PROMPT DETECTION OF L-ASPARAGINASE INACTIVATION IS CRUCIAL TO OPTIMIZE TREATMENT EFFICACY ALSO IN AGGRESSIVE LYMPHOMAS

Journal:	*Hematological Oncology*
Manuscript ID	HON-17-0224.R1
Wiley - Manuscript type:	Letter to the Editor
Date Submitted by the Author:	01-Oct-2017

Complete List of Authors:	Guolo, Fabio; Policlinico San Martino, IRCCS per l'Oncologia, University of Genova, Clinic of Hematology, Department of Internal Medicine (DiMI) Ferrari, Mariella; Istituto Di Ricerche Farmacologiche Mario Negri, Department of Oncology Minetto, Paola; Policlinico San Martino, IRCCS per l'Oncologia, University of Genova, Clinic of Hematology, Department of Internal Medicine (DiMI) Matteo, Cristina; Istituto Di Ricerche Farmacologiche Mario Negri Clavio, Marino; Policlinico San Martino, IRCCS per l'Oncologia, University of Genoa, Clinic of Hematology, Department of Internal Medicine (DiMI) Coviello, Elisa; Policlinico San Martino, IRCCS per l'Oncologia, University of Genoa, Clinic of Hematology, Department of Internal Medicine (DiMI) Ballerini, Filippo; Policlinico San Martino, IRCCS per l'Oncologia, University of Genova, Clinic of Hematology, Department of Internal Medicine (DiMI) Miglino, Maurizio; Policlinico San Martino, IRCCS per l'Oncologia, University of Genova, Clinic of Hematology, Department of Internal Medicine (DiMI) Gobbi, Marco; Policlinico San Martino, IRCCS per l'Oncologia, University of Genoa, Clinic of Hematology, Department of Internal Medicine (DiMI) D'Incalci, Maurizio; Istituto Di Ricerche Farmacologiche Mario Negri Lemoli, Roberto; Policlinico San Martino, IRCCS per l'Oncologia, University of Genova Zucchetti, Massimo; Istituto Di Ricerche Farmacologiche Mario Negri

Keywords:	L-asparaginase, Aggressive lymphoma, silent inactivation

PROMPT DETECTION OF L-ASPARAGINASE INACTIVATION IS CRUCIAL TO OPTIMIZE TREATMENT EFFICACY ALSO IN AGGRESSIVE LYMPHOMAS

RUNNING HEAD: SILENT ASPARAGINASE INACTIVATION IN LYMPHOMA

Fabio Guolo[1], Mariella Ferrari[2], Paola Minetto[1], Cristina Matteo[2], Marino Clavio[1], Elisa Coviello[1], Filippo Ballerini[1], Maurizio Miglino[1], Marco Gobbi[1], Maurizio D'Incalci[2], Roberto Massimo Lemoli[1] and Massimo Zucchetti[2]

Affiliations:

1) Clinic of Hematology, Department of Internal Medicine (DiMI), University of Genoa, IRCCS AOU San Martino-IST, Genova, Italy

2) Department of Oncology, IRCCS Istituto di Ricerche Farmacologiche Mario Negri, Milano, Italy

Corresponding author:

Dr Fabio Guolo, MD

Clinic of Hematology Department of internal medicine (DiMI), University of Genoa, IRCCS AOU San Martino-IST, Genova, Italy

Address: Largo Rosanna Benzi, 10
16132 Genova (Italy)
tel +39 0105554336;
fax +39 0105556938;
e-mail: fabio.guolo21@gmail.com

Keywords: L-Asparaginase, Aggressive lymphoma, silent inactivation

TEXT WORD COUNT: 834

REFERENCE COUNT: 10

To the Editor,

The use of L-asparaginase (L-ASP) has significantly improved the prognosis of acute lymphoblastic leukemia (ALL), especially in pediatric and adolescents-young adult patients.[1]

In L-ASP-containing protocols designed for the treatment of ALL, therapeutic drug monitoring of asparaginase activity is recommended, in order to achieve and maintain appropriate enzymatic exposure, which is required for a complete and protracted depletion of L-asparagine (L-ASN) in serum.[2,3] Serum enzymatic activity of 100 IU/L is generally accepted as the level necessary to obtain the therapeutic depletion of L-ASN .[2,3]

However, the main factor limiting L-ASP activity is the formation of neutralizing antibodies leading to the inactivation of the enzyme and consequent reduction of its activity.[4] Correlations between hypersensitivity manifestations and drug inactivation or increased drug clearance have been reported. Nevertheless, patients often experience the so called “silent inactivation” (i.e. the developing of neutralizing anti-asparaginase antibodies in the absence of evident clinical symptoms, that leads to low or missing enzymatic activity in serum after L-ASP administration). The detection of silent inactivation by testing serum asparaginase activity is therefore essential to verify the achievement of the therapeutic depletion of L-ASN.[3,4]

The efficacy of L-ASP-containing regimens has been recently reported also in peripheral T-Cell lymphomas[5,6] but no information is currently available on the clinical relevance of silent inactivation in this subset of patients.

We report here a case of a 30-years-old man with Hepatosplenic γδ T-Cell Lymphoma (HSL), a rare form of peripheral T-Cell lymphoma with a dismal prognosis. The patient was admitted to our division for persistent fever, intense asthenia and night sweats. Laboratory analysis showed leukocytosis (20000 WBC/mmc), severe anemia and thrombocytopenia, and disseminated intravascular coagulation. Morphological examination of peripheral blood smears showed the

presence of atypical large agranular vacuolated cells. Flow-cytometry revealed a clonal γδ T-Cell population with the following phenotype; CD3+, CD4-, CD8-, TCR γδ+. Bone marrow core biopsy confirmed the diagnosis of HSL. An informed consent allowing collection and reporting of clinical data was obtained, according to the Declaration of Helsinki.

SMILE chemotherapy regimen[7] which includes steroid (dexamethasone), methotrexate, ifosfamide, etoposide and L-ASP was started. The Escherichia-coli derived L-ASP native formulation was administered at the 6000 U/sqm dose intravenously every 48 hours from day 8, for 7 doses, as per SMILE protocol. After the first course of chemotherapy a partial remission was achieved, with a 75% reduction in bone marrow lymphoid infiltration. The response however proved to be transient as a second bone marrow biopsy performed after the second course of therapy showed an increase of neoplastic infiltration. Furthermore no alterations of coagulation tests, that are typically associated with L-ASP therapy, had been observed. Following our experience with ALL patients we checked serum asparaginase activity, through the MAAT™ enzymatic test (kindly provided by Medac GmbH, Germany)[8] and documented inactivation of the enzyme, being detectable only a level of 32 IU/L, 48 hour after the 6thdose of *E. coli* L-ASP. Both clinical and laboratory findings prompted us to substitute *E. coli* L-ASP with the *E. chrysanthemi*-derived enzyme.[9] Following this change, a satisfactory serum asparaginase level of 120 IU/L at 48 hours after the 4th dose of *E. chrysanthemi* L-ASP was obtained. In addition, as proof of concept, we checked by HPLC mass spectrometry the presence of the L-ASN in the serum that resulted undetectable. Most importantly, after the drug shift, bone marrow biopsy showed a recovery of the response, with a maximum reduction of 92% of neoplastic infiltration after the fifth cycle. Patient then received an haploidentical allogeneic bone marrow transplantation after the sixth cycle.

It is known from the pediatric ALL experience that the sub-optimal or the complete inactivation, of the L-ASP serum activity is correlated with a worse prognosis.[3,9] Few data are however available on the clinical utility of enzymatic activity monitoring in adult ALL patients and, as far as we know, the monitoring of L-ASP activity has never been routinely performed in patients affected by mature T-Cell lymphomas.

Although no allergic clinical signs were present, the loss of clinical response together with the lack of toxicity suggested us to check the serum asparaginase activity which allowed us to document a silent inactivation. Since the shift to the *E. chrysanthemi*-derived enzyme led to a recovery and a further improvement of clinical response, we may conclude that this positive effect was due to the recovered activity of L-ASP, which was confirmed by subsequent determinations. This observation is consistent with the clinical management of ALL patients, where the detection of L. ASP inactivation leads to the substitution with *E. chrysanthemi* derived L-ASP, which is usually able to restore the effectiveness of the asparaginase treatment.[9]

In a recent review focusing on the utilization of L-ASP containing regimens in T/NK neoplasms, routine L-ASP activity monitoring is suggested for future trials.[10]

The detection of silent inactivation in our adult HSL patient confirms the clinical utility of planning a regular assessment of serum L-ASP activity, regardless of the diagnosis and the presence of overt allergic reactions, in order to maximize its therapeutic efficacy, eventually through an early shift to an alternative drug preparation.

Authorship and conflict-of-interest statements

All authors declare that they have no conflict of interest to disclose.

Fabio Guolo, Paola Minetto and Massimo Zucchetti designed research

Marino Clavio, Marco Gobbi, Fabio Guolo, Paola Minetto and Massimo Zucchetti wrote the

manuscript

Mariella Ferrari, Cristina Matteo and Massimo Zucchetti performed all the pharmacological analyses

Filippo Ballerini, Elisa Coviello and Maurizio Miglino reviewed the manuscript

Maurizio D'Incalci, Marco Gobbi and Roberto Massimo Lemoli, reviewed the final version of the manuscript

References

1. Kumar K, Kaur J, Walia S, Pathak T, Aggarwal D. L-asparaginase: an effective agent in the treatment of acute lymphoblastic leukemia. *Leuk Lymphoma* 2014; **55**:256-62.

2. Asselin B, Rizzari C. Asparaginase pharmacokinetics and implications of therapeutic drug monitoring. *Leuk Lymphoma* 2015; **56**:2273-80.

3. van der Sluis IM, Vrooman LM, Pieters R, Baruchel A, Escherich G, Goulden N, et al. Consensus expert recommendations for identification and management of asparaginase hypersensitivity and silent inactivation. *Haematologica* 2016; **101**:279-85.

4. Tong WH, Pieters R, Kaspers GJ, te Loo DM, Bierings MB, van den Bos C, et al. A prospective study on drug monitoring of PEG asparaginase and Erwinia asparaginase and asparaginase antibodies in pediatric acute lymphoblastic leukemia. *Blood* 2014; **123**:2026-33.

5. Corradini P, Marchetti M, Barosi G, Billio A, Gallamini A, Pileri S, et al. SIE-SIES-GITMO guidelines for the management of adult peripheral T- and NK-cell lymphomas, excluding mature T-cell leukaemias. *Ann Oncol* 2014; **25**:2339-50.

6. Yao G, Zhou D, Zhou M, Bao C, He D, Li L, et al. Clinical analysis and prognostic significance of L-asparaginase containing multidrug chemotherapy regimen in incipient peripheral T-cell lymphoma. *Int J ClinExp Med* 2015; **8**:9374-83.

7. Kwong YL, Kim WS, Lim ST, Kim SJ, Tang T, Tse E, et al. SMILE for natural killer/T-cell lymphoma: analysis of safety and efficacy from the Asia Lymphoma Study Group. *Blood* 2012; **120**:2973-80.

8. Medac GmbH. Medac Asparaginase-Aktivitäts-Test MAAT, 1 Kit, Reference: 550. http://www.medac-.com

9. Salzer WL, Asselin B, Supko JG, Devidas M, Kaiser NA, Plourde P, et al. Erwinia asparaginase achieves therapeutic activity after pegaspargase allergy: a report from the Children's Oncology Group. *Blood* 2013; **122**:507-14.

10. Yong W. Clinical study of L-asparaginase in the treatment of extranodal NK/T-cell lymphoma, nasal type. HematolOncol. 2016; 34: 61–68 DOI: 10.1002/hon.2207