American Board of Optometry (ABO)

Learning Through Clinical Care
Clinical Case Report
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Ocular Adverse Effects of Tivdak® Infusion Therapy

Ophthalmic Interventions Not An “Ovary-Action”

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ABSTRACT

INTRODUCTION

Of the gynecological cancers, ovarian cancer is the third most commonly occurring, and yet, it serves as the leading cause of death. Due to its insidious onset and pathophysiological mechanism of development, patients are generally subject to a poor prognosis and a significantly high mortality rate.

Tisotumab vedotin-tftv (Tivdak®) was granted accelerated approval by the Food & Drug Administration (FDA) as a novel antibody-drug complex (ADC) for the treatment of cervical & ovarian cancer. Clinical trials, however, have demonstrated an association with ocular toxicity. This case report delineates the baseline ocular presentation in a patient before & after initiation of Tivdak® therapy.

CASE PRESENTATION

A 42-year-old female with ovarian cancer presented for a comprehensive eye examination, seeking clearance to receive Tivdak® therapy, as referred by her managing oncologist. Initial evaluation revealed trace superficial punctate keratitis (SPK) bilaterally. Patient education was provided regarding ocular monitoring requirements and supportive topical ophthalmic therapy. The patient returned to clinic 1 week prior to her next scheduled infusion, presenting with confluent 2+ punctate epithelial keratitis (PEK) bilaterally and a corresponding decrease in vision. Upon review of case history, the patient reported compliance with the adjunctive ophthalmic drug regimen in a manner inconsistent with that which was prescribed.

DISCUSSION

Tivdak® gives rise to the adverse effects of conjunctival reactions, dry eyes, corneal compromise, and keratitis, resulting in visually significant changes that may progress to severe vision loss, corneal ulceration, melting, and perforation. The therapeutic management approach necessitates a baseline eye examination to precede initiation of therapy. Follow-up anterior segment evaluations are also required prior to each subsequent dose.

CONCLUSION

Although Tivdak® has demonstrated a clinically significant efficacy & therapeutic value in the management of gynecological cancers, ocular adverse effects may be ameliorated with consistent examination, proactive monitoring, and prompt interventions as appropriate to guide Tivdak® dose modifications and adjunctive ophthalmic care.

INTRODUCTION

Globally and among the gynecological cancers, ovarian cancer is the third most commonly occurring malignancy,[1,2] following only that of cervical cancer & uterine cancer, and yet, it serves as the leading cause of death.[1,3] Furthermore, despite ovarian cancer's incidence of only 10% relative to that of breast cancer, it is 300% as lethal,[3] a mortality rate that is thought to be attributed to inadequate screening & detection as well as the disease's asymptomatic onset, occult development, and insidious progression.[1,2]

In September 2021, tisotumab vedotin-tftv (Tivdak®) received accelerated approval by the Food & Drug Administration (FDA) as a novel "tissue factor (TF)-directed antibody and microtubule inhibitor conjugate, indicated for the treatment of metastatic cervical [and ovarian] cancer with disease progression on or after chemotherapy."[4-8] Throughout clinical trials, the most common systemic adverse side effects exhibited by patients/subjects on Tivdak® infusion therapy were peripheral neuropathy and hemorrhagic events.[4-8] The most common ocular adverse effects were conjunctival reactions, dry eyes, blepharitis, keratitis, and changes in the ocular surface integrity.[4-9]

This case report delineates the baseline ocular clinical presentation of a patient with recalcitrant ovarian cancer as well as the ocular side effects exhibited upon initiation of Tivdak® infusion therapy.

CASE PRESENTATION

INITIAL EXAMINATION ON 01/16/2024:

A 42-year-old Hispanic female presented to The Eye Care Institute (TECI) at Nova Southeastern University (NSU) for a comprehensive eye examination as referred by her oncologist. The patient was diagnosed with metastatic ovarian cancer in 2022 that proved unresponsive to conventional chemotherapeutic & medical interventions. Upon further probing, the patient indicated that she was seeking clearance to undergo intravenous Tivdak® infusion therapy and reported that her first dose was scheduled to be administered within the week, pending today's baseline eye examination.

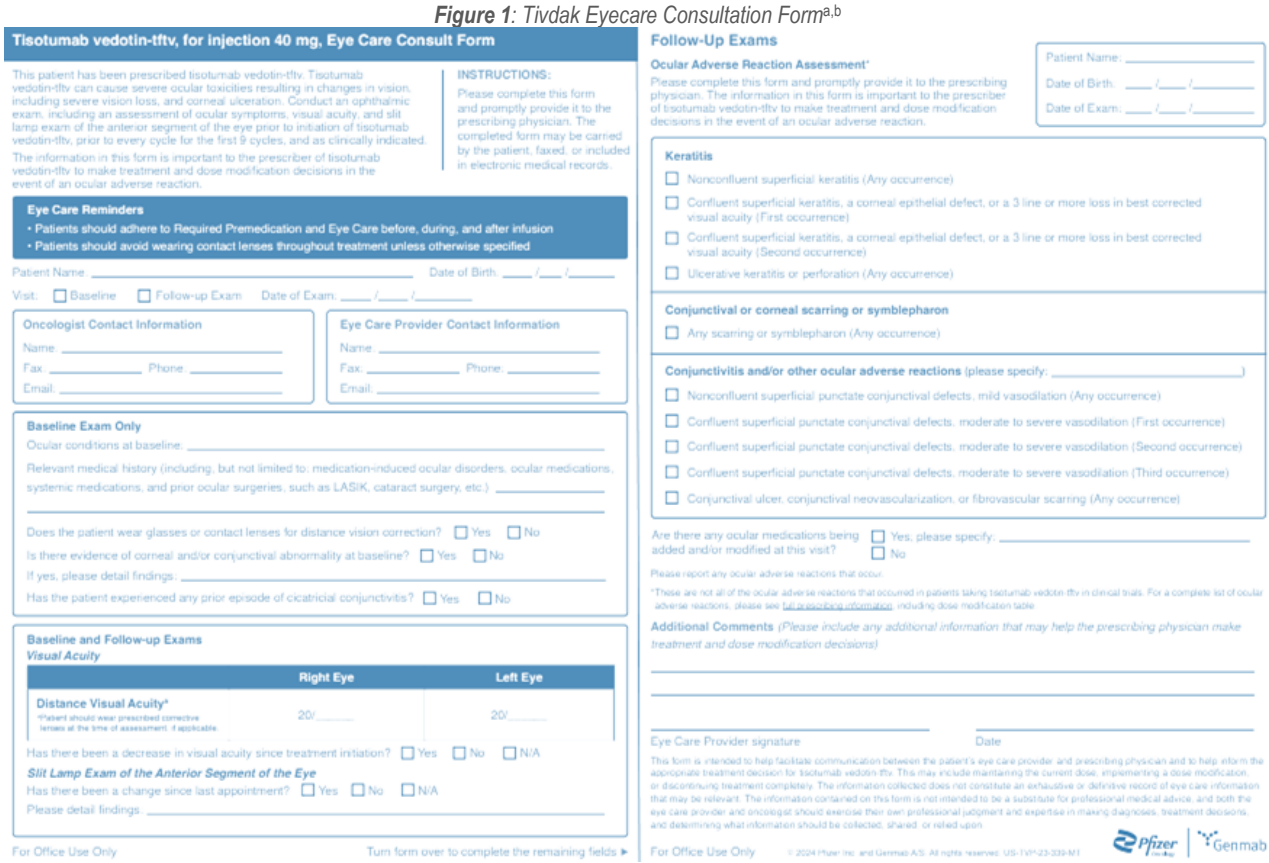
On review of case history, the patient reported a medication/drug regimen including oral supplements for vitamin C 1,000mg qd and vitamin D3 50mcg qd. Otherwise, the patient's medical history, ocular history, family medical history, and social history were unremarkable and non-contributory, and the patient denied any known drug allergies (NKDA) or environmental allergies. The patient also denied any ocular or visual complaints OD/OS/OU and reported that she did not routinely rely on any form of vision correction.

Upon examination, the patient's entering uncorrected visual acuity (VA) was 20/20 OD/OS/OU. Pupillary assessment, ocular motility testing, and confrontation visual fields (CVFs) were unremarkable.

On anterior segment evaluation via slit lamp biomicroscopy (SLB), trace endothelial pigment was observed on the corneas OD/OS in addition to a 1mm linear stromal scar in the inferior cornea OD. Corneal evaluation with sodium fluorescein (NaFl) and a cobalt blue filter revealed a tear break-up time (TBUT) of 3 seconds OD/OS and trace superficial punctate keratitis (SPK) inferotemporally OD/OS. Otherwise, anterior segment findings were within normal limits OD/OS. Intraocular pressures (IOPs) were measured by Goldmann applanation tonometry (GAT) and found to be 15 and 13mmHg OD/OS, respectively.

Posterior segment evaluation via dilated fundus examination (DFE) revealed vitreal syneresis OD/OS and a focal area of congenital hypertrophy of the retinal pigment epithelium (CHRPE) in the inferotemporal peripheral retina OD. Otherwise, posterior segment findings were within normal limits OD/OS.

***Figure 1**: Tivdak Eyecare Consultation Form*[a,b]



Tisotumab vedotin-tftv, for injection 40 mg, Eye Care Consult Form

This patient has been prescribed tisotumab vedotin-tftv. Tisotumab vedotin-tftv can cause severe ocular toxicities resulting in changes in vision, including severe vision loss, and corneal ulceration. Conduct an ophthalmic exam, including an assessment of ocular symptoms, visual acuity, and slit lamp exam of the anterior segment of the eye prior to initiation of tisotumab vedotin-tftv, prior to every cycle for the first 9 cycles, and as clinically indicated.

The information in this form is important to the prescriber of tisotumab vedotin-tftv to make treatment and dose modification decisions in the event of an ocular adverse reaction.

INSTRUCTIONS:
Please complete this form and promptly provide it to the prescribing physician. The completed form may be carried by the patient, faxed, or included in electronic medical records.

Eye Care Reminders
- Patients should adhere to Required Premedication and Eye Care before, during, and after infusion
- Patients should avoid wearing contact lenses throughout treatment unless otherwise specified

Patient Name: _____ Date of Birth: ___/___/_____

Visit: ☐ Baseline ☐ Follow-up Exam Date of Exam: ___/___/_____

Oncologist Contact Information
Name: _____
Fax: _____ Phone: _____
Email: _____

Eye Care Provider Contact Information
Name: _____
Fax: _____ Phone: _____
Email: _____

Baseline Exam Only
Ocular conditions at baseline: _____
Relevant medical history (including, but not limited to: medication-induced ocular disorders, ocular medications, systemic medications, and prior ocular surgeries, such as LASIK, cataract surgery, etc.): _____
Does the patient wear glasses or contact lenses for distance vision correction? ☐ Yes ☐ No
Is there evidence of corneal and/or conjunctival abnormality at baseline? ☐ Yes ☐ No
If yes, please detail findings: _____
Has the patient experienced any prior episode of cicatricial conjunctivitis? ☐ Yes ☐ No

Baseline and Follow-up Exams
Visual Acuity

	Right Eye	Left Eye
Distance Visual Acuity* *Patient should wear prescribed corrective lenses at the time of assessment, if applicable.	20/_____	20/_____

Has there been a decrease in visual acuity since treatment initiation? ☐ Yes ☐ No ☐ N/A

Slit Lamp Exam of the Anterior Segment of the Eye
Has there been a change since last appointment? ☐ Yes ☐ No ☐ N/A
Please detail findings: _____

For Office Use Only Turn form over to complete the remaining fields ▶

Follow-Up Exams

Ocular Adverse Reaction Assessment*
Please complete this form and promptly provide it to the prescribing physician. The information in this form is important to the prescriber of tisotumab vedotin-tftv to make treatment and dose modification decisions in the event of an ocular adverse reaction.

Patient Name: _____
Date of Birth: ___/___/_____
Date of Exam: ___/___/_____

Keratitis
- ☐ Nonconfluent superficial keratitis (Any occurrence)
- ☐ Confluent superficial keratitis, a corneal epithelial defect, or a 3 line or more loss in best corrected visual acuity (First occurrence)
- ☐ Confluent superficial keratitis, a corneal epithelial defect, or a 3 line or more loss in best corrected visual acuity (Second occurrence)
- ☐ Ulcerative keratitis or perforation (Any occurrence)

Conjunctival or corneal scarring or symblepharon
- ☐ Any scarring or symblepharon (Any occurrence)

Conjunctivitis and/or other ocular adverse reactions (please specify: _____)
- ☐ Nonconfluent superficial punctate conjunctival defects, mild vasodilation (Any occurrence)
- ☐ Confluent superficial punctate conjunctival defects, moderate to severe vasodilation (First occurrence)
- ☐ Confluent superficial punctate conjunctival defects, moderate to severe vasodilation (Second occurrence)
- ☐ Confluent superficial punctate conjunctival defects, moderate to severe vasodilation (Third occurrence)
- ☐ Conjunctival ulcer, conjunctival neovascularization, or fibrovascular scarring (Any occurrence)

Are there any ocular medications being added and/or modified at this visit? ☐ Yes; please specify: _____ ☐ No

Please report any ocular adverse reactions that occur.

*These are not all of the ocular adverse reactions that occurred in patients taking tisotumab vedotin-tftv in clinical trials. For a complete list of ocular adverse reactions, please see full prescribing information, including dose modification table.

Additional Comments *(Please include any additional information that may help the prescribing physician make treatment and dose modification decisions)*

_____
_____
_____ _____
Eye Care Provider signature Date

This form is intended to help facilitate communication between the patient's eye care provider and prescribing physician and to help inform the appropriate treatment decision for tisotumab vedotin-tftv. This may include maintaining the current dose, implementing a dose modification, or discontinuing treatment completely. The information collected does not constitute an exhaustive or definitive record of eye care information that may be relevant. The information contained on this form is not intended to be a substitute for professional medical advice, and both the eye care provider and oncologist should exercise their own professional judgment and expertise in making diagnoses, treatment decisions, and determining what information should be collected, shared, or relied upon.

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[a] Figure and information adapted from Seagen, Inc.[5]
[b] Consultation form provided as a healthcare provider resource by Seagen, Inc.[5] as a means to streamline pertinent consultation/examination notes, etc. between oncology and ophthalmology/optometry providers.

Despite the patient's report of a formal diagnosis of ovarian cancer, in an attempt to comply with Tivdak® medical billing requirements, the diagnoses for the encounter were documented to be a presenting history of cervical cancer as well as high risk medication use. No ocular or systemic contraindications were evident upon examination. Patient education was provided regarding ocular monitoring requirements during Tivdak® therapy (evaluation every 3 weeks)[4] and adjunctive topical ophthalmic drug use.[5] Per the therapeutic regimen outlined by the manufacturer prescribing & provider information,[4-6] prescriptions for supportive ophthalmic therapy were electronically sent to the patient's pharmacy of choice for the following medications:

1. brimonidine 0.2% ophthalmic solution
    - 3 drops to be instilled OD/OS immediately prior to each infusion
2. prednisolone acetate 1% ophthalmic suspension
    - 1 drop to be instilled OD/OS immediately prior to each infusion
    - 1 drop to be instilled qid OD/OS for a duration of 72 hours post-infusion

Verbal counseling and physical printed instructions were also provided to the patient. An eyecare consultation form was completed (**Figure 1**), with a copy released to the patient to submit to the managing oncologist.

The patient was also diagnosed with mild dry eye syndrome (DES) OD/OS and instructed to initiate instillation of an OTC preservative-free artificial tears (PFATs) qid, with an iVIZIA sample & coupon provided to the patient.

The patient was then scheduled to return to clinic for an anterior segment evaluation at 3 weeks following her Tivdak® infusion or sooner if advised by her oncologist and/or in the case that any ocular or visual changes arise.

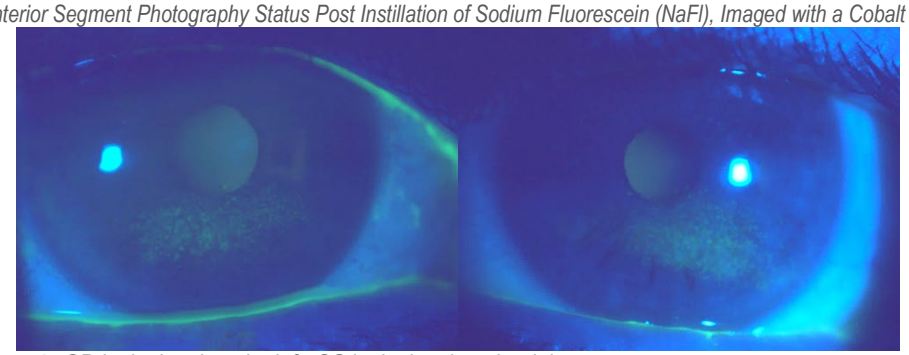
FOLLOW-UP EXAMINATION ON 02/06/2024:

A 42-year-old Hispanic female presented to TECI at NSU for a 3 week follow-up for an anterior segment evaluation related to Tivdak® infusion therapy, administered intravenously for the treatment of her ovarian cancer. Upon inquiry, the patient reported that she had received her first Tivdak® infusion on 01/29/2024, with the next infusion scheduled for 02/14/2024 pending today's anterior segment evaluation. The patient denied any ocular or visual complaints or any changes in vision OD/OS/OU since her last visit.

On review of case history, the patient confirmed that her pharmacological regimen still included the vitamin supplementation reported on her last visit. In addition to the Tivdak® infusions, the patient also updated her medication/drug history to include prednisolone acetate 1% qid OD/OS, brimonidine 0.2% qid OD/OS, and OTC Systane PFATs qid OD/OS, all of which the patient asserted to have been administered beginning the day of her first infusion treatment on 01/29/2024. Further probing was indicated, as the use of these ophthalmic agents was inconsistent with that which was prescribed. Upon further inquiry, the patient stated that she had consistently adhered to this instillation schedule since the day of her last infusion without discontinuation and that she had even last instilled all 3 medications OD/OS the night prior.

On review of systems (ROS), the patient reported a mild & diffuse dermatological rash, onset approximately 2 weeks ago, which she alleged to be constant in severity and stable in presentation. The patient stated that she suspected the rash to be associated with her first Tivdak® infusion, given that in the past, she "usually developed a rash following chemotherapy" and denied any attempts at modifying or alleviating factors. The patient also reported that she had recently recovered from a cold with over-the-counter (OTC) medication and rest, although she denied any current or active illness on the day of her visit. Otherwise, the patient's medical history, ocular history, family medical history, and social history were unchanged, unremarkable, and non-contributory.

***Figure 2**: Anterior Segment Photography Status Post Instillation of Sodium Fluorescein (NaFl), Imaged with a Cobalt Blue Filter*[a,b]



[a] OD is depicted on the left; OS is depicted on the right.
[b] Of note, is confluent 2+ punctate epithelial keratitis (PEK) in the inferior mid-peripheral corneas OS > OD.

Examination revealed an uncorrected VA of 20/30^{-2} OD, 20/60^{-2} OS, and 20/25 OU. Pinholed uncorrected VAs were 20/20^{-3} OD and 20/25^{-1} OS. Pupillary assessment, ocular motility testing, and confrontation visual fields (CVFs) were unchanged & unremarkable.

Anterior segment evaluation via SLB revealed 2+ conjunctival hyperemia and concretions OD/OS. On corneal evaluation with NaFl instillation and a cobalt blue light filter, confluent 2+ punctate epithelial keratitis (PEK) was evident in the inferior mid-peripheral corneas OS > OD (**Figure 2**). Otherwise, anterior segment findings OD/OS were within normal limits and/or unchanged & unremarkable from her last examination. Intraocular pressures (IOPs) were 14mmHg OD/OS, as measured by GAT.

The Common Terminology Criteria for Adverse Events (CTCAE) was developed by the National Cancer Institute (NCI), a subdivision under the National Institutes of Health (NIH). It was conceptualized as a means to standardize the clinical grading & diagnostic criteria for the adverse side effects resulting from chemotherapeutic pharmacological interventions.[10] According to the clinical grading scale outlined by the NIH's CTCAE,[10,12] this patient's clinical presentation and nascent ocular findings following the first Tivdak® administration exemplified grade 2 dry eye and grade 2 keratitis (**Figure 3** and **Table I**).

***Table I**: Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0—Clinical Grading Scale and Ocular Pathology Definitions for the Classification of Ocular Adverse Effects*[a]

Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Conjunctivitis	Asymptomatic or mild symptoms; intervention not indicated	Symptomatic; moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline)	Symptomatic with marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200); limiting self care ADL	Best corrected visual acuity of 20/200 or worse in the affected eye	N/A
Dry eye	Asymptomatic; clinical or diagnostic observations only; symptoms relieved by lubricants	Symptomatic; moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline)	Symptomatic with marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200); limiting self care ADL	N/A	N/A
Keratitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline)	Symptomatic with marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200); corneal ulcer; limiting self care ADL	Perforation; best corrected visual acuity of 20/200 or worse in the affected eye	N/A
Eye disorders - other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated; no change in vision	Moderate; minimal, local or noninvasive intervention indicated; limiting instrumental ADL; best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline	Severe or medically significant but not immediately sight-threatening; limiting self care ADL; decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200)	Sight-threatening consequences; urgent intervention indicated; best corrected visual acuity of 20/200 or worse in the affected eye	N/A
Conjunctivitis: a disorder characterized by inflammation, swelling, and redness to the conjunctiva of the eye					
Dry eye: a disorder characterized by dryness of the cornea and conjunctiva					
Keratitis: a disorder characterized by inflammation to the cornea of the eye					
Blepharitis: an inflammatory condition of the eyelids					

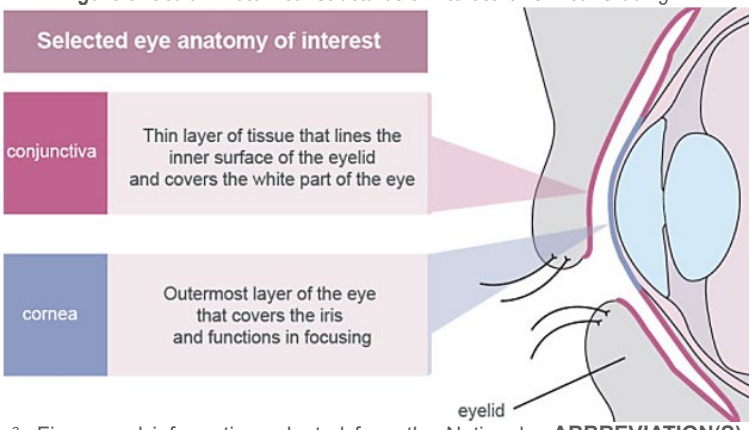
[a] Figure and information adapted from the National Institute of Health (NIH)[10] and Duncan and Jeng[12]; figure compiled by Arn et al.[7]

ABBREVIATION(S): ADL = Activity/ies of daily living; AE = Adverse event(s); N/A = Not applicable

Findings were discussed with the patient, particularly the increase in ocular surface staining OD/OS and the 1-line reduction in best corrected visual acuity (BCVA) OS, which were suspected to manifest and potentially have been exacerbated due to preservative & medication toxicity. The patient was instructed to commence instillation of preservative-free artificial tears q1h OD/OS and to immediately discontinue the instillation of brimonidine 0.2% and prednisolone acetate 1%. A thorough counseling was provided on the resumption of the proper ophthalmic supportive therapy on the day of the next Tivdak® infusion, as previously directed and intended.

Ocular monitoring requirements during Tivdak® therapy (every 3 weeks)[4] and adjunctive topical ophthalmic drug use[5] were reviewed with the patient, and printed instructions were once again provided. Another eyecare consultation form was completed for the encounter (**Figure 1**), with a copy released to the patient to submit to the managing oncologist. A chart summary note for today's encounter and notification regarding today's findings were also relayed to the managing oncologist. Prescriptions for brimonidine 0.2% and prednisolone acetate 1% were renewed and electronically sent to the patient's pharmacy of choice. Upon patient request, copies of the prescriptions were printed and released to the patient upon check-out.

***Figure 3**: Ocular Anatomical Structures of Interest for Clinical Grading*[a]



[a] Figure and information adapted from the National Institute of Health (NIH)[10] and Duncan and Jeng[12]; figure compiled by Arn et al.[7]

ABBREVIATION(S): AE = Adverse event

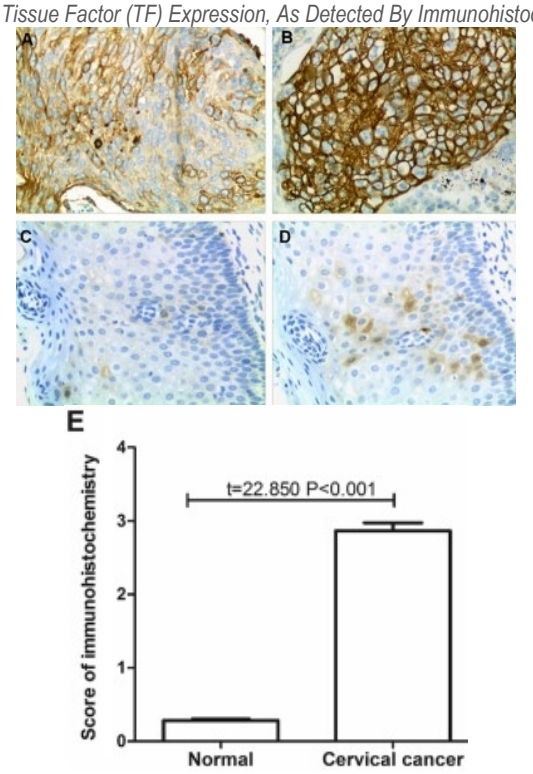
The patient was then scheduled to return to clinic for a 3 week follow-up for a repeat anterior segment evaluation, with instructions to return sooner if advised by her oncologist and/or in the case that any ocular or visual changes arise.

DISCUSSION

MECHANISM OF ACTION (MOA)

Tissue factor (TF)—also referred to as "coagulation factor III," "platelet tissue factor," or the "CD142 glycoprotein"[4,5,7-9,13]—is an evolutionary conserved transmembrane glycoprotein.[14] It is an ideal target in the pharmacotherapy of gynecological cancers due to its expression in approximately 94 – 100% of cervical cancer cells[7,9,15] and 75 – 100% of ovarian cancer cells.[16] Conversely, the expression of TF on the surface of healthy cell membranes is relatively limited.[7,9,15,16]

***Figure 4**: Tissue Factor (TF) Expression, As Detected By Immunohistochemistry*[f]



[A] Low TF expression in a cervical cancer tissue sample
[B] High TF expression in a cervical cancer tissue sample
[C] Negative TF expression in an adjacent healthy tissue sample
[D] Low TF expression in an adjacent healthy tissue sample
[E] Statistical analysis of the immunohistochemistry results
[f] Figure and information adapted from Zhao et al.[17]

TF is an effective point of focus in cancer pathophysiology due to its molecular modulation of oncogenic genes. It is a histological marker of not only the development of cancer but also the *progression* of cancer. In fact, immunohistochemical analysis has found TF to be significantly correlated with cancer metastasis and severity (**Figure 4**).[17] TF is able to stimulate the proliferation of cancer cells by inhibiting tumor suppressor genes (TSGs) & pro-apoptotic proteins (PAPs) and by upregulating cyclins & cyclin-dependent kinases (CDKs) that regulate cell cycle progression.[18] Beyond its capacity for carcinogenesis, TF transcription & expression has also been found to enhance tumor growth and to promote carcinogenic chemotaxis, angiogenesis, and metastasis.[14,19]

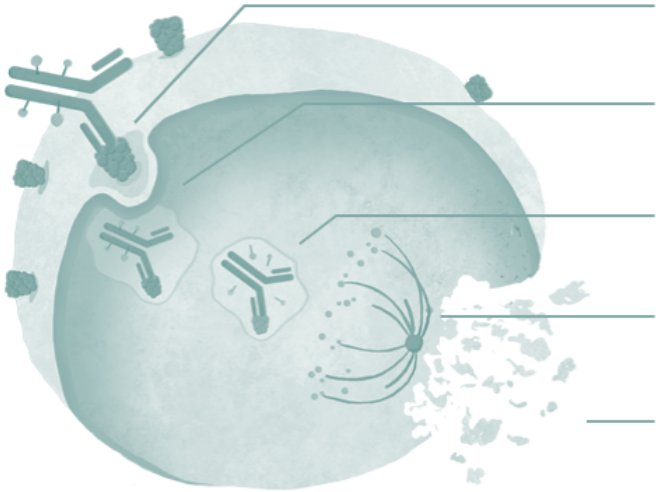
Tivdak®'s mechanism of action (MOA) mobilizes both the innate immune response as well as the adaptive immune response in cancer cells expressing TF.[4-6] The bulk of Tivdak®'s therapeutic efficacy, however, may be derived from its induction of antibody-dependent cellular cytotoxicity (ADCC) and phagocytosis.[20]

Tivdak® is a therapeutic immunomodulating agent that is comprised of 3 constituents (**Figure 5**)[4,5,7-9,13]:

1. A monoclonal immunoglobulin G (IgG) antibody that is directed towards TF
2. Monomethyl auristatin E (MMAE), a cytotoxic conjugate and cell division inhibitor, which may also be referred to as the "chemotherapeutic payload"
3. A protease-cleavable chemical linking component to adjoin the antibody & the cytotoxic component to one another

The anti-carcinogenic MOA of Tivdak® involves the binding of the antibody-drug conjugate (ADC) to TF-expressing cancer cells.[5-9,21] The cancer cells subsequently internalize the ADC-TF complex, which then undergoes lysosomal degradation. [5-9,21] Degradation of the ADC-TF complex via proteolytic cleavage releases MMAE into the cell, which consequently binds to tubulin to induce disruptions in microtubule polymerization.[5-9,21,22] It is through these means that Tivdak® is able to elicit cell cycle arrest and cellular apoptosis (**Figure 6**).[5-9,21,22]

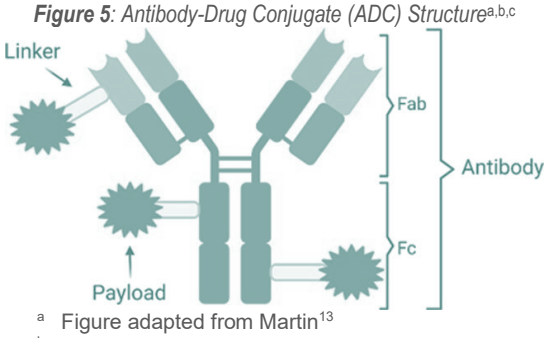
***Figure 6**: The Mechanism of Action (MOA) of Tivdak®*[a]



[a] Figure and information adapted from Seagen Inc.[6]

ABBREVIATION(S): TF = Tissue factor; MMAE = Monomethyl auristatin E

***Figure 5**: Antibody-Drug Conjugate (ADC) Structure*[a,b,c]



[a] Figure adapted from Martin[13]

[b] The fragment antigen-binding region of an antibody is responsible for antigen recognition

[c] The fragment crystallizable region of an antibody interacts with cell surface receptors and immune mediators of the complement system.

ABBREVIATION(S): F_{ab} = The antibody's fragment antigen-binding region; F_c = The antibody's fragment crystallizable region

SYSTEMIC ADVERSE EFFECTS AND CLINICAL MANAGEMENT

Since its original inception, the CTCAE has been expanded upon and updated to a number of iterations, with the latest edition published in 2017.[10] The CTCAE enumerates clinical grading classifications using general guidelines to qualify the severity of a given adverse event (**Table II**). In addition, however, the CTCAE also specifies clinical & diagnostic grading criteria for a variety of anatomical & physiological system organ classes (SOCs) and their corresponding adverse side effects, including—but not limited to—neurological, respiratory, cardiovascular (CV) and/or circulatory, gastrointestinal (GI), etc.

***Table II**: Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0—Clinical Grading Scale for General Classifications of Severity*[a]

Grade	Definition
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

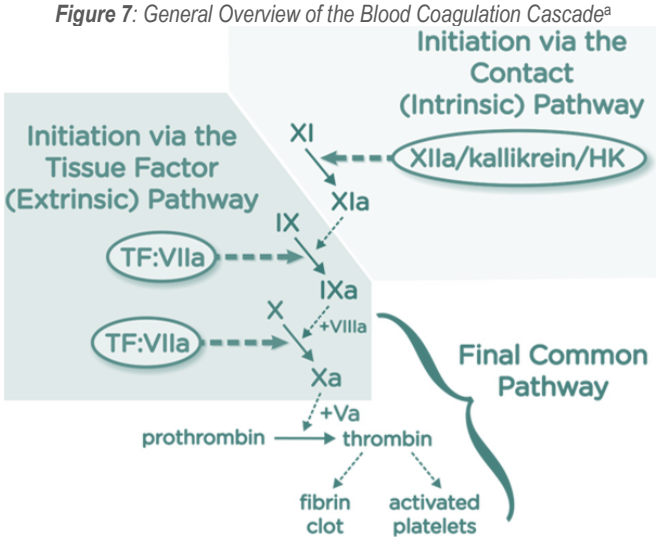
[a] Table and information adapted from the NIH[10] and Jiang et al.[11]

ABBREVIATION(S): ADL = Activity/ies of daily living

Various therapeutic adjustments and/or dose modifications may be warranted for a given chemotherapeutic pharmacological agent, depending on the SOC affected and the clinical presentations of the adverse effects present.

The elements of the CTCAE that may be the most pertinent with respect to Tivdak® concern hemorrhaging (**Table II**) and peripheral neuropathy (**Table III**). These systemic adverse reactions are the most commonly occurring following Tivdak® therapy.[4-8,23]

***Figure 7**: General Overview of the Blood Coagulation Cascade*[a]



[a] Table and information adapted from Smith et al.[24]

ABBREVIATION(S): TF = Tissue factor; VIIa = Factor VIIa; XIIa = Factor XIIa; HK = High molecular weight kininogen; XI = Factor XI; XIa = Factor XIa; IX = Factor IX; IXa = Factor IXa; X = Factor X; Xa = Factor Xa

Clinical trials have found Tivdak® to be associated with hemorrhagic complications, which occurred in 62% of patients.[4] Adverse hemorrhagic reactions included epistaxis, hematuria, hemoptysis, gastrointestinal (GI) bleeding, etc.[4-8,23] As a primary initiator of the blood coagulation cascade (**Figure 7**),[24] TF is essential in the biochemical mechanisms regulating hemostasis.[25] In fact, TF serves as a cofactor for factors VII & VIIa; as a result, Tivdak®'s hemorrhagic adverse side effects are thought to develop as a consequence of its disruption to TF expression and, therefore, downstream coagulation signaling pathways.[26]

Management typically involves the treatment of signs, symptoms, and sequelae rather than the underlying etiology. For the most part, the hemorrhagic adverse side effects of Tivdak® are simply an unintended but reasonably expected consequence of ADCs as a novel treatment modality for cancer malignancies. Hemorrhaging was found to onset at 0 – 6.5 months following initiation of Tivdak® therapy, with a median onset of 0.3 months.[4] However, of the patients who experienced

hemorrhagic adverse reactions in clinical trials, 11% demonstrated a partial resolution (as defined by diminishing severity) and 71% exhibited complete resolution at their last follow-up appointment.[4] Manufacturer prescribing & provider information advises of clinical interventions that facilitate hemostatic stability and neutralize bleeding diatheses,[4-6] but the research data appears to suggest that hemorrhagic adverse events are commonplace and, yet, generally manageable.

In fact, ADCs have been found to be associated with a statistically significant reduction in the rate of hematological adverse events—specifically, leukopenia, lymphocytopenia, and febrile & afebrile neutropenia, although a higher incidence of thrombocytopenia *has* been observed—in comparison to conventional chemotherapeutic approaches.[27] Taking into consideration the relatively ideal risk-to-benefit ratio of ADC administration as a gynecological cancer treatment,[23] clinical interventions for hematopathy may endeavor to alleviate hemorrhagic episodes through dose modifications and supportive measures until the therapeutic index (TI) is improved and patient tolerability is attained.[4-6,28]

***Table III**: Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0—Clinical Grading Scale for Peripheral Neuropathy*[a,b]

Grade	0	1	2	3	4	5
Motor neuropathy	Normal	Asymptomatic, weakness on examination only.	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self-care ADL; assistive device indicated (e.g. cane or walker)	Life-threatening consequences; urgent intervention indicated. Disabling	Death
Sensory neuropathy	Normal	Asymptomatic loss of deep tendon reflexes or parenthesis	Moderate sensory symptoms; or parenthesis limiting instrumental ADL	Severe symptoms; sensory alterations or parenthesis limiting self-care ADL	Life-threatening consequences; urgent intervention indicated. Disability	Death
Neuralgia		Mild Pain	Moderate pain limiting instrumental ADL	Severe pain limiting self-care ADL		

[a] Table and information adapted from the NIH[10] and Izycki et al.[29]

ABBREVIATION(S): ADL = Activity/ies of daily living

Throughout clinical trials, peripheral neuropathy exhibited an onset of 0 – 11.3 months following initiation of Tivdak® therapy, with a median onset of 2.4 months.[4] Adverse reactions of peripheral neuropathy commonly included peripheral sensory neuropathy, peripheral motor neuropathy, peripheral sensorimotor neuropathy, myasthenia, hypoaesthesias, paresthesias, dysesthesias, burning sensations, neuropathic neuralgia, etc.[4-8,23]

Chemotherapy agents that target microtubule structure & function intrinsically give rise to drug-induced peripheral neuropathy as a result of their MOA; their disruption of microtubule polymerization ultimately interferes with the crucial roles of cytoskeletal microtubules in neuronal communication and transport.[22,30]

In most cases, neuropathy resulting from microtubule inhibition agents is reversible and mild to moderate in presentation; however, it should be noted that severe and/or incomplete resolution is nevertheless possible.[4,30,31] Across clinical trials, peripheral neuropathy occurred in 42% of patients, with 8% of cases classified as grade 3.[4-6] In these patients, the grade 3 severity necessitated the termination of Tivdak® therapy.[4-6] However, of the 42% of patients that experienced peripheral neuropathic adverse reactions, 17% demonstrated a partial resolution (as defined by diminishing severity) and 17% exhibited complete resolution at their last follow-up appointment.[4-6]

Fortunately, clinical interventions with respect to neuropathy are, in fact, manageable; microtubule inhibition-based pharmacotherapies appear to be characterized by an incidence and severity that is dependent on the dose administered, the duration of administration, and the frequency of treatment[31,32]

***Table IV**: Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0—Clinical Grading Scale for Respiratory Adverse Effects*[a]

Grade 0	No changes
Grade 1	Asymptomatic, only radiological, or tomographic findings
Grade 2	Symptomatic, does not interfere with daily activities
Grade 3	Symptomatic, interferes with daily activities, requires supplemental O2
Grade 4	Threatens life, requires mechanical ventilation support
Grade 5	Death related severe pneumonitis

[a] Table and information adapted from the NIH[10] and Arroyo-Hernandez et al.[33]

ABBREVIATION(S): O2 = Oxygen

***Table V**: Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0—Clinical Grading Scale for Dermatological Adverse Effects*[a]

DAE	Grade	Description
SJS/TEN	3	Skin sloughing <10% body surface area (BSA) + associated signs (mucous membrane detachment, etc.)
	4	Skin sloughing 10–30% BSA (SJS) or ≥30% BSA (TEN) + associated signs
Rash maculopapular	1	Macules/papules covering <10% BSA ± symptoms (pruritus, burning, etc.)
	2	Macules/papules covering 10–30% BSA ± symptoms (pruritus, burning, etc.), limiting instrumental activities of daily living (ADL), or ≥30% BSA ± mild symptoms
	3	Macules/papules covering >30% BSA + moderate/severe symptoms, limiting self-care ADL
Bullous dermatitis	1	Asymptomatic, blisters covering <10% BSA
	2	Blisters covering 10–30% BSA, painful blisters, or limiting instrumental ADL
	3	Blisters covering >30% BSA, limiting self-care ADL
	4	Blisters covering >30% BSA + fluid/electrolyte abnormalities, ICU/burn unit indicated
	5	Death
Other skin disorders (Other DAEs)	1	Asymptomatic or mild symptoms
	2	Moderate; limiting ADL
	3	Severe or medically significant but not life threatening
	4	Life-threatening consequences
	5	Death

[a] Table and information adapted from the NIH[10] and Kuo and Markova.[34]

ABBREVIATION(S): DAE = Dermatologic adverse event(s); BSA = Body surface area; SJS/TEN = Stevens-Johnson syndrome / toxic epidermal necrolysis; ADL = Activity/ies of daily living; ICU = Intensive care unit

Additional systemic adverse effects whose manifestations may warrant a dose modification, temporary suspension of therapy, or permanent discontinuation of Tivdak® administration include pneumonitis (**Table IV**)[4-6,10] and dermatologic reactions (**Table V**).[4-6,10] Manufacturer prescribing & provider information recommends that patients be monitored for associated signs & symptoms of these complications, as they may prove to be severe, life-threatening, or even fatal.[4-6]

Other commonly occurring systemic adverse effects that were observed in clinical trials include fatigue/malaise, pyrexia, pruritis, abdominal pain, nausea, vomiting, diarrhea or constipation, loss of appetite, myalgia, arthralgia, and alopecia.[4-6] Clinical trials also demonstrated Tivdak® to be associated with select medical laboratory abnormalities, as evident in patients' deterioration from their baseline values (**Table VI**).[4-6,21]

***Table VI**: Laboratory Abnormalities (≥ 20%) That Deteriorated from Baseline Values in Patients Who Received Tivdak ® Therapy*[a,b,c]

LABORATORY PANEL	LABORATORY PARAMETER	ALL GRADES (GRADES 1 – 4)	GRADES 3 or 4
HEMATOLOGY	↓ in HEMOGLOBIN (Hb)	52%	7%

	↓ in LYMPHOCYTE COUNT	42%	8%
	↓ in LEUKOCYTE COUNT	30%	0%
	↓ in NEUTROPHIL COUNT	21%	3%
CHEMISTRY	↑ in [CREATININE]	29%	4%
	↑ in [ALANINE AMINOTRANSFERASE (ALT)]	24%	0%
	↑ in [LACTATE DEHYDROGENASE (LDH)]	22%	0%
	↓ in [SODIUM (Na^+)]	20%	0%
COAGULATION FACTORS	↑ in INTERNATIONAL NORMALIZED RATIO (INR)	26%	0%
	↑ in ACTIVATED PARTIAL THROMBOPLASTIN TIME (APTT)	26%	2%

[a] Table and information adapted from Seagen, Inc.[4-6] and Coleman et al.[21]
[b] The deterioration in laboratory testing values is indicated by "↑" in parameters that increase on worsening or "↓" in parameters that decrease on worsening.
[c] Laboratory testing parameters marked by square brackets ("[" and "]") denote concentration.

In general, systemic adverse side effects and adverse reactions are subject to a clinical management approach consisting of therapeutic adjustments and dose modifications that are implemented when appropriate as outlined by the manufacturer prescribing information (**Table VII**).[4-6,10]

***Table VII**: Tivdak® Dose Modification Guidelines Based on Systemic Adverse Side Effects & Reactions*[a,b]

Severity	Occurrence	Tivdak Dose Modification
Peripheral neuropathy		
Grade 2	Any (initial or worsening of pre-existing condition)	Withold dose until Grade ≤1, then resume treatment at the next lower dose level.
Grade 3 or 4	Any	Permanently discontinue.
Hemorrhage		
Any grade pulmonary or CNS	Any	Permanently discontinue.
Grade 2 in any other location	Any	Withhold until resolved, then resume treatment at the same dose.
Grade 3 in any other location	First occurrence	Withhold until resolved, then resume treatment at the same dose.
	Second occurrence	Permanently discontinue.
Grade 4 in any other location	Any	Permanently discontinue.
Pneumonitis		
Grade 2	Any	Withhold dose until Grade ≤1 for persistent or recurrent pneumonitis, consider resuming treatment at next lower dose level.
Grade 3 or 4	Any	Permanently discontinue.
Severe cutaneous adverse reactions (including Stevens-Johnson syndrome (SJS)		
Suspected (any grade)	Any	Immediately withhold dose and consult a specialist to confirm the diagnosis.
Confirmed Grade 3 or 4	Any	Permanently discontinue.

[a] Table and information adapted from Seagen Inc.[4-6]
[b] Clinical grades of severity correspond to diagnostic criteria as delineated by the NIH's CTCAE for peripheral neuropathy (**Table III**), respiratory adverse effects e.g. pneumonitis, (**Table IV**), and dermatologic adverse effects (**Table V**).[10]

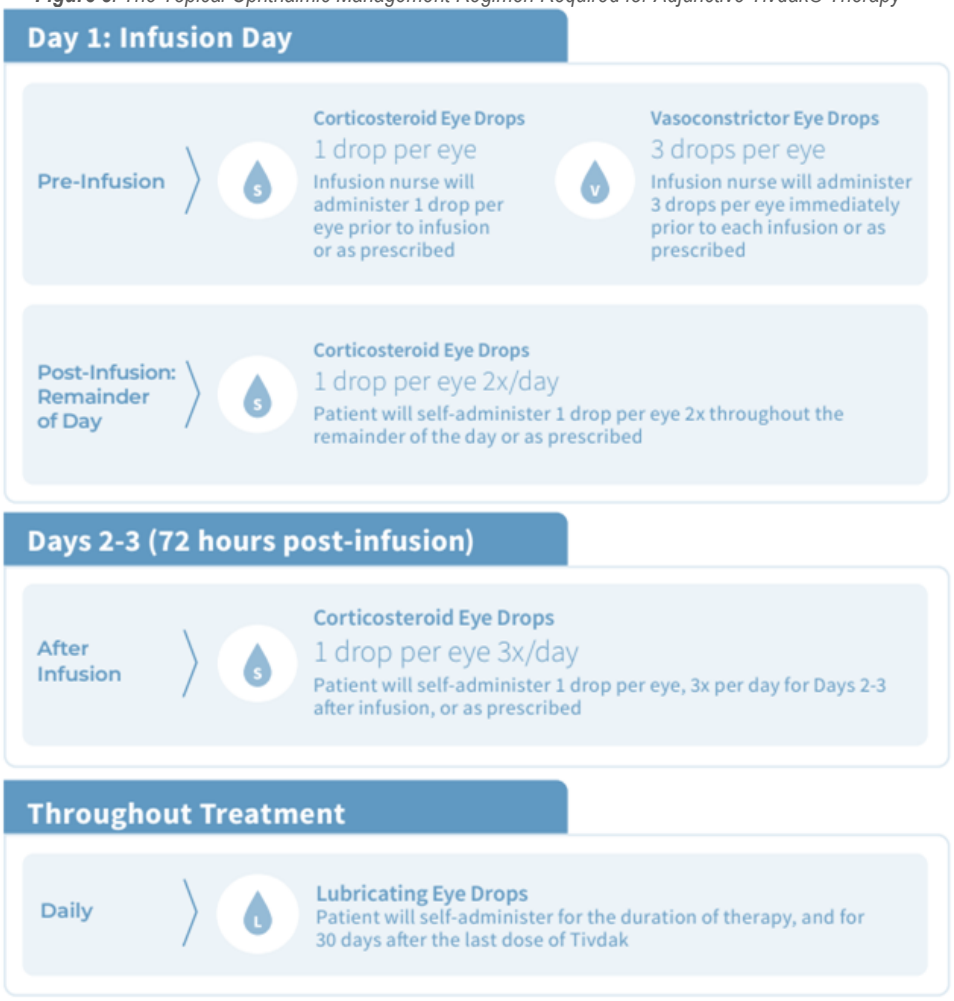
ABBREVIATION(S): CNS = Central nervous system; SJS = Stevens-Johnson syndrome

OCULAR ADVERSE EFFECTS AND CLINICAL MANAGEMENT

Tivdak® is associated with adverse effects indicating ocular toxicity—most commonly, conjunctival reactions, dry eyes, keratitis, corneal changes, and blepharitis, resulting in visually significant changes, including severe vision loss and corneal ulceration.[4-6,9,12] These ocular adverse effects

are thought to develop as a consequence of the eye's "inherently robust blood supply, presence of subpopulations of rapidly dividing cells, and an abundance and variety of cell surface receptors."[9]

***Figure 8**: The Topical Ophthalmic Management Regimen Required for Adjunctive Tivdak® Therapy*[a,b]



[a] Figure and information adapted from Seagen Inc.[5]

[b] Per the manufacturer prescribing & provider information,[4-6] adherence and compliance is advised in order to mitigate the risk, develop, and progression of ocular adverse side effects

The therapeutic management approach requires that a baseline comprehensive ophthalmic examination, complete with VA assessment and SLB examination, be conducted prior to the administration of each infusion in addition to an anterior segment evaluation to be performed prior to each dose thereafter, generally occurring every 3 weeks.[4-6,15,21] As specified by the manufacturer prescribing & provider information (**Figure 8**),[4-6] ocular adverse effects may be abated through a pre-infusion procedure involving the instillation of 3 drops of a vasoconstricting agent OD/OS and 1 drop of a topical corticosteroid OD/OS, both of which are to immediately precede the infusion dose. The α_2 adrenergic agonist, brimonidine 0.2% in this case, was selected for its desired vasoconstrictive effects as well as its anti-inflammatory properties. Likewise, topical corticosteroid therapy has been shown to promote the preservation of ocular surface integrity,[4-6,15,21,35] and prednisolone acetate 1% was chosen for its potency and its ability to ameliorate conjunctival inflammation. Post-infusion mitigation measures included advisement to continue corticosteroid instillation qid for 72 hours from the last Tivdak® dose in addition to instituting a robust instillation of lubricating eyedrops for the duration of therapy, daily for 30 days following the last infusion.[4-6,15,21]

Given the intricacies of adjunctive ophthalmic therapy and its dependence on patient compliance, an exhaustive patient education and detailed guidance should be provided with regard to instillation schedules, signs & symptoms of concern, as well as measures to mitigate exacerbations (hygiene regimens, discontinuation of contact lens wear, irritants to avoid, interventions to provide relief such as cooling eye masks, etc).

KEY TAKEAWAY(S)

The appropriate management of ocular adverse effects, administered in a prompt & timely manner, is critical in the initiation of measures to facilitate their resolution. Holistically, ophthalmic interventions are also vital due to their ability to inform Tivdak® dose modifications (**Table VIII** and **Table IX**).[4]

[a] Table and information adapted from Seagen, Inc.[4-6]

[b] Ocular adverse effects denoted with the "‡" symbol should be referred to an eyecare provider promptly for evaluation of any new onset and/or worsening signs & symptoms.

ABBREVIATION(S): SPK = Superficial punctate keratitis; CNS = Central nervous system.

***Table VIII**: Tivdak® Dose Modification Guidelines Based on Ocular Adverse Side Effects & Reactions*[a,b]

Severity	Occurrence	Tivdak Dose Modification
Keratitis‡		
Nonconfluent superficial keratitis	Any	Monitor.
Confluent superficial keratitis, a corneal epithelial defect, or a 3 line or more loss in best corrected visual acuity	First occurrence	Withhold dose until resolution, or improvement to nonconfluent superficial keratitis, then resume treatment at the next lower dose level.
	Second occurrence	Permanently discontinue.
Ulcerative keratitis or perforation	Any	Permanently discontinue.
Conjunctival or corneal scarring or symblepharon‡		
Any scarring or symblepharon	Any	Permanently discontinue.
Conjunctivitis and other ocular adverse reactions‡		
Nonconfluent superficial punctate conjunctival defects, mild vasodilation	Any	Monitor.
Confluent superficial punctate conjunctival defects, moderate to severe vasodilation	First occurrence	Withhold dose until resolution or improvement to nonconfluent superficial punctate conjunctival defects, mild vasodilation, then resume treatment at the same dose.
	Second occurrence	Withhold dose until resolution or improvement to nonconfluent superficial punctate conjunctival defects, mild vasodilation, then resume treatment at the next lower dose level. If no resolution or improvement to nonconfluent superficial punctate conjunctival defects, mild vasodilation, permanently discontinue.
	Third occurrence	Permanently discontinue.
Conjunctival ulcer, conjunctival neovascularization, or fibrovascular scarring	Any	Permanently discontinue.

***Table IX**: Tivdak® Dose Modification Guidelines*[a]

THERAPEUTIC INTERVENTION	DOSE LEVEL[b]
INITIAL INFUSION DOSE	2.0 mg/kg
1st DOSE REDUCTION	1.3 mg/kg
2nd DOSE REDUCTION	0.9 mg/kg[c]

[a] Table and information adapted from Seagen Inc.[Seagen]
[b] Doses are to be administered via intravenous infusion over a duration of 30 minutes every 3 weeks, not to exceed a maximum dose of 200mg
[c] Administration should be permanently discontinued in patients unable to tolerate dose

This patient's clinical case exemplified the propensity of Tivdak® in eliciting ocular adverse side effects and, therefore, the potential for deterioration(s) in visual perception. In the context of patients' visual function & ocular health as well as their systemic health & overall well-being, the administration of Tivdak® in the management of gynecological cancers inherently requires reciprocity and coordination of care between multiple disciplines of healthcare providers. This patient case was characterized by a need for interprofessional collaboration between the medical specialties of oncology, ophthalmology, and optometry for example. However, even beyond the confines of ocular adverse reactions, there exists a myriad of systemic effects that may arise. Consequently, Tivdak® therapy may necessitate the coordination of care between a diversity of medical domains, such as neurology, hematology, orthopedics, radiology, endocrinology, and more.[4-6,7,8]

The ultimate goal of Tivdak® therapy with respect to cervical & ovarian cancer is the improvement of patient prognosis and, ideally, the prolongment of life. However, the preservation of patients' existing faculties should not be neglected, as it is essential to maintaining their *quality* of life (QOL) and overall health. Furthermore, given the novelty of Tivdak® as an oncologic management approach, a balance between aggressive cancer targeting and the appropriate temperance of adverse effects must be considered and prioritized.

CONCLUSION

ADCs are novel pharmacological agents in oncology. Tivdak® was approved for the management of previously treated recurrent or metastatic gynecological cancer under the FDA's accelerated program.[4-6,22] Clinical trials and research studies demonstrated clinically meaningful and durable efficacy with a manageable profile as far as safety & tolerability[15,21]; however, of those who received treatment, 60% of patients presented with side effects suggestive of ocular toxicity.[4-6]

The early detection & diagnosis of said ocular adverse effects is crucial in that it permits the alleviation of their severity and the palliation of their progression. Whether interventions encompass dose adjustments, supportive measures, and/or the exploration of other avenues of treatment, vigilance against ocular surface compromise avoids prolonged anterior segment toxicity, thereby minimizing the potential for corneal ulceration, melting, and perforation.[22]

Ultimately, collaborative patient-physician relationships and interprofessional cooperation between oncology, ophthalmology, and optometry are imperative in the execution of baseline ophthalmic examination, appropriate mitigation efforts, and routine assessments in the circumvention of ocular sequelae secondary to Tivdak® administration.

CONFLICTS OF INTEREST (COIs)

The author has no conflicts of interest (COIs), competing financial interests, or personal relationships to disclose.

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