Dinutuximab (Unituxin®) Care Guideline

Inclusion Criteria:
- High risk neuroblastoma (NBL) patients receiving Dinutuximab with chemotherapy
- Post-autologous stem cell transplant NBL patients (maintenance therapy)
- Count Requirements:
  - Platelets ≥ 20,000/µL
  - Creatinine < 1.5 mg/dL
  - No evidence of serious infection

Exclusion Criteria:
- Patients not eligible for Dinutuximab

Interventions

- Admit to Oncology
- Nursing ratio: 1:2 on infusion days
- For Children's Oncology Group (COG) protocol patients: confirm study labs are completed and check on study labs throughout treatment days (may need pain scales documented, etc.)

Line Access
- If patient has single lumen CVAD, place PIV on day of first Dinutuximab infusion
- CVAD lines will be heavy due to multiple connections.
  - Ensure line is well secured to avoid pulling or dislodgement of line.

Administration/Dosing
- **Dosage:** 17.5 mg/m^2/day x 4 consecutive days
  - *Begin Dinutuximab 1 hour after GM-CSF (Granulocyte-macrophage colony-stimulating factor).*
- **Medication handling:** Dinutuximab is a will call medication, request from pharmacy 1 hour prior.
  - Has **short stability of 4 hours**, must be hung within 4 hours.
- **Infusion:** given over 14 hours (manufacturer allows 10 - 20 hours).
  - Infusion must come down at hour 20 even if saline flush is still running.
- **Premedication and Supportive Care Medication:**
  - *Begin Dinutuximab 1 hour after GM-CSF (Granulocyte-macrophage colony-stimulating factor)*
  - IV hydration – NS 10mL/kg IV bolus 1 hour prior to infusion. TKO fluids during infusion, or per providers order. Limit amount of IV fluids during infusion to prevent capillary leak syndrome
  - Initiate an opiate continuous infusion/PCA for all patients at the start of therapy
    - For subsequent cycles, consider initiating the same opioid and dosing regime that provided adequate pain control in the prior cycle
    - Upon completion of the course, reduce the PCA dose by 50% for 4 hours, then discontinue and reassess pain control
  - Diphenhydramine IV (0.5 to 1 mg/kg - max dose 50 mg) 20 minutes prior to infusion and q6h ATC
  - Acetaminophen PO (10 to 15 mg/kg - max dose 650 mg) 20 minutes prior to infusion and q4h ATC (max - 75mg/kg/day or 4000mg/day)
  - Gabapentin 5mg/kg/dose (max - 300mg) PO TID, and increase further as needed per provider discretion.
  - Famotidine 0.5 mg/kg/dose (max - 20mg) IV q12h
  - Ibuprofen 10 mg/kg/dose (max – 800mg) q6h PO prn for fever/pain provided patient has adequate platelets and adequate renal function.

Clinical Monitoring
- Place on monitor during infusion
- Vital sign (VS) protocol during infusion:
  - q15 min x 4
  - q30 min x 2
  - q1 until completion of the infusion.
  - If stable 1 hour post infusion, resume q4h per unit protocol
- Strict I&O q4h
- Weight and urine dips BID during infusion days
- Daily Labs:
  - CBC, CMP, Phosphorus
  - Magnesium levels: x2/week or per provider
  - Labs should be drawn once Dinutuximab is complete, if patient does not have double lumen CVAD.
  - Blood cultures: for first fever, pause infusion, wasting 4-5 mL of blood, flush with saline and restart infusion.
    - ➢Consider delaying subsequent blood cultures until after Dinutuximab infusion is complete.

Diet and Activity
- As tolerated

Interventions *(completed in between doses of Dinutuximab):*

- Maintain albumin levels ≥ 3.0 g/dL
  - Give 25% albumin followed by furosemide
- Maintain hemoglobin > 8 g/dL & platelets > 20k
  - Transfusion PRBCs & platelets if under these levels.
- IVIG may interfere with Dinutuximab – avoid IVIG within 2 weeks before and one week after completion of therapy.

Patient Education

- Review expected side effects, necessary interventions and monitoring parameters throughout infusions.
- Educate patient/parents about IVIG and steroids.
- Provide: Unituxin® parent handbook

Discharge Criteria

- Afebrile
- Negative blood cultures
- Pain controlled with oral medications after narcotic PCA is weaned off.
- Ensure patient has GM-CSF doses at home.

Approved Evidence Based Medicine Committee
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Managing Adverse Reactions

For patients experiencing hypotension, increased pain, tachycardia, tachypnea, or high fever – Slowing the infusion rate may assist with decreasing these side effects.

Corticosteroid therapy: Corticosteroids may impair the immune activation that is a critical part of this therapy. Reserve for life-threating conditions, unresponsive to other measures.

If life-threatening reactions occur, stop infusion.

Reaction Signs & Symptoms	Management/Treatment Considerations	Treatment Modifications
Infusion Reactions • Localized urticaria • Rash • Fever • Rigors • Mild bronchospasm to severe cases of angioedema; coughing may be an early sign	• Monitor closely for signs and symptoms of infusion reactions during and for ≥ 4 hours after infusion *Coughing* • If occasional cough occurs, unrelated to anaphylaxis, consider giving bronchodilators and additional antihistamines • Administer oxygen even in the absence of desaturations, to provide comfort and symptom relief	**Onset of mild to moderate adverse reactions (transient rash, fever rigors, localized urticaria that responds to symptomatic treatment):** • Reduce infusion rate by 50% and monitor closely • Administer supportive care measures *After resolution:* • Gradually resume infusion up to a maximum rate of 1.75 mg/m^2/hour • If not tolerated, reduce by 50% **Prolonged or severe adverse reactions (mild bronchospasm without other symptoms, angioedema that does not affect the airway):** *Onset of reaction:* • Pause dinutuximab – administer supportive measures *After resolution:* • If s/s resolve rapidly, resume infusion at reduced rate by 50% and observe closely *First recurrence:* • Discontinue infusion for that day • If symptoms resolve and continued treatment is warranted, premedicate with IV hydrocortisone 1 mg/kg (max dose: 50 mg) and administer infusion at a rate by 50% in PICU. *Second recurrence:* • Permanently discontinue infusion
Capillary Leak Syndrome ***Monitor for:*** • Weight gain • I&Os imbalance • Increased specific gravity (1.030) • Low albumin level • Edema • Vital sign changes (hypotension, tachycardia)	• Early detection and intervention are critical • Assess for edema • Strict I&Os • Monitor electrolytes, hemoglobin, albumin • Maintain oncotic pressure with hemoglobin and albumin in upper limits of normal	**Moderate to severe, but not life-threatening** *Onset of reaction:* • Pause infusion *After resolution:* • Resume infusion at 50% **Life-threatening** *Onset of reaction:* • Discontinue infusion for the current cycle *Subsequent cycles:* • Administer infusion at 50% the previous rate *First recurrence:* • Permanently discontinue dinutuximab

Hypotension
• Systolic blood pressure (SBP) less than the lower limit of normal of age, or SBP decreased by more than 15% compared to baseline
	• Vital signs monitoring (see p1 – Clinical Monitoring)
	• Administer NS bolus, decrease or stop narcotic dose if possible.
		Onset of reaction:
		• Pause infusion
		After resolution:
		• Resume infusion at 50%
		• If BP remains stable for ≥ 2 hours, increase infusion as tolerated to max rate of 1.75 mg/m^2/hour
		First recurrence:
		• Pause infusion
		• Resume infusion at 50% once blood pressure is stable
		In the presence of persistent hypotension, consider the following:
		• Reassess perfusion, end-organ functionality
		• Consider repeat normal saline bolus, OR:
		  • Give albumin if < 3.0 g/dL
		  • Transfuse RBCs if Hgb < 8 g/dL
		If the patient is transferred to PICU:
		• After blood pressure is stable (normotensive) and the patient has been off pressors for 6 hours, dinutuximab may be resumed

Fever • Can be persistent and up to 40°C	• Obtain blood cultures • No antibiotics needed unless history of previous infections or any s/s of infection. • Consider ibuprofen (5-10 mg/kg) q6h, as needed for control of persistent fever or pain	• Continue infusion – unless systemic infection develops • If systemic infection or sepsis (positive blood culture) occurs, discontinue infusion until resolution of infection, the proceed with subsequent cycles of therapy
Neuropathic Pain ***Common Sites:*** • Generalized • Extremity • Back • Abdominal • Musculoskeletal chest pain • Can also report: • Neuralgia or Arthralgia	*Utilize PCA as ordered* *Onset of pain:* • Titrate dosing and consider changes to other medications *Continued pain:* • Change dosing or medication, consult pain management *Severe pain:* • Decrease Unituxin rate by 50%	• Pause infusion if pain is not adequately controlled despite infusion rate reduction and institution of maximum supportive measures. Resume infusion at 50% when pain is controlled.
Ocular Toxicities **Monitor for:** • Fixed, dilated or unequal pupils • Photophobia • Optic nerve disorder • Mydriasis • Eyelid ptosis • Papilledema • Blurred vision	• Pause infusion in patients experiencing dilated pupils with sluggish light reflex or other visual disturbances that do not cause vision loss	*Onset of reaction:* • Discontinue infusion until resolution *After resolution:* • Reduce the infusion dose by 50% *First recurrence or if accompanied by vision loss:* • Permanently discontinue infusion

References

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