7]

To conclude, monitoring of asparaginase PK by means of TDM is a powerful tool.[7] This was confirmed by a recent expert panel discussion that agreed that TDM is useful to improve asparaginase efficacy.[8] Wu *et al.* did a great job to study difficult PK/PD parameters in children suffering from ALL,[1] however new PK/PD challenges need to be explored to further improve individualized treatments.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval statement

This letter to the editor did not require an ethical board approval because it did not contain human or animal trials.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Wing H. Tong https://orcid.org/0000-0002-5462-6012

References

1. Wu J, Chen C, Huang S, et al. Correlation of L-asp activity, anti-L-asp antibody, Asn and Gln With adverse events especially anaphylaxis risks in PEG-asp-contained regime treated pediatric ALL patients. *Technol Cancer Res Treat*. 2020;19:1533033820980113. DOI: 10.1177/1533033820980113.
2. Yang W, Cai J, Shen S, et al. Pulse therapy with vincristine and dexamethasone for childhood acute lymphoblastic leukaemia (CCCG-ALL-2015): an open-label, multicentre, randomised, phase 3, non-inferiority trial. *Clinical Trial Lancet Oncol*. 2021; 22(9):1322–1332. DOI: 10.1016/s1470-2045(21)00328-4.
3. Tong WH, Pieters R, Kaspers GJ, et al. A prospective study on drug monitoring of PEGasparaginase and Erwinia asparaginase and asparaginase antibodies in pediatric acute lymphoblastic leukemia. *Blood*. 2014;123:2026-2033. DOI: 10.1182/blood-2013-10-534347.
4. van der Sluis IM, Vrooman LM, Pieters R, et al. Consensus expert recommendations for identification and management of asparaginase hypersensitivity and silent inactivation. *Haematologica*. 2016;101:279-285. DOI: 10.3324/haematol.2015.137380.
5. Liu Y, Smith CA, Panetta JC, et al. Antibodies predict pegaspargase allergic reactions and failure of rechallenge. *J Clin Oncol*. 2019;37:2051-2061. DOI: 10.1200/jco.18.02439.
6. Kloos R, van der Sluis IM, Mastrobattista E, et al. Acute lymphoblastic leukaemia patients treated with PEGasparaginase develop antibodies to PEG and the succinate linker. *Br J Haematol*. 2020;189:442-451. DOI: 10.1111/bjh.16254.
7. Kloos RQH, Pieters R, Jumelet FMV, et al. Individualized asparaginase dosing in childhood acute lymphoblastic leukemia. *J Clin Oncol*. 2020;38:715-724. DOI: 10.1200/jco.19.02292.
8. Baruchel A, Brown P, Rizzari C, et al. Increasing completion of asparaginase treatment in childhood acute lymphoblastic leukaemia (ALL): summary of an expert panel discussion. *ESMO Open*. 2020;5:e000977. DOI: 10.1136/esmoopen-2020-000977.