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Positive Quality Intervention: Sodium Thiosulfate Injection (PEDMARK®) To Prevent Platinum-Induced Ototoxicity in Pediatric and Adolescent or Young Adult (AYA) Patients

Description: This PQI aims to provide clinical data on the use, administration, and timing of sodium thiosulfate (STS) injection to prevent platinum-induced ototoxicity in pediatric patients and the AYA population.

Background:

Irreversible ototoxicity is a dose limiting side effect of cisplatin therapy.[1] Chemotherapy related hearing loss during childhood has been associated with social, cognitive, and educational impairments with effects carried into adulthood.[2,3] Additionally, as cisplatin is the backbone of chemotherapeutic treatment of testicular cancer, most commonly diagnosed in men in their late 20s to early 30s, safeguarding against lifelong ototoxicity is a critical need.

Sodium thiosulfate (STS) received FDA approval in 2022 to reduce the risk of cisplatin-associated ototoxicity in pediatric patients 1 month of age and older with localized, nonmetastatic solid tumors.[4] STS interacts directly with cisplatin via it's thiol group leading to platinum species inactivation, increases intracellular endogenous antioxidant activity, and scavenges reactive oxygen species, accumulation of which may contribute to cochlear hair cell loss and ultimately ototoxicity.[4,6]

The ACCL0431 trial evaluated hearing loss at 4 weeks post treatment in patients aged 1 to 18 years receiving cisplatin with or without STS for a variety of solid tumor types. Hearing loss occurred in 14 of 49 (28.6%, 16.6, 43.3) patients who received STS versus 31 of 55 patients (56.4%, 42.3, 69.7) treated with cisplatin alone (p=0.00022). Adjusted for stratification variables including prior cranial irradiation, age group, and duration of cisplatin infusion, the likelihood of hearing loss was significantly lower in the STS group compared with control group (odds ratio 0.31, 95% confidence interval 0.13, 0.73; p=0.0036). Another trial, SIOPEL 6, evaluated absolute hearing threshold in children >1 month and <18 years old being treated with cisplatin with or without STS for hepatoblastoma. Administration of STS resulted in a 48% lower risk of hearing loss after treatment with cisplatin.[8]

The National Comprehensive Cancer Network® (NCCN) guidelines recommend the use of STS to prevent cisplatin-induced ototoxicity in pediatric and AYA patients 15-39 years of age (category 2A).[5]

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PQI Process:

- Ensure patient meets parameters for STS prophylaxis
  - ≥ 1 month of age
  - Localized, non-metastatic solid tumor prescribed cisplatin-containing treatment regimen
  - Cisplatin infusion to be administered over 6 hours or less
- Dose

Actual Body Weight	PEDMARK Dose
Less than 5 kg	10 g/m^2
5 to 10 kg	15 g/m^2
Greater than 10 kg	20 g/m^2

- Administration
  - Wait 6 hours post completion of cisplatin infusion prior to STS administration
  - Monitor serum sodium and potassium levels at baseline and as clinically indicated (withhold STS in patients with serum sodium greater than 145 mmol/L)
  - Assess need for administration of antiemetics 30 to 60 minutes prior to STS administration (see antiemetic guidance below)
  - Administer STS via IV infusion over 15 minutes
  - Wait at least 10 hours after STS administration before giving another cisplatin infusion
- Antiemetic guidance
  - Nausea occurred in 8% to 40% of STS patients in clinical trials, with Grade 3 or 4 in 3.8 to 8%. Vomiting occurred in 7% to 85% of patients in clinical trials, with Grade 3 or 4 in 7% to 8%[4]
  - Example appropriate antiemetic premedication regimen (adapted from NCCN Antiemesis Guidelines – High Emetic Risk Parenteral Anticancer Agents Acute and Delayed Emesis Prevention[9])
    - Neurokinin-1 receptor antagonist, plus
    - Serotonin (5-HT3) receptor antagonist, plus
    - Corticosteroid
- Hypersensitivity
  - Hypersensitivity reactions occurred in 8% to 13% of patients in clinical trials[4]
  - Immediately discontinue STS infusion and institute appropriate care if a hypersensitivity reaction occurs
  - Administer antihistamines +/- glucocorticoids (if appropriate) before each subsequent administration of STS if hypersensitivity reaction occurs
  - Permanently discontinue STS for Grade 3 or 4 hypersensitivity

Patient-Centered Activities:

- Review administration schedule of STS especially in relation to cisplatin infusion
- Counsel patient/caregiver on risk of nausea/vomiting
    - If STS to be administered outpatient, ensure patient/caregiver understands prescribed antiemetic regimen and what to take prior to STS infusion
- Advise patient/caregiver that hypersensitivity reactions can occur with STS infusion and that patient will be monitored for this reaction. Patient should alert care team if they develop signs of allergic reaction including rash, hives, chest tightness, wheezing, swelling of the face, lips, tongue, or throat
- Advise patient/caregiver that STS can cause changes in patients' serum sodium and potassium levels and the care team should be alerted if patient develops persistent/worsening fatigue or weakness, restlessness, muscle weakness, or seizures
- Conduct routine evaluations for tinnitus and periodic audiogram to monitor hearing loss associated with platinum-based chemotherapy.[5]
- Financial support resources available at Fennec HEARS™ | PEDMARK® (sodium thiosulfate injection)

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OPTIONAL SODIUM THIOSULFATE (PEDMARK®) PROTOCOL:

NOTE: *Due to the unusual nature of the STS (Pedmark) being delayed for 6 hours s/p Cisplatin completion, the protocol when used in ambulatory care patients, should be scheduled such that each patient is given two appointments daily: one for early morning for traditional treatment and then allow the patient to return in the afternoon for the STS (Pedmark) infusion – similar to how hyperfractionated radiation is administered twice in a treatment day (in that there will be a morning (cisplatin chemotherapy) & afternoon (Pedmark treatment).*

☐ Appropriate diagnosis of _____ (IV cisplatin in a patient 1 month to 39 years of age)

☐ Appropriate monitoring of CBC and chemistries to ensure normal sodium and potassium levels prior to starting of cisplatin infusion.

☐ Appropriate antiemetic predication regimen (contains 5HT3 Receptor antagonist like palonosetron, plus an NK1-inhibitor like fosnetuipitant or an IV dose of a combination of those drugs like netupitant/palonosetron) plus corticosteroid like dexamethasone (with dexamethasone dose lowered per manufacturer recommendation), and the possible inclusion of an H-2 Blocker like famotidine and an antihistamine such as diphenhydramine 25mg IVPB or cetirizine 10mg IVP as clinician believes is warranted). The use of long-acting anti-emetics is best to cover the STS (Pedmark®) delivered 6 hours post the cisplatin infusion's completion.

☐ Premeds administered 30-minutes prior to initiation of cisplatin chemotherapy

☐ Cisplatin chemotherapy is administered over a time NTE a rate of ~1mg/minute or as your institutional protocol allows. Once the Cisplatin is completed – the protocol starts a 6-hour timer, at the completion of 6 hours, the infusion of STS (Pedmark®) begins. [**NOTE**: in multi-day cisplatin regimens, ensuring enough time to allow **10 hours minimally** between finish of STS infusion and the beginning of the next dose if IV cisplatin]

☐ STS (Pedmark®) is then dosed based on body weight (see table below) and prepared in an empty infusion bag and administered over 15 minutes. The medication once prepared is only stable for 18 hours at room temperature and the unused portion should be discarded.

☐ Optional – audiogram testing to document hearing prior to initiation of cisplatin chemotherapy.