Follow our path with asparaginase activity: one technique, but different uses in clinical practice

Daiane Keller Cecconello1,2,3, Ciliana Rechenmacher1,2,3, Klerize Anecely de Souza Silva1, Fernanda Fetter Scherer3, Thomas Dal Bem Prates3, Rebeca Ferreira Marques3, Liane Esteves Daudt1,2,3 and Mariana Bohns Michalowski1,2,3*

Abstract
Acute lymphoblastic leukemia is the most common childhood malignancy. One of the drugs used in the treatment is Asparaginase, and monitoring of its activity levels enables better outcomes. Since 2018, our laboratory has been working to establish a regular analysis of activity. This implementation allowed to qualify care by detecting silent inactivation and also establishing desensitization as a safe way to overcome the lack of Erwinia. We were able to monitor children aged 0 to 18 years who were being treated with PEG-ASNase. The activity was assessed on days 7 (90 samples) and 14 (52 samples) after ASNase infusions. 142 samples were analyzed. 95.7% reached an adequate activity level (≥ 0.1 IU/mL). Patients treated with ASNase can develop allergic reactions. With the activity monitoring, it is possible to circumvent situations like these and implement desensitization protocols for patients who had clinical hypersensitivity without inactivation. Desensitization induces temporary unresponsiveness to drug antigens, allowing the patients to proceed with the prescribed chemotherapy. We have received samples from four patients being treated with different desensitization protocols. Patients tolerated the protocols well. Only one had a grade 2 reaction during the infusion and activity < 0.1 IU/mL, which resulted in the switch to Erwinia. The dose adaptation is a possible and more recent use of ASNase monitoring and we were able to confirm the feasibility of PEG-ASNase desensitization protocols.

Keywords: Acute lymphoblastic leukemia, PEG asparaginase, Enzymatic activity, Desensitization protocols

To the Editor,
Acute lymphoblastic leukemia (ALL) is the disease most commonly seen in children [1]. Due to current chemotherapy regimens, long-term results have improved, being associated with event-free survival and overall survival rates around 80% and close to 90%, respectively [2]. One of the drugs used in the treatment is Asparaginase (ASNase), and the monitoring of its activity levels has allowed for better outcomes [1].

Since 2018, our laboratory has been working to establish a regular analysis of ASNase activity in children being treated in Brazil. Moreover, the data in this study demonstrated that this implementation supported care improvement by detecting silent inactivation [3, 4].

We were able to monitor children aged 0 to 18 years who were being treated for ALL with PEG-ASNase. The activity was assessed after infusions on days 7 (90 samples) and 14 (52 samples) during the first and second infusions of the BFM 2009 protocol induction. As shown in Fig. 1, 142 samples were analyzed, out of which 95.7% (136) reached an adequate activity level (≥ 0.1 IU/mL) and only 4.3% (6) had levels lower than...
expected. These data agree with those described in the literature [5].

Patients treated with ASNase may develop allergic reactions [4]. With activity monitoring, it is possible to avoid situations like this and to implement desensitization protocols for patients who had clinical hypersensitivity to PEG-ASNase without inactivation.

We received samples suspected of having allergy/inactivation from other centers in Brazil. These were monitored with the use of desensitization protocols. These induce temporary unresponsiveness to drug antigens, allowing the patients to proceed with the chemotherapy to which they had a reaction [6].

Desensitization is useful where Erwinia is not easily available.

We have received samples from four patients being treated with different desensitization protocols. The characteristics are in Table 1. There is still limited knowledge on PEG-ASNase desensitization. Concha et al. reported a successful protocol used in five patients. They suggest that patients might benefit from this viable alternative to drug discontinuation [7]. Their protocol is similar to described by Verma et al. [8].

Patients who had allergic reactions may choose to undergo a rechallenge protocol with premedication, switch to Erwinia, or discontinue the therapy. In this study, patients tolerated the protocols. Only one (#2) had a grade 2 reaction and activity <0.1 IU/mL during the infusion, which resulted in the switch to Erwinia.

Similar to described by Verma et al., PEG-ASNase can be administered to patients who had hypersensitivity using desensitization protocols. Most patients sustained levels of activity, making it a cost-effective option [8]. As reported by Swanson et al., in patients who presented angioedema, vomiting, and positive antibodies in the infusion process before undergoing the desensitization protocol, this failed more. Therefore, attention should be paid to this group [9].

The issue is deciding whether to use a desensitization protocol or switch to Erwinia. The protocol in patients with hypersensitivity should be applied with regular monitoring, as this helps to prevent subtherapeutic activity from occurring. Tong et al. showed that patients with inactivation who continued the treatment

Table 1 Characteristics of patients undergoing desensitization protocols

| Patient | 1       | 2       | 3       | 4       |
|---------|---------|---------|---------|---------|
| Gender  | Male    | Male    | Female  | Female  |
| Age (years) | 9 | 5       | 11      | 13      |
| Diagnosis | B-ALL | B-ALL | T-ALL   | T-ALL   |
| Treatment protocol | UK ALL R3 | IC-BFM 2009 | IC-BFM 2009 | IC-BFM 2009 |
| Previous allergy | Yes | Yes    | Yes     | Yes     |
| CTCAE grade | 4 | 2       | 2       | 2       |
| Desensitization protocol | Premedication: cetirizine, famotidine, montelukast, and methylprednisolone. Bags of saline with progressively increasing doses and infusion rates | PEG 2500 UI/m² diluted in 1000 mL of saline. Premedication: hydrocortisone, promethazine, montelukast, and cetirizine | Premedication: promethazine and hydrocortisone | H2 and H1 blockers and corticosteroid pretreatment. 3 bags of saline with different dilution rates: 1:1, 1:10, 1:100 |
| Symptoms during desensitization | No | Yes | No | Yes |
| D7 activity levels (IU/mL) | 0.43 | 0.08 | 0.72 | 0.91 |
| D14 activity levels (IU/mL) | NA | 0.03 | 0.64 | 0.34 |
| Symptoms improved | Yes | Yes | Yes | Yes |

ALL Acute lymphoblastic leukemia, UK United Kingdom, BFM Berlin-Frankfurt-Münster group, IC Intercontinental, CTCAE Common Terminology Criteria for Adverse Events, NA Not available
with PEG-ASNase had a decrease in antibodies and started to show therapeutic activity later. As the recovery of ASNase activity may take an unpredictable amount of time, we recommend switching to *Erwinia* instead of using desensitization approaches. Patients with PEG-ASNase inactivation should continue taking this drug only if *Erwinia* is not available [10].

Dose adaptation is a recent use of ASNase monitoring. As described by Tong et al., patients who were not allergic to PEG-ASNase had a mean activity level of 0.899 IU/mL. They observed that if patients did not have allergy or inactivation, the use of a regimen of 2500 IU/m² led to high serum levels [11]. They reported that dose reduction may be possible, as they used protocols that reduced the dose of PEG-ASNase to 1000 IU/m², and approximately 80% of patients had adequate activity (> 0.1 IU/mL) [12].

We were able to demonstrate how a simple technique can be efficiently incorporated into the treatment of ALL, improving the care of patients. Our data on silent inactivation correlated with those described in the literature. We were able to confirm the feasibility of desensitization protocols in patients who had clinical allergy but no drug inactivation. The impact of dose adjustments on possible adverse effects remains to be studied.

Acknowledgements
Not applicable.

Author contributions
DKC and CR performed laboratory tests. MBM supervised the study. DKC, MBM, KASS, wrote the manuscript. LED, CR, FFS, TDP, RFM provided important clinical information and helped in the interpretation of variants. All authors read and approved the final manuscript.

Funding
Fundo de Incentivo à Pesquisa e Eventos (FIPED) do Hospital de Clínicas de Porto Alegre, Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul (FAPERGS).

Availability of data and materials
Yes.

Declarations

Ethics approval and consent to participate
This project was approved by the Ethics and Research Committee of the Hospital de Clínicas de Porto Alegre (2017-0289).

Consent for publication
Yes.

Competing interests
The authors declare that they have no competing interests.

Author details
1 Post Graduate Program in Child and Adolescent Health, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil. 2 Translational Pediatrics Laboratory, Experimental Research Center, Hospital de Clínicas de Porto Alegre, Porto Alegre, RS, Brazil. 3 Hospital de Clínicas de Porto Alegre, Porto Alegre, RS, Brazil.

Received: 29 June 2022 Accepted: 17 October 2022
Published online: 04 November 2022

References
1. Schore RJ, Devidas M, Bleyer A, Reaman GH, Winick M, Loh ML, et al. Plasma asparaginase activity and asparagine depletion in acute lymphoblastic leukemia patients treated with pegaspargase on Children’s Oncology Group AALL07P4. Leuk Lymphoma. 2019;60(7):1740–8.
2. Jeha S, Pei D, Choi J, Cheng C, Sandlund JT, Coustan-Smith E, et al. Improved CNS control of childhood acute lymphoblastic leukemia without cranial irradiation: St Jude total therapy study 16. J Clin Oncol. 2019;37(35):3377–91.
3. Ceconello DK, Rechenmacher C, Werlang I, Zenatti PP, Yunes JA, Alegretti AP, et al. Implementation of the asparaginase activity assessment technique for clinical use: experience of a Brazilian Center. Sci Rep. 2020;10:21481.
4. Van der Sluis IM, Vrooman LM, Peters R, Banuchel A, Escherich G, Goulden N, et al. Consensus expert recommendations for identification and management of asparaginase hypersensitivity and silent inactivation. Haematologica. 2016;101(3):279–85.
5. Henriksen TL, Højfeldt GS, Schmiegelow K, Frandsen TL, Wehner PK, Schroder H, Nordic Society of Pediatric Hematology and Oncology, NOPHO Group, et al. Prolonged first-line PEG-asparaginase treatment in pediatric acute lymphoblastic leukemia in the NOPHO ALL2008 protocol. Pharmacokinetics and antibody formation. Pediatr Blood Cancer. 2017. https://doi.org/10.1002/pbc.26686.
6. August KJ, Farooki S, Fulbright JM, August A, Portnoy JM, Pommert L, et al. Desensitization to pegaspargase in children with acute lymphoblastic leukemia and lymphoblastic lymphoma. Pediatr Blood Cancer. 2020;67:e28021.
7. Concha S, Barriga F, Ovalle P, Hoyos-Bachiloglu R. A twelve steps desensitization protocol for pediatric patients with hypersensitivity to PEG-asparaginase. Ann Allergy Asthma Immunol. 2020;124(2):208–10.
8. Verma A, Chenk K, Bender C, Gornay N, Leonard W, Barnette P. PEGylated *E. coli* asparaginase desensitization: an effective and feasible option for pediatric patients with acute lymphoblastic leukemia who have developed hypersensitivity to pegaspargase in the absence of asparaginase *Erwinia chrysanthemi* availability. Pediatr Hematol Oncol. 2019;36(5):277–86.
9. Swanson HD, Panetta JC, Barker PJ, Liu V, Inaba H, Reiling MV, et al. Predicting success of desensitization after pegaspargase allergy. Blood. 2020;135(1):71–5.
10. Tong WH, Pieters R, Tissing WJ, van der Sluis IM. Desensitization protocol should not be used in acute lymphoblastic leukemia patients with silent inactivation of PEGasparaginase. Haematologica. 2014;99(7):e102-4.
11. Tong WH, Pieters R, Kaspers GJ, te Loo DMWM, Bierings MB, den Bos CV, 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(13):2026–33.
12. Rizzari C, Citterio M, Zucchetti M, Conter V, Chiesa R, Colombini A, et al. A pharmacological study on pegylated asparaginase used in front-line treatment of children with acute lymphoblastic leukemia. Haematologica. 2010;95(1):24–31.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.