Written By: Shraddha Kansagra, PharmD, BCOP
University of Texas Southwestern Medical Center

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 with disease progression on or after chemotherapy was based on the innovaTV 301 clinical trial. The recommended dose is 2 mg/kg with a maximum dose of 200 mg. Median overall survival was 11.5 months with tisotumab vedotin-tftv (95% CI: 9.8-14.9) vs 9.5 months with IC chemotherapy (95% CI: 7.9-10.7) (P=0.0038). Median progression-free survival was 4.2 months with tisotumab vedotin-tftv (95% CI: 4.0-4.4) vs 2.9 months with IC chemotherapy (95% CI: 2.6-3.1) (P<0.0001). Objective response rate was 17.8% with tisotumab vedotin-tftv vs 5.2% with IC chemotherapy (P<0.0001). The most common (≥25%) adverse reactions including laboratory abnormalities, were hemoglobin decreased, peripheral neuropathy, conjunctival adverse reactions, nausea, fatigue, aspartate aminotransferase increased, epistaxis, alopecia, alanine aminotransferase increased, and hemorrhage. 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 the first 9 cycles, and as clinically indicated. Hemorrhage occurred in 51% of patients with cervical cancer treated with TIVDAK across clinical trials. The most common all grade hemorrhage adverse reaction was epistaxis (33%). Patients should be monitored closely for bleeding events.[1-2]
***Severe cutaneous adverse reactions, including events of fatal or life-threatening Stevens-Johnson syndrome (SJS), have been reported.**

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
    - Practices are using ice packs with a barrier (to keep condensation from dripping into the eye) when cooling pads are unavailable *not recommended by the manufacturer*
- Review the order for any specific dosing and potential 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
- Avoid use with moderate or severe hepatic impairment; monitor closely with mild hepatic impairment
- Review adverse events (AE) and management as required (Table 3)

Patient-Centered Activities:

- Provide Intravenous Cancer Treatment Education (IVE) Sheet
- 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 every cycle for the first nine cycles
    - Assist patients in scheduling 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
- Advise females of reproductive potential to use effective contraception during treatment and for 2 months after the last dose; advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 4 months after the last dose

References:

1. Tivdak (tisotumab vedotin) [prescribing information].
2. Tisotumab vedotin vs chemotherapy in recurrent or metastatic cervical cancer (innovaTV 301). National Library of Medicine. Updated March 12, 2024. Accessed March 26, 2024. https://clinicaltrials.gov/study/NCT04697628.

Supplemental Information:

Table 1: Eye Care Requirements

Ophthalmic Exam (visual acuity and slit lamp)	Prior to starting treatment and prior to each dose for the first 9 cycles
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 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 (max 200 mg)
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	Nonconfluent superficial keratitis (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 or corneal scarring or symblepharon	Any scarring or symblepharon	Permanently discontinue
Conjunctivitis and other ocular AE	Nonconfluent superficial punctate conjunctival defects, mild vasodilation (any occurrence)	Monitor
	Confluent superficial punctate conjunctival defects, moderate to severe vasodilation (first occurrence)	Hold until resolution or improvement; resume at same dose
	Confluent superficial punctate conjunctival defects, moderate to severe vasodilation (second occurrence)	Hold until resolution or improvement. If no resolution or improvement, permanently discontinue
	Confluent superficial punctate conjunctival defects, moderate to severe vasodilation (third 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