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Positive Quality Intervention: Tisotumab vedotin-tftv (Tivdak®) Management

Description: Tisotumab vedotin-tftv is FDA approved for treatment of recurrent or metastatic cervical cancer in patients with disease progression on or after chemotherapy. This PQI will provide information on the management of common adverse events and follow-up required.

Background: Tisotumab vedotin-tftv is first in class antibody drug conjugate that contains a humanized IgG1-kappa monoclonal antibody directed at tissue factor and is conjugated to a microtubule-disrupting agent (monomethyl auristatin E or MMAE) via a protease-cleavable linker. After binding to tissue factor, tisotumab vedotin-tftv is internalized and releases MMAE via proteolytic cleavage resulting in microtubule disruption and cell death. The tisotumab vedotin-tftv FDA approval for recurrent or metastatic cervical cancer was based on the innovaTV 204 clinical trial showing 24% objective response rates and 72% disease control rate.[3] The recommended dose is 2 mg/kg with a maximum dose of 200 mg for patients with weight greater than 100 kg. The median overall survival was 12.1 months and median duration of response was 8.3 months. The most common treatment related adverse events with incidence ranging from 23% to 38% included alopecia, epistaxis, nausea, conjunctivitis, fatigue, and dry eye. The incidence of grade 3 or worse adverse events was 28% or seen in 28 patients out of 101 patients. These included neutropenia, fatigue, ulcerative keratitis, and peripheral neuropathies. Due to the increased incidence of eye toxicities, patients who will be on therapy with tisotumab vedotin-tftv require multiple eye drops, cooling of eyes during infusion, and eye exam prior to each and every dose. Treatment related bleeding events occurred in 39% of patients, including 30% of patients who experienced epistaxis. Patients should be monitored closely for bleeding events.
***Severe cutaneous adverse reactions, including events of fatal or life-threatening Stevens-Johnson syndrome (SJS), have been reported in patients treated with TIVDAK. A cumulative analysis across all safety data sources inclusive of clinical trial and post-marketing data as of 24 May 2023 identified two patients treated with TIVDAK who had severe cutaneous adverse reactions that were considered serious. Both cases were reported as SJS, one of which had a fatal outcome.**

PQI Process: Upon receiving order of tisotumab vedotin-tftv for administration:

- Confirm appropriateness for the specific patient utilizing pertinent information from the EMR
- Ensure that the patient has had an eye exam prior to treatment and has been sent eye drop prescriptions (Table 1)
- Check with the nurse that the patient has brought all the eye drops to the clinic and appropriate eye cooling patch or pads are available in clinic for patient to cool the eyes
    - Many practices are using ice packs with a barrier (to keep condensation from dripping into the patient's eye) when cooling pads are unavailable *not recommended by the manufacturer*
- Review the order for any specific dose adjustment if needed (Table 2)
- Drug interaction consideration: close follow-up of patients who are on concomitant strong CYP3A4 inhibitors is required as strong CYP3A4 inhibitors may increase unconjugated MMAE exposure; this in turn may increase the risk of tisotumab vedotin-tftv adverse events
- Review adverse events (AE) and management as required (Table 3)

Patient-Centered Activities:

- Patient Education
    - Provide eye care guide sheet from Tivdak® website
    - Educate and explain how to administer various eye drops and provide a checklist for patients to remind them about the dosing of their eye drops

- Ensure patient understands the importance of an eye exam prior to each dose
  - Assist patients to schedule these exams
  - Encourage patients to report any eye problems (dry eye, blurry vision, irritation, redness)
- Educate the patient on when to contact the care team and adverse events that should be reported to the care team:
  - Fever of 100.4° F
  - Unusual bleeding (ex. nose bleeds that will not stop, bruises, vaginal bleeding)
  - Black/tarry stools or bloody urine
  - Tingling in fingers and toes
  - Nausea/vomiting/diarrhea
  - Shortness of breath
- Encourage patients to report any new medications started by other providers

References:

1. Tivdak (tisotumab vedotin) [prescribing information].
2. Hong DS, Concin N, Vergote I, et al. Tisotumab Vedotin in Previously Treated Recurrent or Metastatic Cervical Cancer. Clin Cancer Res. 2020;26(6):1220-8.
3. Coleman RL, Lorusso D, Gennigens C, et al. Efficacy and safety of tisotumab vedotin in previously treated recurrent or metastatic cervical cancer (innovaTV 204/GOG-3023/ENGOT-cx6): a multicentre, open-label, single-arm, phase 2 study. Lancet Oncol. 2021;22(5):609-19.

Supplemental Information:

Table 1: Eye Care Requirements

Ophthalmic Exam (visual acuity and slit lamp)	Prior to starting treatment and prior to each dose.
Topical corticosteroids eye drops	Administer 1 drop in each eye 10 minutes prior to infusion and continue for additional 2 times at home on day 1. Continue 1 drop per eye 3x per day on days 2 and 3 after infusion as well.
Topical ocular vasoconstrictor eye drops	Administer 3 drops in each eye 10 minutes prior to infusion.
Topical lubricating eye drops	Administer 1 drop in each eye daily for the duration of therapy and for 30 days after the last dose of therapy. However, Eye care providers may prescribe different frequency of lubricating eye drops due to baseline eye exam.
Cooling eye packs/pads	Start cooling the eyes ~ 10 mins prior to infusion and continuing for a total of 60 minutes. Rotate cooling pads as needed.
Contact Lens	Patients should be instructed to avoid wearing contact lenses throughout therapy.

Table 2: Dose Modifications:

Starting Dose	2 mg/kg
First Dose Reduction	1.3 mg/kg
Second Dose Reduction	0.9 mg/kg
Third Dose Reduction	Permanently Discontinue

Table 3: Adverse events and management

Adverse Event	Severity/Grade	Dose Modification
Keratitis	Superficial punctate keratitis (SPK) (any occurrence)	Monitor
	Confluent superficial keratitis (first occurrence)	Hold until it improves to SPK or normal, then resume at next lower dose
	Confluent superficial keratitis (second occurrence)	Permanently discontinue
	Ulcerative keratitis or perforation (any occurrence)	Permanently discontinue
Conjunctival Ulceration	Any ulceration (first occurrence)	Hold until normal, then resume treatment at next lower dose
	Any ulceration (second occurrence) + scarring or symblepharon (any occurrence)	Permanently discontinue
Conjunctivitis and other ocular AE	Grade 1 (any occurrence)	Monitor
	Grade 2 (first occurrence)	Hold until Grade ≤1; resume at same dose
	Grade 2 (second occurrence)	Hold until Grade ≤1; resume at next lower dose
	Grade 2 (third occurrence) or Grade 3 or 4 (any occurrence)	Permanently discontinue
Peripheral Neuropathy	Grade 2 initial or worsening of pre-existing (any occurrence)	Hold until Grade ≤1; resume at next lower dose
	Grade 3 or 4 (any occurrence)	Permanently discontinue
Hemorrhage	Any grade pulmonary or CNS (any occurrence) OR Grade 3 in any other location (second occurrence) OR Grade 4 in any other location	Permanently discontinue
	Grade 2 in any other location (any occurrence) or Grade 3 in any other location (first occurrence)	Hold until resolved, resume at same dose
Pneumonitis	Grade 2 (any occurrence)	Hold until Grade ≤1 for persistent or recurring pneumonitis; consider resuming at next dose
	Grade 3 or 4 (any occurrence)	Permanently discontinue
Severe Cutaneous Adverse Reactions, Including Stevens-Johnson Syndrome	Any signs/symptoms	Hold until etiology of the reaction has been determined
	Grade 3 or 4 (any occurrence)	Permanently discontinue