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

Description: The purpose of this PQI is to understand the management techniques and interventions when utilizing enfortumab vedotin.

Background: Enfortumab vedotin is a nectin-4 targeting antibody conjugated to the microtubule inhibitor monomethyl auristatin E (MMAE).[1] Enfortumab vedotin is approved by the FDA for the treatment of advanced or metastatic urothelial carcinoma in patients who have previously received a programmed death receptor (PD-1) or programmed death receptor (PD-L1) inhibitor and a cisplatin-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced, or metastatic setting.[1] More recently, the FDA expanded that approval to include patients who are cisplatin-ineligible and have received at least one prior line of systemic treatment.[1] In cohort 1 of the pivotal open-label phase II trial EV-201, patients were heavily pretreated and all had prior cisplatin treatment (50% received ≥3 prior treatments), and the objective response rate was 44%, including 12% complete responses.[2] Adverse effects were common, and 54% of patients had a grade ≥ 3 treatment-related adverse event, but these adverse events were manageable and no single grade ≥ 3 adverse event occurred in more than 10% of patients.[2] Treatment-related adverse effects led to dose reduction in 32% of patients and discontinuation in 12% of patients.[2] Cohort 2 of EV-201, published later, demonstrated the benefit of enfortumab vedotin specifically in patients who had not received cisplatin prior, with 52% of patients achieving an objective response and 20% with complete response.[3] The phase III EV-301 trial confirmed the benefit of enfortumab vedotin compared to chemotherapy after treatment with cisplatin followed by immunotherapy (median overall survival, 12.88 vs. 8.97 months; hazard ratio for death, 0.70; 95% confidence interval, 0.56 to 0.89; P=0.001 with comparable incidence of treatment-emergent adverse events (93.9% in the enfortumab vedotin group and 91.8% in the chemotherapy group).[4]

PQI Process: Upon order of enfortumab vedotin administration

- Confirm appropriateness of enfortumab vedotin utilizing the EMR
- 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 strong CYP3A4 inhibitors should be considered. Dose adjustment is typically not required

Patient Centered Activities:

- Advise patients that skin toxicities for enfortumab vedotin are likely to manifest as dry skin, pruritus, and/or maculopapular rash[1]
    - Severe skin toxicities (10% incidence) included symmetrical drug-related intertriginous and flexural exanthema (SDRIFE), bullous dermatitis, exfoliative dermatitis, and palmar-plantar erythrodysesthesia[1]

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- Advise patients to self-monitor for peripheral sensory neuropathy and motor neuropathy. Sensory neuropathy (44%) was more common than motor (14%)[1,2]
    - See **Chemotherapy Induced Peripheral Neuropathy** PQI

Supplemental Information:

Table 1: Selected Adverse Events and Suggested Interventions

Event	Severity/Incidence	Suggested Intervention	Comments
Skin Reactions	54% (any grade)[1]	Fragrance-free moisturizers/ointments Topical steroids and antihistamines as indicated Systemic steroids as indicated	Median time of onset for severe skin reactions was 0.8 months (range 0.2 – 5.3)[1] Patients in EV-301 with grade 3 rash did not require treatment interruption if symptoms were manageable[4]
Hyperglycemia	11% (any grade)[1] regardless of known hyperglycemia at baseline 68% of patients with baseline hyperglycemia did not experience worsening	Blood glucose test prior to infusion – a basic metabolic panel suffices Does not need to be fasting	BMI and elevated A1c correlated to a higher incidence of grade 3/4 hyperglycemia[1] Patients with baseline A1c ≥ 8% were excluded from EV-201[2] Patients with baseline A1c ≥ 6.5% should be referred to an appropriate provider for glucose management[1]
Ocular Toxicity	Ocular disorders including blurred vision – 46%[1] Dry eye symptoms – 36%[1]	Consider prophylactic artificial tears[1] Consider topical ophthalmic steroids after ophthalmic exams[1]	Median time to onset for ocular disorders was 1.9 months (range 0.3 – 6.2)[1]
Neuropathy	49% (any grade).[1] Peripheral sensory neuropathy was the most common reason for dose reduction	Recommend dose reduction as initial strategy Consider use of gabapentin or duloxetine	The median time to onset of grade ≥ 2 was 3.8 months (range: 0.6-9.2) At the last follow-up in EV-201, 19% had complete resolution and 26% had partial improvement. 76% had resolution or ongoing grade 1 neuropathy[2]
Diarrhea	42% (any grade)[1]	Recommend anti-diarrheal medications for patient as required	Grade 4 diarrhea that resolves to grade ≤2 within 72 hours with supportive management does not require treatment interruption[4]

Table 2: Dose Adjustments for Adverse Events[1]

Administration	IV infusion over 30 minutes on days 1, 8, 15 of a 28-day cycle until progression/toxicity

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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 considerations	No dose adjustment is required for renal dysfunction No current studies in moderate to severe hepatic dysfunction – consider avoiding use Mild hepatic dysfunction does not require an upfront dose reduction	
Adverse Event	Grade/Severity	Dose Modification
Hyperglycemia	Blood glucose > 250 mg/dL	Withhold until ≤ 250 mg/dL, then resume at same dose level
Peripheral neuropathy	2	Withhold until grade ≤ 1, then resume at same dose level. If recurrence, withhold until Grade ≤ 1, then resume and reduce one dose level
	≥ 3	Permanently discontinue
Skin reactions	3	Withhold until grade ≤ 1, then resume at same dose level or consider reducing by one dose level
	4 or recurrent 3	Permanently discontinue
Other non-hematologic toxicities	3	Withhold until grade ≤ 1, then resume at same dose level or consider reducing by one dose level
	4	Permanently discontinue
Hematologic toxicity	3 or Grade 2 thrombocytopenia	Withhold until grade ≤ 1, then resume at same dose level or consider reducing by one dose level
	4	Withhold until grade ≤ 1, then resume and reduce one dose level or discontinue treatment

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

References:

1. Padcev® (enfortumab vedotin- ejfv) [Prescribing Information]. Bothell, WA: Seattle Genetics, Inc.; March 2021.
2. Rosenberg JE, O'donnell PH, Balar AV, et al. Pivotal Trial of Enfortumab Vedotin in Urothelial Carcinoma After Platinum and Anti-Programmed Death 1/Programmed Death Ligand 1 Therapy. *J Clin Oncol*. 2019;37(29):2592-2600.
3. 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. *JCO*. 2021;39(6_suppl):394-394.
4. Powles T, Rosenberg JE, Sonpavde GP, et al. Enfortumab Vedotin in Previously Treated Advanced Urothelial Carcinoma. *N Engl J Med*. 2021;384(12):1125-1135.