Positive Quality Intervention: Enfortum 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 enfortum vedotin.

Background: Enfortum vedotin is a nectin-4 targeting antibody conjugated to the microtubule inhibitor monomethyl auristatin E (MMAE). Enfortum 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. 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. 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. 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. Treatment-related adverse effects led to dose reduction in 32% of patients and discontinuation in 12% of patients. Cohort 2 of EV-201, published later, demonstrated the benefit of enfortum vedotin specifically in patients who had not received cisplatin prior, with 52% of patients achieving an objective response and 20% with complete response. The phase III EV-301 trial confirmed the benefit of enfortum 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 enfortum vedotin group and 91.8% in the chemotherapy group).

PQI Process: Upon order of enfortum vedotin administration

- Confirm appropriateness of enfortum 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
  - Enfortum 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 enfortum vedotin are likely to manifest as dry skin, pruritus, and/or maculopapular rash
  - Severe skin toxicities (10% incidence) included symmetrical drug-related intertriginous and flexural exanthema (SDRIFE), bullous dermatitis, exfoliative dermatitis, and palmar-plantar erythrodysesthesia

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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%)\(^1,2\)
  
  o See **Chemotherapy Induced Peripheral Neuropathy** PQI

**Supplemental Information:**

**Table 1: Selected Adverse Events and Suggested Interventions**

<table>
<thead>
<tr>
<th>Event</th>
<th>Severity/Incidence</th>
<th>Suggested Intervention</th>
<th>Comments</th>
</tr>
</thead>
</table>
| 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  

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade/Severity</th>
<th>Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperglycemia</td>
<td>Blood glucose &gt; 250 mg/dL</td>
<td>Withhold until ≤ 250 mg/dL, then resume at same dose level</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>2</td>
<td>Withhold until grade ≤ 1, then resume at same dose level. If recurrence, withhold until Grade ≤ 1, then resume and reduce one dose level</td>
</tr>
<tr>
<td></td>
<td>≥ 3</td>
<td>Permanently discontinue</td>
</tr>
<tr>
<td>Skin reactions</td>
<td>3</td>
<td>Withhold until grade ≤ 1, then resume at same dose level or consider reducing by one dose level</td>
</tr>
<tr>
<td></td>
<td>4 or recurrent 3</td>
<td>Permanently discontinue</td>
</tr>
<tr>
<td>Other non-hematologic toxicities</td>
<td>3</td>
<td>Withhold until grade ≤ 1, then resume at same dose level or consider reducing by one dose level</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Permanently discontinue</td>
</tr>
<tr>
<td>Hematologic toxicity</td>
<td>3 or Grade 2 thrombocytopenia</td>
<td>Withhold until grade ≤ 1, then resume at same dose level or consider reducing by one dose level</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Withhold until grade ≤ 1, then resume and reduce one dose level or discontinue treatment</td>
</tr>
</tbody>
</table>

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

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