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UNC Pediatric Hematology / Oncology Clinical Guidelines

Topic: Asparaginase Administration and Supportive Care

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**These guidelines have been developed to aid clinicians in making informed decisions about leukemia patients. It is not intended to take the place of physician judgement. Recommendations may not be appropriate in all circumstances.

Summary / Recommendation:

1) Pre-medications: All patients receiving PEG-asparaginase should receive pre-medications
    a. Benadryl 0.5-1 mg/kg (maximum 50 mg/dose) PO or IV
    b. Famotidine 1 mg/kg/dose (maximum 20 mg/dose) PO

2) Administration: PEG-Asparaginase should be administered over 2 hours#

3) Therapeutic Drug Monitoring*: Asparaginase level should be collected:
    a. 1 hour after completion of PEG-asparaginase infusion
    b. 7 ± 3 days after PEG-asparaginase infusion
    c. Patients with asparaginase level .01 < 0.4 at Day 7 ± 3 after receiving PEG-asparaginase should be have a repeat asparaginase level drawn at Day 14 ± 3

4) Re-challenge**: In addition to premedication above, patient with previous reactions to PEG-asparaginase who will be re-challenged should all receive hydrocortisone of a pre-medication:
    a. Hydrocortisone 1 mg/kg/dose (maximum 100 mg) IV

5) Switch to Erwinia Asparaginase:
    a. Patients with Grade ≥ 3 adverse event occurring after premedication.
    b. Patients with asparaginase level < 0.1 at Day 7 ± 3 after receiving PEG-asparaginase should be switched to Erwinia. (This level suggest the presence of a neutralizing antibody)
    c. Patients with asparaginase level .01 < 0.4 at Day 7 ± 3 after receiving PEG-asparaginase should be have a repeat asparaginase level drawn at Day 14 ± 3 and discussed at tumor board

#Priming and vitals monitoring –

- Priming – 15 milliliters over 5 minutes
- Vital signs will monitored every 15 minutes for the first hour and every 30 minutes in the second hour. Patients will be kept on continuous pulse oximetry throughout the infusion.

*Lab Ordering – Order referral lab and enter in comments “Asparaginase assay activity”. The asparaginase activity levels are collected in red top tubes and sent to NEXT molecular analytics. The lab does not accept Saturday specimens, so levels obtained on Fridays are not sent until Monday. Turn-around time is 24 hours, but the referral lab uploading results can take an extra day.

**Re-challenge infusions –

- Infusions on Tuesdays and Fridays will only start after completion of all sedation
- Patients will be placed on continuous cardiorespiratory monitoring and pulse oximetry

Background / Data Summary:[1-3]

Asparagine depletion with various forms of asparaginase is important to treat lymphoblastic leukemia and lymphoblastic lymphoma. Currently, two forms of asparaginase are available in the United States. E. coli asparaginase in pegylated format and Erwinia chrysanthemi in immediate acting format. The pegylated form of E. coli asparaginase (PEG-asparaginase) is the preferred form because of prolonged, sustained asparagine depletion and ease of administration. When PEG-asparaginase is not tolerated due to severe infusion reaction or inactivation, patients can be treated with Erwinia asparaginase.

Concerns with PEG-asparaginase reactions are twofold.

1) Immediate clinical concern for anaphylaxis
2) Manifestation of inactivation of asparaginase, leading to ineffective anti-leukemic therapy

In the absence of pre-medications or therapeutic drug monitoring, reports consistently indicate that ~20% of patients are switched from PEG-asparaginase (E. coli derived) to Erwinia asparaginase. The problems with transitioning to Erwinia asparaginase are three-fold.

1) Decreased prolonged, sustained depletion of asparagine, potentially reducing anti-leukemic effect
2) Patient experience because effects Erwinia asparaginase must be delivered intramuscularly.
3) Cost to the patient, hospital, health system

Recent publications describing a combination of premedication for all patients receiving PEG-asparaginase combined with therapeutic drug monitoring, showed

1) Reduction in adverse events for patients receiving PEG-asparaginase
2) Reduction in patients switching to Erwinia asparaginase
3) Safe re-challenge of patients with previous reactions to PEG-asparaginase who had not received premedication prior to previous reaction.

With the above data, we are implementing routine premedication and therapeutic drug monitoring for all patients receiving PEG-asparaginase.

References:

1 Marini, B. L. *et al.* A single-center multidisciplinary approach to managing the global Erwinia asparaginase shortage. *Leuk Lymphoma*, 1-15, doi:10.1080/10428194.2019.1608530 (2019).

2 Cooper, S. L. *et al.* Universal premedication and therapeutic drug monitoring for asparaginase-based therapy prevents infusion-associated acute adverse events and drug substitutions. *Pediatr Blood Cancer* **66**, e27797, doi:10.1002/pbc.27797 (2019).

3 Salzer, W., Bostrom, B., Messinger, Y., Perissinotti, A. J. & Marini, B. Asparaginase activity levels and monitoring in patients with acute lymphoblastic leukemia. *Leuk Lymphoma* **59**, 1797-1806, doi:10.1080/10428194.2017.1386305 (2018).