National Community Oncology Dispensing Association, Inc.
PASSION FOR PATIENTS

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Seattle Cancer Care Alliance
Updated 5/20/20

Positive Quality Intervention: Enfortumab Vedotin (Padcev) management for advanced or metastatic urothelial carcinoma

Description:

The purpose of this PQI is 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 was granted accelerated approval 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 platinum-based chemotherapy in the neoadjuvant/adjuvant, locally advanced, or metastatic setting.[1] In the pivotal phase II trial, patients were heavily pretreated (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]

PQI Process:

Upon order of enfortumab vedotin administration

- Confirm appropriateness of enfortumab vedotin utilizing the EMR
- Review the adverse events Table (#1) on Page 2 with the interventions suggested as needed.
- Review Table (#2) on Page 3 for dose specific adjustments as required
- Drug Interaction Considerations[1]
    - Enfortumab vedotin is metabolized via CYP 3A4, and concomitant use of an antibody-drug conjugate containing MMAE and strong CYP3A4 inhibitors should be considered. Dose adjustment is typically not required.

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Table 1: Selected Adverse Events and interventions suggested

Event	Severity/Incidence	Suggested Intervention	Comments
Skin Reactions	54% (any Grade)[1]	Fragrance-free moisturizers/ointments Topical steroids as indicated Systemic steroids as indicated	Median time of onset for severe skin reactions was 0.8 months (range 0.2 – 5.3).[1]
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 (If unable: a basic metabolic panel is possible to use). 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 the trial.[1,2] 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/duloxetine	The median time to onset of Grade ≥ 2 was 3.8 months (range: 0.6 – 9.2). At the last follow-up in the trial, 19% had complete resolution and 26% had partial improvement. 76% had resolution or ongoing Grade 1 neuropathy.
Diarrhea	42% (any Grade)[1]	Prepare anti-diarrheal medications for patient as needed	

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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 or 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 considerations	No dose adjustment is required for renal dysfunction No current studies in moderate to severe hepatic dysfunction – consider avoiding use in this scenario. 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

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]
- Advise patients to self-monitor for peripheral sensory neuropathy and motor neuropathy. Sensory neuropathy (44%) was more common than motor (14%).[2]
- Enfortumab vedotin has an NCCN emetic risk category of "Moderate" on the day of treatment and patients should receive anti-emetic medications prior to infusion according to institutional standards.[3]

References:

1. Padcev (enfortumab vedotin- ejfv) [Prescribing Information]. Bothell, WA: Seattle Genetics, Inc.; December 2019.
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. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology. Antiemesis. Version 1.2020. February 19, 2020.