Tisotumab vedotin-tftv

An HCP Tool from AIM with Immunotherapy

Tisotumab vedotin-tftv (Tivdak®) is an antibody-drug conjugate that links an antibody directed against tissue factor to a microtubule inhibitor drug. It indicated for the treatment of adult patients with for recurrent or metastatic cervical cancer with disease progression on or after chemotherapy.

Clinical trial results of tisotumab vedotin-tftv

In a phase 3 innovaTV 301 (NCT04697628) study, tisotumab vedotin-tftv was shown to significantly improve overall survival, progression-free survival and objective response rate versus chemotherapy.

- There was a 30% reduction in the risk of death with tisotumab vedotin-tftv vs chemotherapy (investigator's choice of either topotecan, vinorelbine, gemcitabine, irinotecan, or pemetrexed).
- There was a clinical median overall survival of 11.5 months vs 9.5 months for those treated with chemotherapy.
- Confirmed objective response rate was 17.8% for tisotumab vedotin-tftv versus 5.2% with chemotherapy.
- Most patients (87.6%) experienced adverse effects [grade ≥3: 29.2%], like ocular, peripheral neuropathy, and bleeding.

Molecular biology and pharmacology

The class of therapeutics that encompasses antibody-drug conjugates contain agents with three components: the monoclonal antibody, the chemotherapy payload, and the linker which connects these molecules. Some antibodies may have multiple linkers and several payloads attached. The antibody is directed against a cell-surface receptor on the cancer cell. Essentially, antibody-drug conjugates are a sophisticated means of delivering therapeutics directly into cancer cells.

Tissue factor is highly expressed in cervical cancer cells and increased among patients with metastasis. In this way, tisotumab vedotin-tftv is a human monoclonal immunoglobulin G1 that uses tissue factor to enhance delivery of the chemotherapeutic payload more selectively to cervical cancer cells. This spares normal cells in the surrounding milieu and minimizes collateral damage, which is a major limitation of chemotherapy.

More specifically, tisotumab vedotin-tftv is composed of the human antibody conjugated to a protease-cleavable linker to a payload. The payload of tisotumab vedotin-tftv is monomethylauristatin E, which is an antimitotic agent that targets the tubulin pathway. It binds to tubulin and inhibits microtubule polymerization, causing growth arrest. Tubulin dynamics are a major target for taxane chemotherapy drugs. A benefit of tisotumab vedotin-tftv is its induction of bystander killing from freed monomethylauristatin E that impacts surrounding cancer cells.

Binding of the antibody to the receptor causes internalization of the antibody-drug conjugate into the cell. Alternatively, nonspecific endocytosis or micropinocytosis may also internalize the payload into the cell. Once inside the cell, cellular trafficking occurs and the cargo is sorted through the endosomal compartments. These compartments have sequentially lower pH which detaches the payload from the linker and the antibody. Once free, the payload interferes with a key molecular process required by the cancer cell. Usually, these processes are involved in DNA synthesis, transcription, cell replication, or tubulin dynamics required for mitosis. When these critical processes fail repeatedly, the cell dies.

DRUG DOSING AND ADMINISTRATION

Prior to infusion

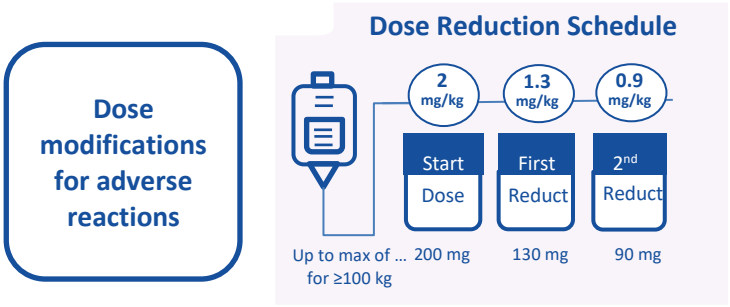
Premedication and eye care is necessary before, during, and after infusion. Due to the association of severe ocular toxicities with antibody-drug conjugates, an ophthalmic exam should be performed before each of the first nine cycles of tisotumab vedotin-tftv. The exam should assess any ocular symptoms, visual acuity, and slit lamp exam of the anterior segment of the eye. Some symptoms reported by patients include blurred vision and foreign-body sensation. Conjunctivitis may present as a sign with 26-31% of patients manifesting it, none at or above grade 3.

Administration

The recommended dose for tisotumab vedotin-tftv is 2 mg/kg (up to a maximum of 200 mg for patients ≥100 kg) administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity.

Dose Reduction Schedule

For adverse reaction response to tisotumab vedotin-tftv, modifications of the dose may be necessary. The graphic illustrates the dose reduction schedule. After the recommended starting dose 2 mg/kg (up to a maximum of 200 mg for patients ≥100 kg), the first dose reduction ("Reduct" in the graphic) is 1.3 mg/kg or up to a maximum of 130 mg for patients (≥100 kg). For the second dose reduction, 0.9 mg/kg or up to a maximum of 90 mg for patients (≥100 kg) is given.



SIDE EFFECTS AND MANAGEMENT

The most common adverse reactions, including laboratory abnormalities, of tisotumab vedotin-tftv were hemoglobin decrease, peripheral neuropathy, conjunctival adverse reactions, nausea, fatigue, aspartate aminotransferase increased, epistaxis, alopecia, alanine aminotransferase increased, and hemorrhage.

Ocular Toxicity

There is a boxed warning associated with tisotumab vedotin-tftv for ocular toxicity. Ocular adverse effects were reported in a majority (60%) of patients during clinical trials. The drug can cause severe ocular toxicities resulting in changes in vision, including severe vision loss and corneal ulceration. Patients should avoid wearing contact lenses for the entire duration of therapy.

Although the mechanisms are unclear, this adverse effect is associated with antibody-drug conjugates and must be managed to minimize treatment interruption and drug discontinuation. Ocular toxicities are hypothesized to be off-target effects that are attributed to the chemotherapy payload, not the antigen expressed on normal cells or the antibody.

Premedications are required, eye drops are continued during the infusion, and after the dose of tisotumab vedotin-tftv. An ophthalmic exam should be performed before each of the first nine cycles of tisotumab vedotin-tftv administered.

Most ocular events are reversible with dose delay or dose reduction. Tisotumab vedotin-tftv is withheld upon ocular toxicity until resolution or clinical improvement. After improvement, the drug is resumed at a reduced dose. In the case of severe toxicity, tisotumab vedotin-tftv may be permanently discontinued. With any scarring or symblepharon associated with conjunctival or corneal scarring, the drug is permanently discontinued.

PRE-MEDICATION, POST-INFUSION AND MANAGEMENT

Cold packs: Patients should use cooling eye pads during each infusion
Topical corticosteroid eye drops: one drop in each eye prior to each infusion. Continue to administer eye drops in each eye three times daily for 72 hours after each infusion.
Topical lubricating eye drops: Administer for therapy duration and for 30 days after the last dose
Topical ocular vasoconstrictor drops: Administer in each eye immediately prior to each infusion

Peripheral Neuropathy

Microtubule inhibitor antineoplastic agents commonly cause peripheral neuropathy. In antibody-drug conjugates, this is especially frequent with vedotin or monomethylauristatin E. Tisotumab vedotin-tftv resulted in 11%-39% of patients reporting peripheral neuropathy, with 6%-7% grade ≥3. At grade 2, withhold dose until Grade ≤1, then resume treatment at the next lower dose level. The drug is permanently discontinued for grade 3 or 4. Duloxetine decreases pain and nonpainful symptoms of peripheral neuropathy, like numbness and tingling.

Bleeding

In a phase II trial, treatment-related bleeding occurred in 39% of patients receiving tisotumab vedotin-tftv. The bleeding may manifest as rectal hemorrhage, cystitis hemorrhage, epistaxis, or vaginal bleeding. At grade 2, in any location other than pulmonary or CNS, withhold until resolved, then resume treatment at the same dose. At grade 3, in any location other than pulmonary or CNS, withhold until resolved, then resume treatment at the same dose. For the second grade 3 occurrence or first grade 4, permanently discontinue. With any grade of hemorrhage in the pulmonary system or CNS, permanently discontinue tisotumab vedotin-tftv.

Pneumonitis

In clinical trials, less than 1% of patients experienced pneumonitis. Unfortunately, severe, life-threatening, or fatal pneumonitis can occur in patients treated with antibody drug conjugates containing vedotin. Patients should be monitored for pulmonary symptoms including hypoxia, cough, dyspnea or interstitial infiltrates on radiologic exams.

In addition, infectious, neoplastic, and other causes for such symptoms should be excluded through appropriate investigations. For grade 2, the dose is withheld until Grade ≤1, then resumed at the next lower dose level. Permanently discontinue if grade 3 or 4 effects present.

Other Serious Adverse Events

A report of a patient with an **infusion site extravasation** injury occurred with tisotumab vedotin-tftv. It is a rare but serious adverse event of antibody-drug conjugates. The antimitotic payload, monomethylauristatin E, is similar to taxanes used in chemotherapy, which have vesicant-like effects. The antibody is neutral.

For infusion site extravasation, prompt identification and an attempt to aspirate the agent before removing the canula is necessary. Then, use of daily application of topical clobetasol 0.05%, opioids, and Mepitel One Silicone and PolyMem Silver dressing may resolve the injury. Surgical intervention and consultation with plastic surgery may be necessary. To avoid future extravasation, an implanted central venous access device placement occurred prior to the next cycle.

For suspicions of **severe cutaneous adverse reactions**, including Stevens-Johnson syndrome, immediately withhold the dose of tisotumab vedotin-tftv. Then, consult with a specialist to confirm the diagnosis. Do not administer the drug. Stevens-Johnson syndrome is a life-threatening reaction related to pharmacogenetics. It causes the skin to detach and may be fatal. In clinical trials, severe cutaneous reactions occurred in 1.6% of patients with cervical cancer. One patient had a fatal outcome.

Although clinical trials occur under varying conditions and cannot be directly predictive of the clinical experience, severe reactions may occur. During clinical trial, **33% of patients had serious adverse reactions** and 15% of patients permanently discontinued tisotumab vedotin-tftv as a result of the reaction. The most common serious reactions were urinary tract infection (4.8%), small intestinal obstruction (2.4%), sepsis (2%), abdominal pain (2%), and hemorrhage (2%).

Fatal adverse reactions occurred in 1.6% of patients during clinical trials. These manifested as acute kidney injury (0.4%), pneumonia (0.4%), sepsis (0.4%) and Stevens-Johnson syndrome (0.4%).

Based on the mechanism of action and animal studies, tisotumab vedotin-tftv can case fetal harm. Patients should be advised to use effective contraception during treatment and for 2 months after the last dose for females and for 4 months after the last dose for males.

OTHER TAKEAWAYS ABOUT ADMINISTRATION

- Premedication is required for ocular toxicity
- Most side effects occur during the initial doses and are not likely to lead to discontinuation
- Educate patients and caregivers about side effects and the importance of reporting symptoms as soon as possible.
- Advise patients to take pictures of any skin changes for documentation

QUESTIONS & ANSWERS

Q. **How long will patients stay on tisotumab vedotin-tftv?**

A. The healthcare provider will decide how many infusions are needed for each patient receiving treatment with tisotumab vedotin-tftv. The drug will be administered by intravenous infusion into the vein over 30 minutes with cold packs on the eyes during each infusion.

Q. **Are there signs that a patient can identify that may indicate bleeding or hemorrhage?**

A. There are some signs or symptoms of bleeding during treatment with tisotumab vedotin-tftv. These may include blood in the stool, which looks like black tar, blood in the urine, coughing up blood, vomiting blood, unusual vaginal bleeding, or any other unusual or heavy bleeding.

Q. **How would a patient know if they are having a severe skin reaction to the drug?**

A. Patients who experience severe skin reactions may see rings on the skin, have rashes or itching that continues to get worse, have blisters or see peeling of their skin, have fever or flu-like symptoms, see swollen lymph nodes or have painful sores or ulcers in the mouth, nose, throat, or genital area.

Q. **How often do patients discontinue tisotumab vedotin-tftv due to adverse events?**

A. There is a low rate of discontinuation due to adverse events. In the clinical trial, 15% of patients permanently discontinued tisotumab vedotin-tftv due to treatment-related adverse events.

PATIENT RESOURCES

ADDITIONAL INFORMATION RESOURCES

American Cancer Society
https://www.cancer.org/

This is Living With Cancer
Health and wellness, personal stories and articles.
https://www.thisislivingwithcancer.com

NIH: National Cancer Center
https://www.cancer.gov/types/cervical

FINANCIAL ASSISTANCE

Pfizer Patient Assistance Program
Provides free Pfizer medicines to eligible patients through their doctor's office or at home.
https://www.pfizerrxpathways.com/resources/patients

Cancer Financial Aid Coalition
Facilitates communication, educates and advocates for patients.
www.cancerfac.org

Centers for Medicare and Medicaid Services (CMS)
Apply to determine if you are eligible for government assistance.
www.cms.gov or www.medicare.gov
1-800-633-4227

Lazarex Foundation
Provides assistance with travel costs for clinical trial participation. Ask your social work counselor for a referral if you have been consented to a clinical trial for melanoma.
www.lazarex.org

Needymeds
Database to search for free or low-cost medications, help with medical transportation and other resources.
www.needymeds.org

Patient Advocate Foundation
Provides assistance with mediation, financial stability, and other assistance. Funds subject to availability. Patient must meet their eligibility for financial assistance.
www.patientadvocate.org
1-800-532-5274

The Sam Fund for Young Adult Survivors of Cancer
Assists cancer survivors ages 21-39 with their transition into post-treatment life. This program distributes grants and scholarships in an effort to enable survivors to pursue goals.
www.thesamfund.org
info@thesamfund.org

PRESCRIPTION ASSISTANCE

CancerCare Co-Payment Assistance Foundation
Helps with the cost of medication. Availability of funds for patients with Stage IV melanoma subject to availability.
www.cancercarecopay.org
1-866-552-6729

Medicine Assistance Tool
Database to search for patient assistance resources offered by pharmaceutical companies.
www.medicineassistancetool.org/

Patient Advocate Foundation Co-Pay Relief
Provides direct financial support to patients who medically qualify. Availability of funds for patients with Stage IV melanoma subject to availability.
www.copays.org
1-866-512-3861

Good Days
Formerly known as the Chronic Disease Fund. Provides assistance with insurance co-pays, and prescription medications. Availability of funds for patients with Stage IV melanoma subject to availability.
www.mygooddays.org

HealthWell Foundation
For patients who cannot afford insurance premiums, co-payments, co-insurance, or other out-of-pocket health care costs. Availability of funds for patients with Stage IV melanoma subject to availability. Patient must also meet eligibility for financial assistance.
www.healthwellfoundation.org or grants@healthwellfoundation.org
1-800-675-8416

The Assistance Fund, Inc
Provides prescription copay and financial assistance, including health insurance premiums. Availability of funds for patients with Stage IV melanoma subject to availability.
www.theassistancefund.org
1-855-845-3663

PAN Foundation
Provides financial assistance to cover out-of-pocket treatment costs. Availability of funds for patients with Stage IV melanoma subject to availability.
www.panfoundation.org
1-866-316-PANF (7263)

Patient Assistance Program
Comprehensive database of patient assistance programs offering free medications.
www.rxassist.org
info@rxassist.org

HOUSING

American Cancer Society – Hope Lodge
Provides free housing during treatment appointments. Requires a referral from your social worker.
www.cancer.org/
1-800-227-6333

American Cancer Society – Extended Stay America
Partnership to offer discounted rooms for patients who have to be away from home for cancer treatment.
https://www.cancer.org/about-us/our-partners/extended-stay-america.html
1-800-227-2345

Healthcare Hospitality Network
Connects patients and their caregivers looking for lodging near their healthcare provider
https://members.hhnetwork.org/locate-a-house
1-800-318-8861

Joe's House
Helping patients with cancer find lodging throughout the U.S.
https://www.joeshouse.org/lodging?state=0
1-877-563-7468

National Council of State Housing Agencies
Emergency rental assistance programs available by state. Federal grants still available in some areas.
https://www.ncsha.org/emergency-housing-assistance/

TRANSPORTATION (AIR AND GROUND)

Air Charity Network
Provides access for people in need who are seeking free air transportation to specialized health care facilities
http://aircharitynetwork.org/
1-877-621-7177

Corporate Angel Network
Nonprofit organization that helps cancer patients by arranging free travel on corporate aircraft
https://www.corpangelnetwork.org/
info@corpangelnetwork.org
1-914-328-1313

Medicaid
Ground transportation only. Sets up rides and provides mileage reimbursement for Medicaid patients only.
1-877-633-8747

Mercy Medical Angels
Provides free medical transportation (flights, gas cards, bus and train tickets) for patients with financial needs who need to travel more than 50 miles. Patients must meet their eligibility for financial assistance.
www.mercymedical.org/

Pilots for Patients
Provides free flights to people in need of medical treatment. Patient must be medically stable to fly and be ambulatory. Ask your social worker about a referral.
www.pilotsforpatients.org
1-318-322-5112

ADDITIONAL RESOURCES

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Markides DM, Hita AG, Merlin J et al. Antibody-Drug Conjugates: The Toxicities and Adverse Effects That Emergency Physicians Must Know. *Ann Emerg Med*. 2024:S0196-0644(24)01142-9. doi: 10.1016/j.annemergmed.2024

Son J, Cain KE, Marten CA et al. Tisotumab vedotin extravasation injury in a patient with recurrent cervical cancer. *Gynecol Oncol Rep*. 2024;56:101525. doi: 10.1016/j.gore.2024.101525

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U.S. Food and Drug Administration. FDA approves tisotumab vedotin-tftv for recurrent or metastatic cervical cancer. Available at https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-tisotumab-vedotin-tftv-recurrent-or-metastatic-cervical-cancer. Accessed 12.12.24. Updated 4.29.2024.