Desensitization protocol should not be used in acute lymphoblastic leukemia patients with silent inactivation of PEGasparaginase
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LETTERS TO THE EDITOR

Asparaginase antibodies (AAs) neutralize asparaginase and are often accompanied by a clinically overt allergic reaction, but in a proportion of the patients these antibodies occur without any signs of hypersensitivity, termed as silent inactivation.1-4 Vrooman et al. and Panosyan et al. showed that children with silent inactivation of native E. coli asparaginase had poorer outcomes as they were not switched to another asparaginase preparation that retained its activity.4 A case report described the successful use of desensitization courses in a patient with severe hypersensitivity reaction to native E. coli asparaginase.2 Therefore, we analyzed children with newly diagnosed acute lymphoblastic leukemia (ALL) from our drug monitoring program to see whether continuation of asparaginase in case of silent inactivation may have resulted in desensitization, disappearance of AAs and recovery of asparaginase activities.

All children received eight doses of native E. coli asparaginase in the induction phase. Children who were stratified as moderate or high-risk patients received 30 weeks of PEGasparaginase (15 doses). In case of an allergy to PEGasparaginase, they were switched to Erwinia asparaginase (Erwinia-asp). All asparaginase preparations were given intravenously (Online Supplementary Appendix).

Definitions of silent inactivation of PEGasparaginase and Erwinia-asp and antibody positivity of serum antibodies against native E. coli asparaginase (Coli-AAA), against PEGasparaginase (PEG-AAA), and against Erwinia-asp (Erwinia-AAA) are given in the Online Supplementary Appendix and have been previously described.6 Seven out of 89 (8%) patients had silent inactivation of PEGasparaginase. Those patients had already developed Coli-AAA during the consolidation phase after receiving native E. coli asparaginase in induction.6 Two out of 7 silent inactivation patients were switched to Erwinia-asp based upon real-time asparaginase measurements after two PEGasparaginase infusions showing asparaginase activities of zero. The other 5 patients continued with PEGasparaginase, because real-time asparaginase measurements were not available at that moment. All 5 patients achieved sufficient PEGasparaginase activities (≥100 μ/L) while continuing with PEGasparaginase.

Figure 1 shows the Coli-AAA and PEG-AAA per patient in relation to the PEGasparaginase activities over time in these 5 patients. Patient A had PEGasparaginase trough activity level of 536 μ/L after the second dose of PEGasparaginase. Three patients (B-D) had PEGasparaginase trough activities of 100 μ/L or more after the third PEGasparaginase infusion (181 μ/L; 1485 μ/L; 587 μ/L, respectively). Patient E showed a PEGasparaginase trough activity level of 381 μL after the seventh dose of PEGasparaginase. All PEGasparaginase trough activities were zero in all 5 patients till these became measurable. In all 5 patients, Coli-AAA were present already before the start of the first PEGasparaginase infusion. Thereafter, the Coli-AAA declined in all 5 patients during PEGasparaginase therapy coinciding with the rise of asparaginase activities. PEG-AAA were absent in all 5 patients at the start of the intensification phase. In one patient (A) these PEG-AAA remained absent, in 2 patients (C and D) there was a mild increase followed by a decrease to zero and in 2 patients (B and E) a strong increase and decrease to zero. The decrease in AAs coincided with the rise in asparaginase activity.

These data demonstrate that asparaginase antibodies decline over time in patients with silent inactivation of PEGasparaginase. Also in patients without an allergy and without silent inactivation, antibodies against PEGasparaginase and Erwinia-asp developed and decreased back to normal levels when continuing asparaginase for (very) prolonged time periods (Online Supplementary Figures S1 and S2).

Previous reports had described desensitization of patients with clinical allergies to asparaginase. Desensitization protocols were designed to administer asparaginase in a much lower starting dose and prolonged infusion time.7-8 The dose needs to be increased gradually, for example within a few days, till the total dose is given.9 Continuous administration of the antigen leads to a decrease in T-helper 2 cells (secreting IgE which is associated with an allergic reaction) and increase in T-helper 1 cells (responsible for delayed hypersensitivity and synthesis of IgG) resulting in less allergic symptoms.5 It has been suggested that immunosuppression induced by combined dexamethasone and asparaginase may lower antibody formation.2 The influence of subsequent dexamethasone courses as used in this therapy schedule for five days every three weeks could play an additional role in PEGasparaginase desensitization.

In contrast to the allergic patients, PEGasparaginase was continued without any clinical signs in our patients with silent inactivation. This, finally, resulted in a decrease of asparaginase antibodies and recovery of therapeutic PEGasparaginase activities (≥100 μ/L) in all patients. We thereby, unintentionally, desensitized the patients by continuing the full PEGasparaginase dose every two weeks. Sufficient PEGasparaginase activities were found for the first time after 2-7 PEGasparaginase infusions, therefore after 2-12 weeks in these patients with silent inactivation who continued PEGasparaginase.

Of note, it is questionable whether patient A indeed showed a truly silent inactivation. This patient had a PEGasparaginase trough activity level of 536 μ/L after two PEGasparaginase infusions. To avoid unintended silent inactivation diagnosis, we suggest taking 2 independent samples to confirm silent inactivation if this is suspected. Also, it should be ensured that the correct asparaginase preparation is administered, and not native E. coli asparaginase with a short half-life instead of PEGasparaginase.11

The important question is how to manage patients in case of allergy to or silent inactivation of PEGasparaginase: use a desensitization protocol or switch preparation to Erwinia-asp? Most childhood ALL protocols prescribe PEGasparaginase during a much shorter intensification period than 30 weeks. Therefore, no time is available to apply a “wait-and-see policy” and to wait to see whether desensitization occurs during an undefined time period, e.g. 2-12 weeks as found in the present study. As the intensification phase is of crucial importance in the treatment of ALL, and given that adequate asparaginase therapy improves outcome, it is not worth taking the risk of a desensitization course if this does not have a certain outcome. Therefore, we recommend a switch to Erwinia-asp in case of allergy to or silent inactivation of PEGasparaginase. Only if Erwinia-asp is not available, patients with silent inactivation of PEGasparaginase should continue this drug.

In conclusion, our data show that 5 silent inactivation patients continuing with PEGasparaginase had antibodies that declined over time. These patients had therapeutic
Figure 1. Individual Coli-AAA levels and PEG-AAA levels versus PEGasparaginase activity levels of children with silent inactivation of PEGasparaginase. Upper horizontal dotted line; PEGasparaginase activity level of 100 U/L which is associated with complete asparagine depletion (lower level of quantification of 0.2 μM). Lower horizontal dotted line; above the cut-offs: Coli-AAA and PEG-AAA positive.
PEG asparaginase activity thereafter. However, as recovery of asparaginase activity takes an unpredictable and sometimes long time period, we do not advise such desensitization approaches, but we do recommend a switch to Erwinia-asp. A significant proportion of patients treated for a prolonged period with PEGasparaginase or Erwinia-asp develops antibodies without influencing asparaginase activity that disappears with continued use of the same asparaginase product.

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The online version of this article has a Supplementary Appendix.

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