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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) Products :
    a. Pegylated asparaginase products:
        i. ONCASPAR (pegaspargase): current use only for patients aged ≥22 years
        ii. ASPARLAS (calaspargase pegol – mknl): current use is for patients aged 1 month to 21 years.
    b. All other asparaginase products:
        i. RYLAZE (asparaginase erwinia chrysanthemi (recombinant) rywn): patients aged 1 month or older who have developed hypersensitivity to *E.coli*-derived asparaginase or those who require short-acting asparaginase product (i.e. Capizzi cytarabine in AML or relapsed ALL therapy)

2) Pre-medications (administer 30-60 minutes prior to asparaginase administration):
    a. ASPARLAS (calaspargase pegol – mknl):
        i. Diphenhydramine 0.5-1 mg/kg (maximum 50 mg/dose) PO or IV
        ii. Famotidine 1 mg/kg (maximum 20 mg/dose) PO or IV
        iii. Acetaminophen 15 mg/kg (maximum 650 mg/dose) PO or IV
        iv. Ondansetron 0.15 mg/kg (maximum 8 mg/dose) IV
    b. RYLAZE (asparaginase erwinia chrysanthemi (recombinant) rywn):
        i. Ondansetron 0.15 mg/kg/dose (maximum 8 mg/dose) IV
        ii. Can consider addition of diphenhydramine, famotidine, and/or acetaminophen at doses above if patient has had a previous reaction to RYLAZE.

3) Administration:
    a. ASPARLAS (calaspargase pegol – mknl):
        i. Product should be administered as an IV infusion over 2 hours total, with 10% of the infusion administered over the first hour and the remaining 90% administered over the second hour
            1. Rapid prime 15 mL over 5 minutes before infusion starts.
            2. Administer ~10% (13 mL/hr) for first hour, then administer ~90% (117 mL/hr) for second hour until infusion is complete.
            3. Infusion instructions are standard for all patients, regardless of patient-specific total volume. Infusion may finish slightly before or after 2-hour mark.
        ii. Vital signs will be monitored every 15 minutes for the first hour and every 30 minutes in the second hour. Observe for 1 hour post infusion.

iii. Patients will be kept on continuous pulse oximetry throughout the infusion
iv. Dosing for obese patients (≥95% BMI for patients < 20 years):
1. Dose capping at 3,750 units/dose is permissible in cases of baseline obesity.

b. RYLAZE (asparaginase erwinia chrysanthemi (recombinant) rywn):
i. Intramuscular (IM) injections on Monday (25 mg/m^2), Wednesday (25 mg/m^2), Friday (50 mg/m^2) dosing schedule.
1. Monday and Wednesday doses should be administered between 0800 - 0900
2. Friday dose should be administered at 1400 or later
ii. Patients should NOT be scheduled for every 48-hour dosing unless admitted to the hospital
iii. Patients will be monitored for one hour post injection

4) Hypersensitivity reactions:
a. Treatment plans have emergency orders prepopulated in the event of a reaction. For complete guidelines for treatment, please visit the Pediatric Infusion Hypersensitivity & Anaphylaxis Reactions Guidelines on the Pharmacy Clinical Guidelines Intranet page.
i. PRN Hypersensitivity medications should be pulled from Pyxis and available for use at bedside
ii. Medications should be returned to Pyxis machine after completion of 1 hour post-infusion monitoring
b. Serum asparaginase activity (SAA) levels obtained during a reaction should be interpreted with caution for patients who did not receive the full dose of medication.
c. Ammonia levels are optional and should be interpreted with caution as no evidence supports direct correlation with infusion reactions and/or silent inactivation.
i. MUST be sent on ice or the lab will reject specimen

5) Therapeutic Drug Monitoring:
a. ASPARLAS (calaspargase pegol – mknl):
i. SAA levels should be standardly collected:
1. 1 hour after completion of infusion
2. 7 ± 3 days after infusion
3. Patients with SAA levels of <0.4 at Day 7 ± 3 should have a repeat level on day 14 ± 3 after infusion

Time Point After Infusion Complete	Serum Asparaginase Activity	Action
1 hour	< 0.5 IU/mL	Switch to RYLAZE
7 days	< 0.3 IU/mL	Switch to RYLAZE
14 days	< 0.1 IU/mL	Switch to RYLAZE

b. RYLAZE
i. At this time, SAA levels are not standardly indicated following doses of RYLAZE as levels are unlikely to influence clinical decisions.
ii. Providers reserve the right to order SAA level should they be concerned about silent inactivation and therefore would consider discontinuation of the drug.
1. Consult clinical pharmacist for timing of lab draw.
c. How to order SAA levels:
i. Order “asparaginase enzyme activity” lab. This is a send-out lab.
ii. The levels are collected in red top tubes and sent to NEXT molecular analytics.
iii. Levels are batched and sent out on Mondays and Thursdays only.
1. Levels obtained on a Friday afternoon, or over the weekend, will not be sent out until Monday.

iv. Turn-around time is 24-72 hours, but the uploading of results can take additional days.

6) Re-challenge ASPARLAS:
    a. Patients *should* be re-challenged with ASPARLAS (calaspargase pegol – mknl) if they had a grade 1 or 2 adverse event occurring after premedication and had therapeutic SAA levels.
        i. In the event a re-challenge is to be attempted before SAA levels result, proceed with re-challenge and either continue with calaspargase pegol – mknl desensitization or switch to RYLAZE if necessary based on SAA levels as they result.
    b. Patients being re-challenged with ASPARLAS (calaspargase pegol – mknl) should receive the following pre-medications:
        i. Diphenhydramine 0.5-1 mg/kg (maximum 50 mg/dose) PO or IV
        ii. Famotidine 1 mg/kg (maximum 40 mg/dose) PO
        iii. Acetaminophen 15 mg/kg (maximum 1000 mg/dose) PO or IV
        iv. Either hydrocortisone 1 mg/kg (maximum 100 mg) IV, methylprednisolone 1 mg/kg (maximum 125 mg) IV or similar corticosteroid
    c. Patients will be placed on continuous cardiorespiratory monitoring and pulse oximetry

7) Desensitization ASPARLAS:
    a. Initial calaspargase pegol – mknl desensitization is to occur inpatient at NC Children's Hospital
        i. Discussion between primary attending and 5CH nurse manager must occur in advance to determine whether desensitization can occur on 5CH vs. PICU.
        ii. Patient must have 1:1 nursing care for the entire desensitization and for 1 hour after the completion of infusion.
    b. Patient factors to consider with a calaspargase pegol – mknl desensitization:
        a. Patient is considered to have a true IgE-mediated hypersensitivity over other nonallergic infusion reactions.
        b. Patient is not a silent inactivator to calaspargase pegol – mknl based on SAA levels.
    b. Scheduled pre-medications
        a. Evening prior to desensitization
            i. Diphenhydramine 1 mg/kg IV (max 50 mg)
            ii. Famotidine 1 mg/kg IV (max 20 mg)
            iii. Methylprednisolone 2 mg/kg IV (max 125 mg)
            iv. Montelukast 4-10 mg PO (age-based dosing)
        b. 1 hour prior to infusion start
            i. Montelukast 4-10 mg PO (age-based dosing)
            ii. Ondansetron 0.15 mg/kg IV (max 8 mg)
        c. 30 minutes prior to infusion start
            i. Acetaminophen 15 mg/kg (maximum 650 mg/dose) PO or IV
            ii. Diphenhydramine 1 mg/kg IV (max 50 mg)
            iii. Famotidine 0.5 mg/kg IV (max 20 mg)
            iv. Methylprednisolone 2 mg/kg IV (max 125 mg)
        d. All PRN hypersensitivity reaction (HSR) medications must be pulled from Pyxis and available at bedside prior to start of infusion.
    c. Dosing strategies
        a. Dose: calaspargase pegol – mknl 2,500 units/m^2 rounded down to the nearest measurable dose
            i. Drug preparation:
                1. Dosage form: 3,750 units/5 mL (750 units/mL) in a single-dose vial

2. Calaspargase pegol – mknl drug volume mixed with NS to equal a concentration between 10-15 units/mL
3. Drug is stable for *** hours once mixed

d. Administration Time:
    a. Desensitization will be completed in ~3 hours if infusion is able to be titrated as written
e. Example Desensitization:
    a. The same bag will be used for the entirety of the desensitization and WILL be completely infused
    b. Bag concentration: 10-15 units/mL
    c. Example steps:
        i. Step 1: Start at 1 mL/hr for 15 minutes
        ii. Step 2: Increase to 2 mL/hr for 15 minutes
        iii. Step 3: Increase to 4 mL/hr for 15 minutes
        iv. Step 4: Increase to 8 mL/hr for 15 minutes
        v. Step 5: Increase to 15 mL/hr for 15 minutes
        vi. Step 6: Increase to 30 mL/hr for 15 minutes
        vii. Step 7: Increase to 60 mL/hr for 15 minutes
        viii. Step 8: Increase to 90 mL/hr for 15 minutes
        ix. Step 9: Increase to 120 mL/hr for 15 minutes
        x. Step 10: Increase to 150 mL/hr for remainder of infusion

8) <u>Switch to RYLAZE</u>:
    a. All above indications, or patients with Grade ≥ 3 adverse event occurring after premedication.

Background / Data Summary:

Asparagine depletion with various forms of asparaginase is important to treat lymphoblastic leukemia and lymphoblastic lymphoma. Currently, there are two forms of asparaginase available for use in pediatric acute lymphoblastic leukemia, lymphoblastic lymphoma, and acute myeloid leukemia. Calaspargase pegol-mknl (ASPARLAS), a pegylated long-acting formulation, and asparaginase erwinia chrysanthemi (recombinant)-rywn (RYLAZE ™) an immediate acting formulation. Previously, E.coli asparaginase in its pegylated form (ONCASPAR) had been used in pediatric patients, however since December 01, 2022, ONCASPAR is now only being used in patients greater than or equal to 22 years.

The pegylated form of asparaginase (ASPARLAS) is the preferred form because of prolonged, sustained asparagine depletion and ease of administration. When ASPARLAS is not tolerated due to severe infusion reaction or inactivation, patients can be treated with RYLAZE. (**see comparison table on page 6**).

Concerns with ASPARLAS reactions are twofold:

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

In the absence of premedication or therapeutic drug monitoring (SAA levels), reports consistently indicate that ~20% of patients are switched from pegylated asparaginase formulations to Erwinia asparaginase. The concerns with transitioning to Erwinia asparaginase are three-fold:

1) Reduction in prolonged, sustained depletion of asparagine, potentially reducing anti-leukemic effect
2) Patient experience - delivered intramuscularly and requires 6 doses and therefore, 6 clinic visits for every 1 dose of calaspargase-pegol
3) Increased cost to the patient, hospital, and health system

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

1) Reduction in adverse events for patients receiving ASPARLAS
2) Reduction in patients switching to RYLAZE
3) Safe re-challenge of patients with previous reactions to pegylated asparaginase products (ONCASPAR or ASPARLAS) 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 pegylated asparaginase products.

The RYLAZE package insert recommends 9 doses of RYLAZE to replace a single dose of ASPARLAS, administered on a Monday, Wednesday, Friday schedule. This accounts for the 3 weeks (21 days) of asparaginase depletion ASPARLAS would have provided for the patient had they tolerated the dose. However, most pediatric studies have been successfully completed with 14 days of asparaginase depletion, and therefore 14 days of coverage is sufficient. Patients needing to switch to RYLAZE after failing ASPARLAS will need to complete 6 doses of RYLAZE for each ASPARLAS dose using a Monday, Wednesday, Friday dosing schedule. It is possible this standard may change in the future.

Asparaginase formulations:

There are only two formulations available for pediatric patients at this time, both highlighted in blue, RYLAZE™ and ASPARLAS™. Drugs in columns that are grey are no longer available to pediatric patients.

	E. coli-asparaginase	E. coli asparaginase pegylated	Calaspargase	Asparaginase erwinia chrysanthemi	Asparaginase erwinia chrysanthemi (recombinant)-rywn
Brand name	ELSPAR®	ONCASPAR®	ASPARLAS™	ERWINAZE™	RYLAZE™
Date Approved	1978	1994	2018	2011	2020
Bacteria derived from	*Escherichia coli*			*Erwinia Chrysanthemi*	*Pseudomonas fluorescens*
Common name	Asparaginase	PEG-asparaginase	Calaspargase pegol-mknl	Asparaginase *Erwinia chrysanthemi*	Asparaginase *Erwinia chrysanthemi (recombinant)-rywn*
Protein modification	None (Native)	Pegylated	Pegylated	None (Native)	None (Recombinant)
Half-life	Short 26 hours	Long 6 days	Long 16 days	Short 16 hours	Short 18.2 hours
Frequency of administration	Every 24 hours	Every 14 days	Every 21 days	Three times weekly	Every 48 hours Or M/W/F
Route of administration	IV/IM	IV/IM	IV	IV/IM	IM

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