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Positive Quality Intervention: Brentuximab Vedotin (Adcetris®): Neuropathy and Neutropenia Management

Description: Brentuximab vedotin is a CD30-directed antibody drug conjugate (ADC) indicated as front-line treatment for patients with classical stage III/IV Hodgkin's Lymphoma (cHL) or CD30-expressing peripheral T-cell lymphomas (PTCL) in combination with multiagent chemotherapy.[1] This PQI will review how to safely manage select toxicities associated with brentuximab vedotin.

Background: ADCs offer a unique modality of drug delivery to cancer cells expressing specific targets. In the case of brentuximab vedotin (BV), a monomethyl auristatin E (MMAE) is attached via a linker to a mAb directed against CD30. Upon binding to CD30 on the cell surface, BV is internalized and the linker is cleaved to release MMAE, which then exerts its cytotoxic effect.[1] The efficacy of brentuximab vedotin for cHL and CD30-expressing PTCL was established from the Echelon-1 and Echelon-2 trials, respectively.[2,3] In both trials, outcomes favored the BV + chemotherapy combination over standard of care chemotherapy. For PTCL, only a positive expression of CD30 is required for patients to be eligible for therapy.[1] Adverse events included neuropathy and hematologic toxicities.[1-3] Clinicians need to be aware of recommended interventions to optimally and safely manage neuropathy and neutropenia in patients receiving brentuximab vedotin. This is particularly important in patients with HL as they can be treated with curative intent.

PQI Process:

- **Neutropenia Prevention and Management**
  - Patients initiating front-line therapy with brentuximab vedotin for HL or PTCL should receive granulocyte colony-stimulating factor (G-CSF) beginning with Cycle 1, Day 1
  - The choice of G-CSF therapy should follow institutional standard and formulary. The use of long acting G-CSF agents is appropriate when indicated as both treatment regimens are administered every 14 or 21 days
  - Brentuximab vedotin for HL offers a bleomycin-free treatment option for patients
  - All patients who experience Grade ≥3 neutropenia who did not receive primary G-CSF prophylaxis should receive it with subsequent cycles
  - CBC with differential should be assessed prior to each dose of brentuximab vedotin
- **Neuropathy Prevention and Management**
  - Neuropathies, primarily sensory rather than motor, may be seen in approximately >50% of patients. In clinical trials, most patients experienced only Grade 1 or 2 neuropathy and majority improved with intervention
  - Symptoms of hypo- or hyperesthesia, paresthesia, discomfort, burning sensation, weakness, tingling and neuropathic pain should be assessed with each cycle
  - Counsel patients to report any numbness or tingling in their hands or feet or muscle weakness

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Table: Dose Adjustments for Neuropathy

Brentuximab Vedotin Dose[1]	Grade	Intervention
1.8 mg/kg (max 180 mg) every 3 weeks + CHP*	2	Sensory: Continue Motor: Reduce to 1.2 mg/kg
	3	Sensory: Reduce to 1.2 mg/kg Motor: Discontinue
	4	Discontinue
1.2 mg/kg (max 120 mg) every 2 weeks + AVD**	2	Reduce to 0.9mg/kg
	3	Hold until recovers to ≤ grade 2 and restart at 0.9 mg/kg Consider modifying other neurotoxic chemo
	4	Discontinue

* PTCL indication in combination with cyclophosphamide, doxorubicin and prednisone
**HL indication in combination with doxorubicin, vinblastine, and dacarbazine

Patient Centered Activities:

- Educate patients to report any fevers or signs of an infection such as coughing or congestion to their healthcare provider immediately
    - Some patients may require supportive care with G-CSF agents for neutropenia; supplemented with antihistamines if associated bone pain occurs (ex. Loratadine)
    - Patients should contact their provider if they utilize the *Neulasta On-Pro* device and have any warning sounds/lights or if the device is removed
- Many patients (especially those with HL) may under report symptoms due to a concern of diminished efficacy with interventions. Building a rapport with these patients and helping them understand the balance between safety and efficacy is important
    - Tests to help assess for neuropathy include buttoning a shirt or picking up a coin off of a flat surface
    - Colder temperatures may exacerbate the neuropathies
    - Patients who initially do not report with a caregiver and later do could be underreporting symptoms

References:

1. Adcetris® (brentuximab vedotin) [prescribing information]. Bothell, WA: Seattle Genetics; November 2018.
2. Connors JM, Jurczak W, Straus DJ, et al. Brentuximab Vedotin with Chemotherapy for Stage III or IV Hodgkin's Lymphoma. *N Engl J Med*. 2018;378(4):331-344.t
3. Horwitz S, O'connor OA, Pro B, et al. Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): a global, double-blind, randomised, phase 3 trial. *Lancet*. 2019;393(10168):229-240.