LETTER TO THE EDITOR
Pharmacokinetic and Clinical Considerations for Monitoring Asparaginase Activity Levels During Pegaspargase Therapy

To the Editor: We read with interest the report by Bleyer et al. providing recommendations for therapeutic drug monitoring of asparaginase (ASNase) activity levels during treatment with pegaspargase [1]. Adequate asparagine depletion has been correlated with improved clinical outcomes and we applaud the authors' initiative in developing and sharing a protocol for monitoring ASNase activity levels during pegaspargase therapy [2,3]. However, we would like to comment on several parameters outlined in the proposed recommendation.

The authors suggest a target ASNase activity level of $\geq$0.05 IU/ml 4–7 days following pegaspargase treatment. However, based on in vivo pharmacokinetic/pharmacodynamic (PK/PD) models from the AALL07P4 trial and an analysis by Douer et al., a target level of $>$0.05 IU/ml is inadequate [4,5]. With a mean half-life of 5–7 days, PK/PD data suggests that on days 4–7, ASNase activity levels are typically between 0.6–1.2 IU/ml depending on the dose utilized and whether the dose is given during induction or consolidation [4,5]. Levels are near the higher end of this range with larger doses (e.g., 2500 IU/m^2) and during consolidation courses. More importantly, following pegaspargase treatment, asparagine repletion occurs when ASNase activity levels drop below 0.2–0.4 IU/ml [4,5]. This is in contrast to earlier data with native *Escherichia coli* ASNase in which asparagine repletion occurred when ASNase activity dropped below 0.1 IU/ml [6,7]. Using the proposed algorithm by Bleyer et al., a level of 0.1 on days 4–7 would prompt no change in therapy, yet at levels this low, asparagine is likely no longer depleted. With pegaspargase, the majority of patients' ASNase activity levels do not drop below 0.2 IU/ml until day 21 [4,5]. A day 4–7 ASNase level which is already below 0.2 likely indicates the formation of neutralizing antibodies and should prompt clinicians to seriously consider switching to Erwinia asparaginase. Patients who have adequate levels on day 4–7 but low day 14–21 trough levels ($<$0.2) can be considered for a pegaspargase dose increase or interval decrease.

The authors recommend testing ASNase activity for patients with clinical hypersensitivity and in those with prior exposure to ASNase, such as in the relapsed setting. However, there is little to no correlation between the formation of anti-ASNase antibodies and clinical hypersensitivity reactions [8]. Hypersensitivity does not always lead to antibody production, and antibody production can occur despite a lack of hypersensitivity. For example, in the CCG-1961 trial, 29% of patients without clinical hypersensitivity developed anti-ASNase antibodies and had a significantly higher relapse rate [8,9]. Thus, it is difficult to discern based upon clinical parameters which patients may benefit from monitoring ASNase activity levels. Testing ASNase activity solely in patients with clinical hypersensitivity or prior exposure may lead to overlooking patients who are at an increased risk of therapeutic failure associated with inadequate asparagine depletion. Due to the relatively low cost of ASNase activity testing compared with the cost of relapse, the clinical availability of the assay, and the strong correlation between asparagine depletion and improved survival, we believe ASNase activity levels should be monitored in all patients undergoing pegaspargase therapy.

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Abbreviations: ASNase, asparaginase; PK/PD, pharmacokinetic/pharmacodynamic

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