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Positive Quality Intervention: Enfortumab Vedotin-ejfv (Padcev®) Management for Advanced or Metastatic Urothelial Carcinoma

Description: The purpose of this PQI is to understand the management techniques and interventions related to the utilization of enfortumab vedotin-ejfv.

Background: Enfortumab vedotin-ejfv (EV) is a nectin-4 targeting antibody conjugated to the microtubule inhibitor monomethyl auristatin E (MMAE).[1] EV is approved by the FDA as single agent for the treatment of locally advanced or metastatic (LA/m) urothelial carcinoma in patients who: 1) previously received a programmed death receptor (PD-1) or programmed death receptor ligand (PD-L1) inhibitor and a cisplatin-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced, or metastatic setting, or 2) are cisplatin-ineligible and have received at least one prior line of therapy.[1] Clinical trials ranging from phase IB to III conducted over the past decade, including EV-201, EV-301, EV-103/KEYNOTE-869, and EV-302/KEYNOTE-A39 consistently demonstrated survival benefits in patients treated with enfortuman vedotin, first as monotherapy and later combined with pembrolizumab, compared to chemotherapy.[2-6] Enfortumab vedotin is now also approved in combination with pembrolizumab as initial treatment for LA/m urothelial cancer. Use of this combination treatment is discussed in another PQI: Positive Quality Intervention: Enfortumab Vedotin-ejfv (Padcev®) and Pembrolizumab (Keytruda®) Management for Advanced or Metastatic Urothelial Carcinoma

PQI Process: Upon order of enfortumab vedotin administration

- Confirm appropriateness of enfortumab vedotin utilizing the EMR
  - Testing for nectin-4 or PD-L1 expression is not required and is not used for treatment decisions
- Review adverse events and interventions suggested as needed (see Supplemental Information: Table 1)
- Review dose specific adjustments as required (see Supplemental Information: Table 2)
- Drug interaction considerations[1]
  - Enfortumab vedotin is metabolized via CYP3A4, and concomitant use of an antibody-drug conjugate containing MMAE and dual P-gp and strong CYP3A4 inhibitors should be considered; dose adjustment is typically not required and has not been studied but this interaction may result in increased toxicities

Patient-Centered Activities:

- Administer appropriate anti-emetics for pre-medication. Across trials, fewer than 20% of patients treated with enfortumab vedotin experienced vomiting.[1] Among patients who had vomiting, < 5% had severe (Grade 3-4) vomiting.[3]
- Advise patients that skin toxicities for enfortumab vedotin are likely to manifest as dry skin, pruritus, and/or maculopapular rash[1]
  - Severe (Grade 3-4) skin toxicities (14% incidence) included symmetrical drug-related intertriginous and flexural exanthema (SDRIFE), bullous dermatitis, exfoliative dermatitis, and palmar-plantar erythrodysesthesia and need to be evaluated urgently[1]
  - Enfortumab vedotin has a boxed warning for Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)
    - Discontinue treatment if SJS or TEN are confirmed, or if or Grade 4 or recurrent Grade 3 skin reactions occur

    - Most common in first cycle but may occur later in therapy
- Advise patients to self-monitor for and report symptoms of peripheral neuropathy. Sensory neuropathy (38%) was more common than motor (7%).[1] EV-pembrolizumab combination has shown a higher incidence of peripheral neuropathy compared to EV monotherapy (67% versus 53%, respectively).[1]
    - See **Chemotherapy Induced Peripheral Neuropathy** PQI
- Skin and soft tissue reactions following infusion site extravasation occurred in 1% of patients across single agent trials and 0.3% of patients (2 patients) experienced Grade 3-4 reactions.[1] Symptoms worsened until 2-7 days after infusion and resolved within 1-4 weeks of the symptom peak. Monitor for infusion site extravasation and stop the infusion if it occurs.[1]
- Patient Assistance: **NCODA Financial Assistance Tool**

References:

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6. Powles, T., Valderrama, B. P., Gupta, S., Bedke, J., Kikuchi, E., Hoffman-Censits, J., Iyer, G., Vulsteke, C., Park, S. H., Shin, S. J., Castellano, D., Fornarini, G., Li, J.-R., Gümüş, M., Mar, N., Loriot, Y., Fléchon, A., Duran, I., Drakaki, A., … van der Heijden, M. S. (2024). Enfortumab vedotin and pembrolizumab in untreated advanced urothelial cancer. *New England Journal of Medicine*, *390*(10), 875–888.
7. Lacouture, M. E., Patel, A. B., Rosenberg, J. E., & O'Donnell, P. H. (2022). Management of Dermatologic Events Associated With the Nectin-4-directed Antibody-Drug Conjugate Enfortumab Vedotin. *The oncologist*, *27*(3), e223–e232.

Supplemental Information:

Table 1: Selected Adverse Events and Suggested Interventions

Event	Severity/Incidence*	Suggested Intervention	Comments*
Skin Reactions	58% (any Grade), 17% Grade 3-4[1,3-5]	Fragrance-free moisturizers/ointments, antihistamines, topical or systemic steroids as indicated[7]	Median time of onset for severe skin reactions was 0.6 months (range 0.1 – 8)[1,3-5]
Hyperglycemia	17% (any Grade) regardless of known hyperglycemia at baseline[1,3-5] Fatal events occurred in 2 patients Baseline hyperglycemia or BMI ≥30 kg/m^2 were associated with a higher rate of treatment-emergent hyperglycemia[5]	Blood glucose test prior to infusion – as part of basic metabolic panel is appropriate Does not need to be fasting	BMI and elevated A1c correlated to a higher incidence of Grade 3/4 hyperglycemia.[1,3-5] Patients with baseline A1c ≥ 6.5% should be referred to an appropriate provider for glucose management[1,3-5] Patients with HbA1c ≥8% were excluded from clinical trials
Ocular Toxicity	Ocular disorders including blurred vision, keratitis, limbal stem cell deficiency, etc. – 40%[1,3-5] Dry eye symptoms – 30%[1, 3-5]	Consider prophylactic artificial tears[1] and consider topical ophthalmic steroids after eye exams[1,3-5]	Median time to onset for ocular disorders was 1.7 months (range 0 – 30.6)[1,3-5]

Neuropathy	53% (any Grade)[1,3-5] Peripheral sensory neuropathy was the most common reason for dose reduction With pembrolizumab: 67% any Grade, 36% Grade 2, 7% Grade 3[1,2]	Recommend dose reduction as initial strategy to prevent worsening neuropathy Consider use of gabapentin or duloxetine for treatment of sensory neuropathy†	The median time to onset of Grade ≥ 2 for single agent was 4.9 months (range 0.1 – 20).[1,3-5] Of patients who had data on resolution (N = 296), by time of final evaluation 11% had total resolution, 89% had residual neuropathy. Of those with residual symptoms, 50% had Grade ≥ 2[1]
Diarrhea	24-45% (any Grade)[1,3-5]	Recommend as needed or scheduled anti-diarrheal medications	Grade 4 diarrhea that improves to < Grade 2 within 72 hours with supportive management does not require discontinuation of treatment[5]

* Data for single agent enfortumab vedotin unless otherwise noted

† Limited data for treatment of motor neuropathy

Table 2: Dose and Adjustments for Adverse Events[1]

Administration	Single agent: IV infusion over 30 minutes on days 1, 8, 15 of a 28-day cycle until progression/toxicity	
Starting dose	1.25 mg/kg up to 125 mg*	
First dose reduction	1 mg/kg up to 100 mg*	
Second dose reduction	0.75 mg/kg up to 75 mg*	
Third dose reduction	0.5 mg/kg up to 50 mg*	
Renal/hepatic dysfunction	No dose adjustment is required for renal dysfunction No current studies in moderate to severe hepatic dysfunction (total bilirubin >1.5 x ULN and AST any) – consider avoiding	
Adverse Event	**Grade/Severity**	**Dose Modification**
Hyperglycemia	Blood glucose > 250 mg/dL	Hold until ≤ 250 mg/dL, then resume at same dose level
Peripheral neuropathy	2	Hold until Grade ≤ 1, then resume at same dose level or reduced by one level
	≥ 3	Permanently discontinue
Skin reactions	3	Hold until Grade ≤ 1, then resume at same dose level or reduced by one level
	4 or recurrent 3	Permanently discontinue
Other non-hematologic toxicities	3	Hold until Grade ≤ 1, then resume at same dose level or reduced by one level
	4	Permanently discontinue
Hematologic toxicity	3 or 2 thrombocytopenia	Hold until Grade ≤ 1, then resume at same dose level or reduced by one level
	4	Hold until Grade ≤ 1, then resume at same dose level or reduced by one level
Pneumonitis	2	Hold until Grade ≤ 1 for persistent or recurrent Grade 2, consider dose reduction by one level
	≥ 3	Permanently discontinue

* Based on actual body weight. Dose is capped for patients ≥100 kg