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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 enfortumab 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]
  - The MMAE portion of EV is metabolized via CYP3A4, and concomitant use of an antibody-drug conjugate containing MMAE with dual P-gp and/or 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:

1. Padcev® (enfortumab vedotin- ejfv) [Prescribing Information].
2. Hoimes CJ, Flaig TW, Milowsky MI, et al. Enfortumab vedotin plus pembrolizumab in previously untreated advanced urothelial cancer. J Clin Oncol. 2023;41(1):22-31.
3. Yu EY, Petrylak DP, O'Donnell PH, et al. Enfortumab vedotin after PD-1 or PD-L1 inhibitors in cisplatin-ineligible patients with advanced urothelial carcinoma (EV-201): a multicentre, single-arm, phase 2 trial. Lancet Oncol. 2021;22(6):872-882.
4. Balar AV, McGregor BA, Rosenberg JE, et al. EV-201 Cohort 2: Enfortumab vedotin in cisplatin-ineligible patients with locally advanced or metastatic urothelial cancer who received prior PD-1/PD-L1 inhibitors. J Clin Oncol. 2021;39(6_suppl):394-394.
5. Powles T, Rosenberg JE, Sonpavde GP, et al. Enfortumab vedotin in previously treated advanced urothelial cancer. N Engl J Med. 2021;384(12):1125-1135.
6. Powles T, Valderrama BP, Gupta S, et al. Enfortumab vedotin and pembrolizumab in untreated advanced urothelial cancer. N Engl J Med. 2024;390(10):875-888.
7. Lacourture ME, Patel AB, Rosenberg JE, O'Donnell PH. Management of Dermatologic Events Associated with the Nectin-4-directed Antibody-Drug Conjugate Enfortumab Vedotin. Oncologist. 2022;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), 14% 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	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 pembrolizumab: 67% any Grade, 36% Grade 2, 7% Grade 3[1,2]		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
Pneumonitis/Interstitial Lung Disease	2	Hold until Grade ≤ 1, then resume at same dose level or consider reduction by one level
	≥ 3	Permanently discontinue
Peripheral neuropathy	2	For 1st occurrence, hold until Grade ≤ 1, then resume at same dose level. For recurrence, hold until Grade ≤ 1, then resume reduced by one level
	≥ 3	Permanently discontinue
Skin reactions	Persistent or recurrent Grade 2	Consider holding until Grade ≤ 1, then resume at same dose level or reduced by one level
	3	Hold until Grade ≤ 1, then resume at same dose level or reduced by one level
	Suspected SJS or TEN	Immediately hold, consult specialist to confirm diagnosis. If not SJS or TEN, see Grade 2-4 skin reactions
	Confirmed SJS or TEN; Grade 4 or recurrent Grade 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

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