Enfortumab Vedotin

Nursing perspectives on the management of adverse events in patients with locally advanced or metastatic urothelial carcinoma

Amanda Pace, BSN, RN, OCN®, Blaine Brower, MSN, RN, FNP-BC, Dawn Conway, BSN, RN, OCN®, and Dayna Leis, BSN, RN, OCN®

BACKGROUND: Many patients with locally advanced or metastatic urothelial carcinoma (mUC) need additional treatment options beyond PD-1 or PD-L1 inhibitors and platinum-based chemotherapies. Enfortumab vedotin-ejfv (EV) is an antibody–drug conjugate directed at Nectin-4 that received accelerated approval for treatment of adults with locally advanced or mUC previously treated with PD-1/PD-L1 inhibitors and platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced, or metastatic settings.

OBJECTIVES: This article provides practical considerations and recommendations regarding common and potentially treatment-limiting adverse events that may arise with EV therapy.

METHODS: The clinical data that supported the approval of EV are reviewed, and supporting safety and management considerations are provided based on the authors’ experience.

FINDINGS: EV therapy can be optimized through patient and caregiver education, proactive patient monitoring, early identification of adverse events, and timely intervention to alleviate symptoms.

KEYWORDS
antibody–drug conjugates; enfortumab vedotin; adverse drug event; assessment

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LOCALLY ADVANCED OR METASTATIC UROTHELIAL CARCINOMA (mUC) is an aggressive and incurable disease that disproportionately affects older adults, often those with a history of smoking and comorbidities, including cardiovascular disease and diabetes. Safe and effective treatment options are limited. Platinum-based chemotherapy, the standard initial therapy for mUC, is often difficult to tolerate and responses often are short-lived. In the second-line setting, approved programmed cell death protein-1 (PD-1) or programmed cell death-ligand 1 (PD-L1) inhibitor therapies provide meaningful responses in 13%–29% of patients with mUC (Balar et al., 2017; Bristol-Myers Squibb, 2020; EMD Serono, 2019; Merck, 2020; Powles et al., 2017; Rosenberg et al., 2016). Subsequent therapies, including single-agent taxanes, have low objective response rates of only 11%–13% (Bellmunt et al., 2017; Powles et al., 2018). Therefore, a great unmet need for effective treatment options exists throughout the mUC treatment journey.

Enfortumab vedotin-ejfv (EV) received accelerated approval from the U.S. Food and Drug Administration (FDA) in December 2019 for treatment of adults with locally advanced or mUC previously treated with a PD-1 or PD-L1 inhibitor and a platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced, or metastatic setting (Astellas Pharma, 2019). EV is an antibody–drug conjugate (ADC) that comprises monomethyl auristatin E (MMAE) as the active anticancer component (Challita-Eid et al., 2016; Doronina et al., 2003; Liu et al., 2020). MMAE induces cell death by disrupting the microtubule apparatus. Unlike other microtubule-disrupting agents, such as taxanes and vinca alkaloids, EV is designed to target the delivery of MMAE to specific cells by using an antibody-delivery mechanism directed against Nectin-4, which is highly expressed in UC and involved in cellular processes associated with oncogenesis (Challita-Eid et al., 2016; Doronina et al., 2003; Liu et al., 2020). EV is administered via IV on days 1, 8, and 15 of each 28-day cycle.

EV-201 (NCT03219333) is a global, phase 2, single-arm study of EV in patients with locally advanced or mUC previously treated with platinum-containing chemotherapy and anti–PD-1/PD-L1 therapy (cohort 1) or anti–PD-1/PD-L1 therapy in patients who are platinum-naïve and cisplatin-ineligible (cohort 2) (Rosenberg et al., 2019). In cohort 1, the basis for the FDA's
accelerated approval of EV, the objective response rate was 44%, with 12% complete response per Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. The median response duration was 7.6 months, and the estimated median progression-free survival and overall survival were 5.8 months and 11.7 months, respectively. With an additional year of follow-up, median overall survival was extended to 12.4 months (O’Donnell et al., 2020). In the confirmatory randomized phase 3 trial (EV-301), median overall survival with EV was 12.88 months, as compared to 8.97 months for patients randomized to standard chemotherapy (Powles et al., 2021).

As with many anticancer therapies, EV is associated with adverse events (AEs). The most common treatment-emergent AEs across the EV trials were peripheral neuropathy (56%), fatigue (56%), decreased appetite (52%), rash (52%), alopecia (50%), nausea (45%), diarrhea (42%), dysgeusia (42%), dry eyes (40%), dry skin (26%), pruritis (26%), and vomiting (18%) (Astellas Pharma, 2019). The 16% discontinuation rate related to AEs (Astellas Pharma, 2019), which is consistent with other therapies in this population (Bellmunt et al., 2017; Powles et al., 2021).

FIGURE 1.
CASE STUDY OF ADVERSE EVENT PRESENTATION AND MANAGEMENT DURING ENFORTUMAB VEDOTIN THERAPY

A 69-year-old male former smoker presented with stage III muscle-invasive bladder cancer. His treatment course consisted of four cycles of cisplatin-based neoadjuvant chemotherapy with subsequent radical cystectomy. Six months after surgery, the patient had metastatic recurrence with pelvic and retroperitoneal lymphadenopathy and multiple pulmonary nodules. He received pembrolizumab for 11 months before disease progression, at which time he initiated enfortumab vedotin (EV).

At initiation, the patient reported no peripheral neuropathy from prior cisplatin chemotherapy, and baseline laboratory values suggested no history of diabetes. Toward the end of EV cycle 1, the patient developed grade 1 maculopapular rash and mild pruritis, affecting his upper chest and back. He was treated with an over-the-counter low-potency topical corticosteroid with improvement noted in symptoms. In cycle 2, his itching and rash recurred, involving the torso and arms and covering approximately 15% of his body surface area (grade 2), with significant associated pruritis. The patient was prescribed a high-potency topical corticosteroid with plans for dermatology referral should the rash progress further. At this time, he also reported mild numbness and tingling, now involving the entire foot and lower legs bilaterally. He reported a trip and near fall, as well as numbness involving the first three fingers of bilateral hands, interfering with his ability to button his shirts or zip his pants. Examination revealed evidence of impaired sensation in bilateral upper and lower extremities determined to be grade 2. The EV dose was withheld.

When the patient returned after a three-week delay for reconsideration of cycle 4 therapy, he reported improvement in the numbness and tingling in his hands, legs, and feet. He noted improvement in fine motor function of his hands, and his gait was stable on examination. The peripheral neuropathy symptoms were determined to be grade 1, and EV was resumed at the same dose. His rash had resolved after the treatment delay but recurred intermittently as treatment continued, typically improving after his week off from EV. The rash remained grade 1 with use of high-potency topical steroids, as needed. As he continued through cycle 5 of EV therapy, grade 2 peripheral neuropathy symptoms recurred, and EV was withheld. Two doses were held, and the beginning of cycle 6 was delayed by one week, at which time peripheral neuropathy symptoms returned to grade 1, and EV was resumed at a reduced dose. The patient noted that his rash appeared less frequently, and he required fewer days of topical steroid while receiving the reduced dose of EV.

“The most enfortumab vedotin adverse events can be mitigated with medication, self-care, and dose modifications.”

Clinical Management of Adverse Events
This article provides practical recommendations to help nurses, advanced practitioners, and other clinicians manage select EV-related AEs based on published literature and guidelines when available, as well as expert opinion and clinical experience. Always refer to the current EV prescribing information for the most up-to-date dose modification and toxicity management guidance as new data becomes available. Summaries of...
key nursing and patient education considerations are provided in Figures 2 and 3, respectively. Although thorough assessment is essential to identify and address any AE or functional decline, this article focuses on skin reactions, peripheral neuropathy, ocular disorders, and hyperglycemia, with additional discussion of gastrointestinal and hematologic toxicities. With proactive monitoring, identification, and management of these AEs, nurses can help prevent or alleviate symptoms that might otherwise lead to treatment interruption or discontinuation.

Skin Reactions
Skin reactions are anticipated during EV treatment because of the presence of low-to-moderate levels of Nectin-4 in skin keratinocytes, sweat glands, and hair follicles (Challita-Eid et al., 2016). In the EV clinical trials, skin reactions occurred in 54% of EV-treated patients (26% maculopapular rash, 30% pruritus), including 10% with grade 3–4 reactions that included symmetrical drug-related intertriginous and flexural exanthema, bullous dermatitis, exfoliative dermatitis, and palmar-plantar erythrodysesthesia (Astellas Pharma, 2019). Treatment-related rash often presented during the first cycle in EV-201 cohort 1, with a median onset of 0.53 months (range = 0.03–7.39) from the start of treatment (Rosenberg et al., 2019). At the time of last follow-up, among those who experienced rash, 73% had complete resolution (median = 0.72 months, range = 0.03–2.66), 20% showed improvement (median = 0.72 months, range = 0.03–7.2), and those with ongoing rash had predominantly grade 1 (75%).

Although maculopapular rash and pruritus were the most commonly reported skin reactions, presentation was variable in terms of type of reaction (i.e., rash, dry skin, pruritus, and hyper/hypopigmentation), type of rash (i.e., maculopapular, pustular, erythematous, and bullous), distribution (i.e., localized or widespread), location (i.e., chest, back, arms, thighs, axillae), and characterization (i.e., itchy and/or painful). Although skin reactions often occur early, they may occur or recur at any time during treatment. Most skin reactions are mild and transient; however, serious presentations (including mucosal involvement, bullous lesions, or exfoliation) require prompt referral to dermatology for management based on specific etiology and diagnosis.

**RISK FACTORS:** Currently, there are no identified risk factors for developing skin reactions while on EV treatment. In general, characteristics that may predispose patients to skin reactions include prior history of a dermatologic condition, rash/pruritus, allergies, dry skin, immunosuppression, and/or high sun exposure.

**FIGURE 2.**
**PATIENT EDUCATION AND COUNSELING CONSIDERATIONS FOR SYMPTOM MONITORING AND MANAGEMENT IN PATIENTS ON ENFORTUMAB VEDOTIN THERAPY**

**SKIN REACTIONS**
- Potential for skin reactions and presenting signs or symptoms
- Importance of early reporting and management to mitigate toxicity
- Skin protection, including covering with clothing/hats and sunscreen use
- Consideration of prophylactic gentle, unscented moisturizers, creams, or emollients twice daily
- Avoidance of hot baths/showers if experiencing pruritus
- Appropriate use of topical or systemic steroids and antihistamines (if clinically indicated)

**PERIPHERAL NEUROPATHY**
- Potential for sensory and motor neuropathy and signs and symptoms to report
- Importance of early reporting and management to mitigate toxicity
- Hard-soled slippers or shoes to reduce risk of foot injury (for patients with impaired sensation)
- Regular self-examination of feet for injury or impaired skin integrity (for patients with impaired sensation)

**OCULAR DISORDERS**
- Potential for ocular toxicity and symptoms to monitor for or report
- Artificial tears to maintain moisture of the eyes

**HYPERGLYCEMIA**
- Potential for and symptoms of hyperglycemia
- Diet and activity to promote metabolic health and glucose control
- Rationale and technique for monitoring blood glucose readings at home (if clinically indicated)
- Antihyperglycemic medications and adherence reinforcement (if clinically indicated)

**GASTROINTESTINAL EVENTS**
- Potential gastrointestinal toxicities, including reduced appetite, taste changes, nausea, and diarrhea
- Use of over-the-counter antidiarrheal and reporting symptoms not responding to antidiarrheals within 24 to 48 hours
- BRAT diet and avoidance of dairy and heavily spiced foods while experiencing diarrhea
- Adequate oral hydration with reduced appetite, oral intake, and/or diarrhea
- Nonpharmacologic strategies for taste changes and reduced appetite

**HEMATOLOGIC EVENTS**
- Potential hematologic toxicity
- Need for a thermometer in the home
- Immediately reporting temperature of 100.4°F or greater
- Frequent hand hygiene

**Note.** Based on information from Astellas Pharma, 2019; Bensadoun et al., 2013; Lyckholm et al., 2012; Murtaza et al., 2017; Rehwoldt et al., 2009; Salzmann et al., 2019; Wu & Adamson, 2019.
ENFORTUMAB VEDOTIN

MONITORING/PREVENTION: Advise patients of the potential for skin reactions, common presentations, and the importance of early reporting. For patients with a skin reaction, full-body examination helps ensure accurate estimation of the affected body surface area. Treating mild skin reactions allows for more rapid and effective management, potentially preventing development of severe skin reactions that could lead to treatment delays.

General advice for skin care during and after cancer treatment includes sunscreen (SPF 30 or greater and free of para-aminobenzoic acid); lukewarm rather than hot showers; proper hydration; frequent use of emollients; mild detergents and skin cleansers; alcohol-free, fragrance-free hypoallergenic moisturizers; hypoallergenic makeup; and avoidance of over-the-counter (OTC) acne medications (Bensadoun et al., 2013).

PERIPHERAL NEUROPATHY
- Recognize and manage peripheral neuropathy early to help reduce potential for severe or irreversible peripheral neuropathy.
- Perform peripheral neuropathy evaluation; perform review of systems and conduct passive and active physical assessments, including musculoskeletal and neurologic examinations.
- Evaluate for alternative contributing etiologies of symptoms (e.g., benign spinal disorders, vascular dysfunction, metastatic spinal cord compression).
- Consider specialty referral, as appropriate.
- Hold enfortumab vedotin for grade 2 or greater peripheral neuropathy until grade 1 or lower. Reduce enfortumab vedotin dose for recurrent grade 2 neuropathy.

OCULAR DISORDERS
- Many patients report bothersome dry eyes and reflexive excessive tearing; recommend artificial tears or ophthalmic steroids (if indicated after ophthalmic evaluation) to alleviate dry eyes and reflexive excessive tearing.
- Refer to ophthalmology/optometry at onset of new or worsened ocular symptoms.

HYPERGLYCEMIA
- Optimize glucose control prior to initiating therapy, if cancer status allows.
- Consider baseline hemoglobin A1C testing.

INTERVENTIONS: As detailed in Table 1, dose interruption, reduction, and/or permanent discontinuation is recommended for grade 3–4 skin reactions, based on National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.03, and body surface area estimation.

Pharmacologic therapies for rash include topical corticosteroids, such as OTC hydrocortisone (low potency), triamcinolone (medium potency), and clobetasol (high potency); oral or topical antihistamines (diphenhydramine or less-sedating antihistamines, such as cetirizine) (Wu & Adamson, 2019); and systemic corticosteroids for severe cases (Rosenberg et al., 2019; Salzmann et al., 2019; Wu & Adamson, 2019). Topical antibiotics or antifungals may be needed to treat secondary infections. Nonpharmacologic strategies for anticancer treatment-induced rash include fragrance-free moisturizers applied twice daily.

FIGURE 3.
NURSING CONSIDERATIONS FOR SYMPTOM MONITORING AND MANAGEMENT IN PATIENTS ON ENFORTUMAB VEDOTIN THERAPY

SKIN REACTIONS
- Perform thorough assessment for presence and extent of rash at each visit.
- Refer for dermatology evaluation and joint management for rashes that involve the mucosa, bullous lesions or exfoliation, or do not respond to over-the-counter or prescription topical steroids, systemic antihistamines, or dose holds.
- Hold enfortumab vedotin for grade 3 or greater skin reactions; see prescribing information for details on resuming drug and dose reductions.
- Monitor for secondary skin infections.

GASTROINTESTINAL EVENTS
- Monitor for gastrointestinal symptoms at each visit.
- Consider referral to primary care and/or endocrinology for collaborative monitoring and management of treatment-emergent hyperglycemia, as indicated.

HEMATOLOGIC EVENTS
- Monitor complete blood count with differential prior to each enfortumab vedotin dose.
- Hold enfortumab vedotin for grade 3 or greater hematologic toxicity or grade 2 or greater thrombocytopenia.
- See prescribing information for guidance on dose reductions.

Note. Based on information from Astellas Pharma, 2019; Bensadoun et al., 2013; Lyckholm et al., 2012; Murtaza et al., 2017; Rehwaldt et al., 2009; Salzmann et al., 2019; Wu & Adamson, 2019.
(ideally within 15 minutes after showering/bathing). In general, gentle, unscented creams and emollients, such as white petrolatum at least twice daily, are recommended prophylactically and after rash appears (Bensadoun et al., 2013). Creams containing anti-itch ingredients, such as pramoxine, camphor, menthol, or oatmeal, may be helpful for itchy rash (Pernambuco-Holsten, 2013).

A referral to dermatology for evaluation and further management is indicated for skin reactions that exceed 30% of body surface area (grade 3 or higher), involve the mucosa, bullous lesions, or exfoliation, or do not respond to a combination of steroids, antihistamines, and dose modifications. Early referral to dermatology for lower-grade skin reactions is also a reasonable approach for proactive evaluation and management.

**Peripheral Neuropathy**

Peripheral neuropathy (PN) is a clinically relevant adverse effect of several anticancer therapies, including platinum- and taxane-based chemotherapies and MMAE-containing ADC agents, that may limit treatment duration and impair quality of life (Hershman et al., 2014; Masters et al., 2018). In EV-201 cohort 1, treatment-related PN occurred in 50% of patients, with sensory PN (i.e., pain/burning, numbness, tingling, or loss of sensation) reported more frequently (44%) than motor PN (i.e., loss of coordination and/or muscle weakness) (14%) (Rosenberg et al., 2019). Most PN was grade 1–2, and onset occurred at a median of 2.43 months (range = 0.03–7.39) after starting treatment. At last evaluation, 76% of patients who experienced any grade PN had resolution or ongoing grade 1 PN, with a median of 1.18 months (range = 0.26–4.86) to improvement and 1.48 months (range = 0.23–11.6) to resolution.

**RISK FACTORS:** In addition to certain anticancer therapies, risk factors for PN include comorbidities (e.g., diabetes mellitus), older age, spinal involvement of mUC, and nonmalignant spinal disease. In EV-201 cohort 1, where grade 2 or higher PN was an exclusion criterion, 52% of patients with PN at baseline had worsening PN during treatment, similar to the rate of PN in the overall population (Rosenberg et al., 2019). Therefore, pre-existing PN does not appear to be a risk factor for worsening PN with EV therapy.

**MONITORING/PREVENTION:** Early identification and management of PN is essential. Assess and document symptoms, perform a thorough neurologic and musculoskeletal evaluation, and assess impact on daily function at baseline and at each clinical visit. Table 2 provides a checklist for PN assessment, which can be helpful for evaluating the extent and severity of PN. Referral to specialty providers may be necessary to assess for other contributing factors, such as vascular evaluation of circulatory etiologies.

<table>
<thead>
<tr>
<th>TABLE 1.</th>
<th>ENFORTUMAB VEDOTIN DOSE REDUCTION AND MODIFICATIONS</th>
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</thead>
<tbody>
<tr>
<td>ADVERSE REACTION</td>
<td>SEVERITY</td>
</tr>
<tr>
<td>Hematologic toxicity</td>
<td>Grade 3 or grade 2 thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>Blood glucose greater than 250 mg/dl</td>
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<tr>
<td>Peripheral neuropathy</td>
<td>Grade 2</td>
</tr>
<tr>
<td></td>
<td>Grade 3 or greater</td>
</tr>
<tr>
<td>Skin reactions</td>
<td>Grade 3 (severe)</td>
</tr>
<tr>
<td></td>
<td>Grade 4 or recurrent grade 5</td>
</tr>
<tr>
<td>Other nonhematologic toxicity</td>
<td>Grade 3</td>
</tr>
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<td></td>
<td>Grade 4</td>
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</tbody>
</table>

Note. The recommended starting dose is 1.25 mg/kg, up to 125 mg. The first dose reduction is 1 mg/kg, up to 100 mg; the second dose reduction is 0.75 mg/kg, up to 75 mg; and the third dose reduction is 0.5 mg/kg, up to 50 mg.

Patients have different levels of tolerance for PN symptoms, and underreporting the magnitude of PN is a concern among patients wishing to avoid treatment delay or discontinuation. In the authors’ experience, early detection and management has the potential to allow some recovery from symptoms and prevent worsening PN. Educate patients and caregivers about signs and symptoms of PN (sensory PN: pain/burning, numbness, tingling, or loss of sensation; motor PN: loss of coordination, muscle weakness) and the importance of prompt reporting and management to reduce risk of severe and potentially irreversible symptoms.

INTERVENTIONS: EV-related PN is managed using a combination of dose interruptions, reductions, and discontinuation using CTCAE grading criteria. Dose interruption is recommended at the first sign of grade 2 PN until improvement to grade 1 or resolution. For a recurrent episode, EV should be held, then resumed at a lower dose. Grade 3 or higher PN warrants permanent discontinuation of EV. In addition, significant or refractory PN justifies referral to neurology for evaluation and management.

For patients with grade 2 or lower PN who continue on EV, consider adjunctive pharmacologic therapy for PN symptoms. Although there are no agents specifically recommended for managing EV-associated PN, the American Society of Clinical Oncology (ASCO) and joint European expert clinical practice guidelines recommend duloxetine and other alternatives for painful PN (Hershman et al., 2014; Jordan et al., 2020).

Nonpharmacologic therapies may be used for PN, but evidence to support their efficacy is lacking. Physical and occupational therapies and rehabilitation support may help improve functional deficits resulting from PN (National Institute of Neurological Disorders and Stroke [NINDS], 2018). For motor PN, mechanical aids such as hand or foot braces may reduce physical disability and pain, improve gait disturbances, and help prevent foot injuries (NINDS, 2018).

Ocular Disorders

Ocular events occurred in 46% of EV-treated patients (Astellas Pharma, 2019). The majority of these events were associated with dry eyes, including blurred vision and corneal events of keratitis and limbal stem cell deficiency. Dry eye symptoms occurred in 36% of patients and blurred vision in 14% of patients, with a median onset of 1.9 months (range = 0.3–6.2) from starting treatment.

RISK FACTORS: Older age is a risk factor for dry eyes (Schaumberg et al., 2009). Ocular manifestations, such as keratitis and corneal ulcerations, have been reported with other anticancer therapies, including ADC agents (Eaton et al., 2015; Harman, 2016), and were exclusion criteria for the EV-201 trial. Contact lens use increases the risk of developing keratitis; therefore, favoring eyeglasses while on treatment is prudent.

MONITORING/PREVENTION: Baseline and routine eye examinations are not required (Astellas Pharma, 2019) but may be considered for patients with known ocular disorders. Artificial tears are recommended for prophylaxis of dry eyes and may help with reflexive tearing. In the authors’ experience, patients reported that blurry vision, dry eyes, and reflexive tearing can have a significant impact on quality of life and disrupt activities such as driving, reading, and watching television.

### TABLE 2.
CHECKLIST FOR NURSING ASSESSMENT AND MANAGEMENT OF PERIPHERAL NEUROPATHY IN PATIENTS ON ENFORTUMAB VEDOTIN THERAPY

<table>
<thead>
<tr>
<th>Screening Questions at Every Visit</th>
<th>IF Patient Answers Yes</th>
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<tbody>
<tr>
<td>Have you developed any numbness, tingling, or discomfort in your hands or feet since starting treatment?</td>
<td>Continue with questioning.</td>
</tr>
<tr>
<td>Have you developed any new or worsened weakness in your arms or legs since starting treatment?</td>
<td>Perform complete pain assessment: PQRST or other comprehensive pain assessment. Consider pharmacologic agents for neuropathic pain.</td>
</tr>
<tr>
<td>Do you have pain or discomfort, such as burning or pins and needles?</td>
<td>Conduct functional assessment of fine motor skills: observe patient buttoning, zipping, threading a needle, and/or signing their name. Assess upper-extremity strength and sensation. Conduct physical and/or occupational therapy and home safety assessment. Educate on safety precautions for ischemic or thermal injury prevention.</td>
</tr>
<tr>
<td>Do you have numbness or tingling in your fingers or hands or weakness in the arms?</td>
<td></td>
</tr>
<tr>
<td>Do these symptoms interfere with writing, grasping small objects, or fastening clothes?</td>
<td></td>
</tr>
<tr>
<td>Do you have numbness or tingling in your toes or feet or weakness in your legs?</td>
<td>Conduct functional assessment of gait and balance. Assess lower-extremity strength and sensation. Educate on fall precautions and use of assistive devices, as warranted.</td>
</tr>
<tr>
<td>Do these symptoms interfere with your ability to walk or interfere with your balance?</td>
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</table>

PQRST—provocation, quality, region, strength, and timing

INTERVENTIONS: Dose modifications for symptomatic ocular disorders are guided by the EV prescribing information regarding other nonhematologic toxicities. These include dose interruption for grade 3 events and permanent discontinuation for grade 4 events.

In general, grade 3 or lower dry eyes can be managed with artificial tears or ophthalmic topical steroids (if indicated after ophthalmic evaluation). Consider referral to ophthalmology/optometry for dry, watery eyes; blurred vision; eye pain; or other ocular symptoms that persist or recur. Advise patients and caregivers to alert their eye care professional about their EV therapy.

Hyperglycemia
In clinical trials, diabetes has been reported in 20% of patients with mUC (Galsky et al., 2018; Niegisch et al., 2018). Hyperglycemia in patients on anticancer therapy may be associated with acute and serious clinical scenarios, such as infection; acid-base, fluid, and electrolyte disorders; and progression to ketoacidosis, in addition to the long-term cardiovascular, renal, and neuropathic risks. In EV-201 cohort 1, patients with a history of diabetes mellitus were included, but those with uncontrolled diabetes (i.e., hemoglobin A1C of 8% or greater, or 7% or greater with associated diabetes symptoms) were excluded. At baseline, 15% of patients had hyperglycemia. Treatment-related hyperglycemia was observed in 11% of patients overall, including 32% of those with and 8% of those without preexisting hyperglycemia, with a median onset of 0.58 months (range = 0.26–9.23) from starting treatment (Rosenberg et al., 2019). Median time to improvement of hyperglycemia was 0.89 months (range = 0.59–1.18), and median time to resolution was 1.12 months (range = 0.26–6.47).

RISK FACTORS: When evaluating hyperglycemia in a patient on anticancer therapy, consider potential risk factors, including but not limited to diabetes mellitus, illness/infection, and use of systemic steroids. Hyperglycemia occurred in the EV clinical trials, and grade 3 or greater events increased consistently in patients with higher body mass index and higher baseline hemoglobin A1C (Astellas Pharma, 2019).

MONITORING/PREVENTION: Assessing baseline hemoglobin A1C is prudent before starting EV, and routine monitoring of nonfasting blood glucose levels is recommended prior to each EV dose. If hyperglycemia is present, investigate all potential etiologies, including steroid use and infection (Davies et al., 2018). Consider home glucose monitoring if pre-dose blood glucose values are increasing.

Patients with a history of diabetes or hyperglycemia should continue to see their endocrinologist/primary care provider and inform them of their EV therapy. For these patients, consider optimizing blood glucose control prior to starting EV as their cancer status allows. Educating patients about the potential for hyperglycemia, the importance of recognizing and reporting symptoms, and the potential for serious complications is essential. Advise patients to watch for and report frequent urination, increased thirst, blurred vision, confusion, drowsiness, loss of appetite, fruity breath smell, nausea, vomiting, or stomach pain. Counseling on lifestyle modifications, such as a healthy diet low in simple carbohydrates, regular exercise, and weight loss (if indicated) is sensible.

INTERVENTIONS: Patients who experience hyperglycemia should be treated according to the local standard of care, including use of oral and/or injectable antihyperglycemic medication and consideration of referral to endocrinology. For nonfasting blood glucose greater than 250 mg/dl, withhold EV, regardless of the cause, until blood glucose has improved to 250 mg/dl or lower and then resume at the same dose level (Astellas Pharma, 2019).

Gastrointestinal Adverse Events
Patients on anticancer therapy often experience gastrointestinal AEs, such as nausea, diarrhea, vomiting, appetite loss, and dysgeusia, which can lead to decline in nutritional and hydration status. Ensuring adequate nutrition and hydration is essential to avoid complications, such as renal dysfunction, functional decline, fluid–electrolyte imbalance, and fatigue. Dose modifications for gastrointestinal AEs are guided by the EV prescribing information regarding other nonhematologic toxicities. Patients may better tolerate dysgeusia symptoms if they are aware of the potential for taste alterations and reduced appetite (Murtaza et al., 2017). Supportive care strategies include using lemon juice and chewing gum prior to meals; having small frequent meals, good oral hygiene; drinking water with meals; using plastic instead of metal utensils; using more/less salt and flavoring for food; and avoiding foods with strong smells (Murtaza et al., 2017; Rehwaldt et al., 2009). Zinc supplements may be helpful for dysgeusia, but current evidence is conflicting (Lyckholm et al., 2012; Murtaza et al., 2017).

Hematologic Adverse Events
Hematologic toxicities may occur at any time during anticancer therapy. Dose interruption, reduction, and/or permanent discontinuation of EV is recommended for grade 3–4 hematologic laboratory abnormalities or grade 2 or greater thrombocytopenia. Although the incidence of treatment-related grade 3–4 hematologic toxicities in EV-201 cohort 1 was less than 10% (Rosenberg et al., 2019), these are important side effects requiring patient education and nurse management. Regular monitoring is necessary to detect hematologic laboratory abnormalities, including neutropenia, anemia, and thrombocytopenia.

IMPLICATIONS FOR PRACTICE
- Enhance nursing knowledge of the enfentumab vedotin (EV) mechanism of action and applications for use in patients with cancer.
- Promote effective nursing assessment and management of select EV-related adverse events.
- Inform nurses on critical components of patient education around select potential adverse events, presenting symptoms, and what or when to report to providers.
**Implications for Nursing**

Oncology nurses, including bedside, infusion, clinical trials, advanced practice, and oncology nurse navigators, have an essential role in monitoring and managing AEs in patients undergoing cancer treatment, as well as educating patients and caregivers about expectations regarding AEs. Nursing assessment, including discussion with patients and caregivers, active and passive physical examination, and review of laboratory assessments, is critical for the safe care of patients receiving EV. Given the weekly administration schedule, nurses are positioned to play a critical role in identifying and managing treatment-emergent AEs. Through careful monitoring and prompt intervention, most EV-related AEs can be mitigated with medications, self-care, and/or dose modifications, potentially maximizing patient benefit from this promising therapy.

**Conclusion**

EV monotherapy has consistently shown activity in patients with locally advanced UC or mUC, and therapeutic clinical trials are ongoing in other disease settings and in combination with other anticancer agents. Nursing familiarity with this drug, its effects, and appropriate patient monitoring and management is poised to become increasingly important in the clinical oncology setting.

Amanda Pace, BSN, RN, OCN®, is a research nurse in genitourinary medical oncology at the Dana-Farber Cancer Institute in Boston, MA; Blaine Brower, MSN, RN, FNP-BC, is a nurse practitioner in genitourinary medical oncology at University of North Carolina Healthcare in Chapel Hill; Dawn Conway, BSN, RN, OCN®, is a nurse navigator in genotypeiu medical oncology at University of Chicago Medicine in Illinois; and Dayna Leis, BSN, RN, OCN®, is a senior clinical research nurse in genitourinary medical oncology at NYU Langone Health in New York. Pace can be reached at apace2@partners.org, with copy to CJONEditor@ons.org. (Submitted July 2020. Accepted October 21, 2020.)

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