

Increasing completion of asparaginase treatment in childhood acute lymphoblastic leukaemia (ALL): summary of an expert panel discussion



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ABSTRACT

Insufficient exposure to asparaginase therapy is a barrier to optimal treatment and survival in childhood acute lymphoblastic leukaemia (ALL). Three important reasons for inactivity or discontinuation of asparaginase therapy are infusion related reactions (IRRs), pancreatitis and life-threatening central nervous system (CNS). For IRRs, real-time therapeutic drug monitoring (TDM) and premedication are important aspects to be considered. For pancreatitis and CNS thrombosis one key question is if patients should be re-exposed to asparaginase after their occurrence. An expert panel met during the Congress of the International Society for Paediatric Oncology in Lyon in October 2019 to discuss strategies for diminishing the impact of these three toxicities. The panel agreed that TDM is particularly useful for optimising asparaginase treatment and that when a tight pharmacological monitoring programme is established premedication could be implemented more broadly to minimise the risk of IRR. Re-exposure to asparaginase needs to be balanced against the anticipated risk of leukemic relapse. However, more prospective data are needed to give clear recommendations if to re-expose patients to asparaginase after the occurrence of severe pancreatitis and CNS thrombosis.

INTRODUCTION

With current multiagent chemotherapy, event-free survival (EFS) rates for children with acute lymphoblastic leukaemia (ALL) have improved substantially over the last four decades. The overall survival is now above 90% with the best available treatment programmes in high-income countries. Asparaginase therapy is a key component of these programmes. Since 1978 asparaginase is on WHO list of essential drugs.^{1,2} However, its use is associated with several toxicities that can lead to inactivation, alteration or discontinuation of therapy. Failure to receive the entire prescribed course of asparaginase therapy has been associated with lower cure rates in multiple childhood ALL studies.^{2–6} Therefore, guidelines to ensure that patients receive the full course are crucial.

An expert group met in October 2019 during the Congress of the International Society for Paediatric Oncology in Lyon to discuss strategies to achieve continued and active asparaginase treatment including therapeutic drug monitoring (TDM) for asparaginase activity levels and premedication to prevent infusion related reactions (IRRs), thus managing clinical hypersensitivity, silent inactivation and non-allergic reactions, as well as re-exposure of patients after pancreatitis and central nervous system (CNS) thrombosis.

Asparaginase

The aim of asparaginase therapy is to achieve plasma asparagine depletion (defined as less than 0.1–0.2 μM).⁶ Maximum benefit is achieved through optimal dosing and treatment schedules, which results in extended, although not necessarily continuous, depletion of asparagine.^{3,7}

Preparations and administration routes of asparaginase therapy have varied over the decades, with native *Escherichia coli* asparaginase being used originally. Intramuscular (IM) polyethylene glycolated *E. coli* asparaginase (PEG asparaginase) was first introduced as a second-line agent for patients who developed hypersensitivity after *E. coli* asparaginase therapy and later became the preferred first-line treatment in countries where it is available due to a longer half-life and greater asparaginase activity levels.^{8,9} Intravenous PEGylated (PEG) asparaginase, with a similar half-life and potency to IM administration of PEG asparaginase, is now standard of care in many but not all collaborative ALL groups, due to its better comfort. The third marketed preparation, *Erwinia* asparaginase, is derived from the bacterium *Erwinia chrysanthemi*. It is indicated for the treatment of patients with ALL who have developed hypersensitivity to

E. coli-derived asparaginase preparations.¹⁰ PEG asparaginase has a plasma half-life of 5–8 days, native *E. coli* asparaginase between 8 and 30 hours, and *Erwinia* asparaginase of 4–22 hours.

Of importance, adherence to the scheduled duration of asparagine depletion is associated with superior cure rates. Thus, in a recent Children's Oncology Group (COG) study, patients who were able to receive all scheduled exposure to asparaginase were found to be at lower risk of relapse than those for whom doses were omitted. This was also the case for patients with hypersensitivity reactions who were shifted to formulations with a shorter half-life, for example, *Erwinia* asparaginase.⁴ An earlier Dana-Farber Cancer Institute (DFCI) ALL Consortium study (91-01) showed that patients who tolerated 25 or fewer weeks of asparaginase had a significantly worse outcome than those who received at least 26 weeks of asparaginase.³ Noteworthy, 30 weeks of PEG asparaginase exposure were associated to a similar EFS whether asparaginase was administered at 2 or 6 weeks intervals.⁷

Infusion-related reactions

As a large molecule of bacterial origin, asparaginase can cause an immune reaction with neutralising antibodies decreasing asparaginase activity in treated patients. This can present with or without a clinically visible allergic reaction—the former defined as clinical hypersensitivity and the latter as silent inactivation.^{11 12}

Clinical hypersensitivity presents with local and mild to systemic and life-threatening symptoms including dyspnoea, hypotension often appearing after pruritus, oedema, rash, cough and vomiting, which can lead to discontinuation of treatment. Depending on the number of exposures and treatment lines, chemotherapy background and administration route, the rates of clinical hypersensitivity to PEG asparaginase may range from 3% to 24%.¹³

Silent inactivation is particularly relevant as the decreased and non-effective asparaginase activity is symptomless and will stay undetected if TDM is not performed. Recently with the wider use of PEG asparaginase the rate of silent inactivation has become lower than in the past with reported incidences of only 0%–8%.^{14–18}

However, non-allergic infusion reactions are becoming increasingly common with the use of intravenous PEG asparaginase. Non-allergic infusion reactions often occur shortly into the infusion and their symptoms may easily be misinterpreted as allergic hypersensitivity reactions.^{19 20} While true antibody-mediated hypersensitivity reactions occur most commonly after the second or third exposure to PEG asparaginase, the timing of infusion-related adverse events are less predictable and may already be seen with the first exposure during induction.

In the case of clinical hypersensitivity with inactivation or diagnosed silent inactivation, the standard step of management is the prompt switch to *Erwinia* asparaginase therapy. This has led to an unmodified outcome in two large COG studies devoted to National Cancer Institute

(NCI) standard risk B-ALL (AALL0331) and NCI high risk B-ALL (AALL0232).⁴

Premedication could lead to a further reduction of IRRs (see the section on Premedication below).²¹ Also it has to be recognised that regular shortages of *Erwinia* asparaginase are occurring worldwide. These have prompted some investigators to introduce so-called desensitisation protocols with the aim to re-expose to PEG asparaginase after initial reactions while ensuring efficacy.^{22 23}

Therapeutic drug monitoring

In addition to the identification of patients with silent inactivation, TDM of asparaginase can be used in clinical practice to adjust asparaginase doses in individual patients to achieve optimal asparaginase activity (eg, in the Dutch Childhood Oncology Group (DCOG) ALL 11).¹⁷ It is also increasingly used to distinguish between real hypersensitivity and non-allergic reactions.

There are different ways to undertake TDM of asparaginase therapy, yet expert consensus recommends the monitoring of serum asparaginase activity (SAA), with an SAA level ≥ 0.1 IU/mL to discriminate patients with sufficient activity to ensure therapeutic benefit. This is now the most commonly used practice.²⁴

In Europe, the DCOG, the Associazione Italiana di Ematologia e Oncologia Pediatrica (AIEOP), the Berlin-Frankfurt-Münster (BFM) group and the recently formed Western European ALLTogether consortium all recommend routine measurement of asparaginase activity in real time to identify patients needing a switch to an alternative asparaginase formulation due to inactivation. Importantly, inactivating antibodies may be directed towards the PEG component in which case a shift to native *E. coli* asparaginase rather than to *Erwinia* asparaginase would be an option.²⁵ However, PEG antibodies are not monitored outside research settings.

In addition to this application, the use of TDM as a dose-adjustment tool is increasing.^{17 18} Individualised dosing protocols using TDM to guide asparaginase dose adjustment have been associated with improved outcomes when compared with patients where asparaginase activity monitoring was not used. This is despite of the fact that the individualised group overall did not receive higher asparaginase dosing, with detection of silent inactivation as a possible explanation.²⁶

The 2016 'Consensus expert recommendations for identification and management of asparaginase hypersensitivity and silent inactivation' state that asparaginase activity should be evaluated in all patients receiving asparaginase and define silent inactivation as PEG asparaginase activity < 0.1 IU/mL on day 7 and/or below the lower limit of quantification on day 14.²⁴

When it comes to distinguishing between clinical hypersensitivity and non-allergic reactions, the occurrence of clinical symptoms without a measurable decrease in asparaginase activity can be considered evidence of a non-allergic infusion reaction rather than true allergy.²⁷ However, if the intravenous infusion of PEG asparaginase

has been stopped within minutes interpretation of low activities is not possible as the infused amount is negligible. This represents an important limitation of TDM for discrimination between non-allergic and allergic infusion reactions.

Premedication

Historically, with relatively high incidences of silent inactivation and without the availability of TDM, premedication with histamine antagonists or steroids has generally been avoided, for fear of masking clinical symptoms as the only indicator of potential inactivation of asparaginase.

Nowadays, with the possibility of measuring asparaginase activity it is unnecessary to avoid the use of premedication. Additionally, premedication has the advantage of reducing the incidence and severity of infusion-related adverse events, which can be distressing and require additional medical resources. In a recent retrospective study, universal premedication with histamine antagonists and in selected cases corticosteroids significantly reduced the rate of acute adverse event rates and thus unwarranted substitutions of PEG asparaginase to the more expensive and shorter half-life *Erwinia* asparaginase. Patients tolerated the infusion without clinical symptoms and with SAA levels above the optimal range. Also, a substantial financial saving was achieved.²¹ Importantly, this strategy requires as an indispensable prerequisite to have a tight real-time TDM in place for each PEG asparaginase dose administered to detect silent inactivation.⁴

PANEL DISCUSSION

The TDM experiences of the international AIEOP BFM ALL2009 treatment protocol, as well as the DFCI Consortium 05–001 and 11–001 and DCOG ALL11 trials,^{15 17 28} show that detection of silent inactivation after the second and further doses is achievable in real time in the context of an international protocol with one expert laboratory measuring SAA levels in each country for all the patients enrolled onto the protocol; however, at a high organisational and financial effort. Consensus expert recommendations when to measure SAA are in place and are shown in [box 1](#).²⁴ One challenge for universal TDM is that most samples will demonstrate ‘adequate’ SAA, and so testing will rarely lead to a change in clinical practice. Therefore

Box 1 Therapeutic drug monitoring: when to measure?²⁴

- ▶ With native *Escherichia coli* asparaginase, consider measuring at least trough serum asparaginase activity (SAA) level after the first dose and after every reintroduction*.
- ▶ With *Erwinia* asparaginase consider measuring at least trough SAA level 48–72 hours after the first-dose administration**.
- ▶ With PEG asparaginase consider measuring at least SAA levels within 7–14 days after each dose.

*In some protocols adopting prolonged schedules weekly monitoring is often offered/performed.

** Thereafter SAA should be measured once a week as trough level.

it could also be questioned if real time TDM should be conducted in all patients given the relatively small percentage of patients with silent inactivation or whether it should be restricted to the patient subsets that account for the highest number of relapses.

The panel agreed that (1) TDM is useful and necessary and should be undertaken in all patients treated with asparaginase, and (2) when a tight TDM is in place, premedication could also be safely included.

The cost of TDM and premedication is not trivial but is also cost saving due to fewer patients with severe IRRs, fewer patients shifting to costlier asparaginase preparations due to wrongly classified hypersensitivity which is of utmost importance in a context of unstable supply, and reduced number of relapses due to fewer patients with silent inactivation or suboptimal SAA levels.

Recommendations from the panel regarding TDM and premedication

- ▶ TDM should be undertaken in all patients treated with asparaginase.
- ▶ If TDM is undertaken, patients could also be premedicated.

Re-exposure after asparaginase-associated pancreatitis

Pancreatitis is a life-threatening toxicity of asparaginase treatment, highly associated with cumulative asparaginase dose.^{7 29–31} Depending on several factors the incidence of pancreatitis has been shown to range between 2% and 18%.³² However, comparison on incidence and severity has been hampered by varying awareness and missing consensus on definition of asparaginase-associated pancreatitis (AAP). To address the latter, 15 international childhood ALL study groups agreed on uniform diagnostic criteria for AAP.¹² These criteria are identical to globally used criteria for acute pancreatitis within gastroenterology³³ and state that at least two of the three following criteria must be met:

- ▶ Abdominal symptoms suggestive of AAP.
- ▶ Imaging findings characteristic of acute pancreatitis (ultrasound, CT or MRI).
- ▶ Serum amylase (total or pancreas specific) or lipase or both three times or more above the upper limit of normal. Studies have emphasised the importance of measuring both lipase and amylase due to poor correlation between these, and in general lipase is a better biomarker for AAP.^{30 31}

Frequent symptoms of AAP include abdominal pain, vomiting, nausea, back pain and fever. Moreover, AAP is associated with both a high risk of acute complications (hypovolemic shock, need of assisted mechanical ventilation and pseudocysts) and persisting complications (persistent need of insulin therapy and abdominal pain).^{30 31}

Age is the only clinical risk factor for pancreatitis with patients older than 6 years having a significantly increased risk of developing pancreatitis.³⁴ In addition, single-nucleotide polymorphisms (SNPs) associated with



elevated risk of alcohol-associated pancreatitis including *PRSSI-PRSS2* variants have also been found to impact the risk of AAP.²⁹ Also, a correlation between the SNPs in *MYBBP1A*, *IL16* and *SPEF2* with pancreatitis has been described.³⁵ Nevertheless, the impact of these variants is limited and predicting the risk of AAP and disease trajectories is not yet possible.³⁰

Since truncation of asparaginase therapy has been associated with reduced EFS, re-exposing AAP patients to asparaginase could be relevant to fully re-establish the probabilities of cure.⁴ However, studies on the risk of re-exposing these patients are scarce and only observational. In a large Ponte Di Legno international case based observational cohort study, Wolthers *et al* identified 96 patients who were re-exposed to asparaginase. Of these, 46% developed a second AAP.

Of note in the prospective NOPHO ALL2008 trial, out of 34 patients re-exposed to asparaginase, that is, a fifth of all patients having a first AAP, 15 developed a second AAP (44%).³⁴ In the Ponte di Legno study, no risk factors for developing a second AAP could be identified, not even timing and severity of the first AAP, presence of complications or levels of pancreatic enzymes. Importantly, the overall risk of complication and mortality rates were not higher after the second AAP compared with the first. Furthermore, after re-exposure a median of 3.5 PEG asparaginase doses were tolerated before a second AAP corresponding to more than 8 weeks of asparaginase depletion.³⁰

PANEL DISCUSSION

The expert panel discussed the lack of sufficient prospective data and how to improve the evidence regarding re-exposure after pancreatitis and the management of patients with suspected pancreatitis reaching four recommendations.

Recommendations from the panel regarding pancreatitis

- ▶ In suspected pancreatitis all patients should undergo physical examination, be evaluated by CT, ultrasound or another medical imaging modality, and be subject to blood samples including both lipase and amylase.
- ▶ All study groups should use the Ponte di Legno toxicity working group consensus criteria for pancreatitis.
- ▶ In case of AAP and if asparaginase therapy is truncated, the decision on re-exposure should balance the anticipated risk of relapse vs the risk of a second AAP.
- ▶ Randomised studies are difficult to perform in this setting but at least prospective studies are encouraged to develop evidence-based guidelines for re-exposure. These studies should re-expose patients based on clear inclusion and exclusion criteria and provide adequate guidelines on how to manage the clinical course.

Re-exposure after CNS thrombosis

Though CNS thrombosis is a relatively rare event in patients treated with asparaginase, an important clinical question is when and who to re-expose to asparaginase

after its occurrence. Asparaginase is associated with a decrease in the production of several proteins involved in coagulation and fibrinolysis and may increase the risk of thrombosis.^{36–38} More than two-thirds of asparaginase-associated thrombotic events occur within 4 weeks after asparaginase administration.³⁹ One challenge is that they are likely attributable to multiple factors. Thus, male gender, older age, concomitant drugs and genetically determined thrombophilia factors may all play a role.⁴⁰ The incidence of symptomatic thrombosis varies in clinical trials and has been reported with both *E. coli*—and *Erwinia*-derived asparaginase. The frequency of CNS thrombosis in patients treated with asparaginase varies between 0.4% and 5% and in general accounts for almost one-third of all thromboses observed in children with ALL.^{39–45} Literature specific to CNS thrombosis is limited and it is difficult to extract evidence on the results of re-exposure to asparaginase in CNS thrombosis cases. The recurrence rate varies between 0% and 17%, but is based on too few patients to draw reliable conclusions.^{44 46 47} The DCOG ALL10 study found that recurrence probably cumulates with the initial thrombosis risk for long term sequelae, mostly epilepsy (9 out of 22 survivors of 26 cases with CNS thrombosis).⁴³

PANEL DISCUSSION

Due to the lack of data, the currently available management recommendations in different protocols are vague if not absent. They include the possibility of re-exposure to asparaginase once thromboprophylaxis (mostly low-molecular-weight heparin) is given, clinical symptoms have completely resolved, and MRI imaging has normalised or at least fully stabilised. Special conditions such as the presence of a Factor V Leiden or other genetic predispositions need to be considered. It is up to the clinician to weigh the risk of leukaemia recurrence versus the genetic thrombophilic condition and the risk of local recurrence of thrombosis.

Recommendation regarding CNS thrombosis

- ▶ There is a so far unmet need for large and deeply phenotyped cohorts of ALL patients with asparaginase-associated thrombosis.
- ▶ Re-exposure with asparaginase should be considered provided low-molecular-weight heparin is given, clinical symptoms have resolved and MRI imaging has normalised or at least fully stabilised.

CONCLUSION

Failure to receive the entire prescribed course of asparaginase therapy has been associated with increased risk of relapse in childhood ALL. The panel agreed that TDM should be implemented broadly and that premedication together with TDM may be important to lower the IRRs caused by asparaginase. More prospective data are needed to give clear recommendations regarding whom

to re-expose to asparaginase after the occurrence of pancreatitis and CNS thrombosis.

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