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Advancements in Therapy for Bladder Cancer: Enfortumab Vedotin

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Author's disclosure of conflict of interest is found at the end of this article.

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Abstract

The treatment paradigm for urothelial carcinoma (UC), a common genitourinary cancer, has significantly expanded in recent years. Enfortumab vedotin, a Nectin-4–targeted antibody-drug conjugate, was recently approved by the U.S. Food & Drug Administration for patients with advanced or metastatic UC following chemotherapy and immunotherapy. Approval of enfortumab vedotin was based on findings from the EV-201 trial, which demonstrated objective response rates of 44%. Patients treated with enfortumab vedotin should be monitored for specific toxicities, including peripheral neuropathy, rash, and hyperglycemia. In this article, the clinical implications of enfortumab vedotin for the treatment of advanced UC are reviewed.

Urothelial carcinoma (UC) is the sixth most common cancer in the United States and the second most common genitourinary cancer, with 81,400 new cases and 17,980 deaths estimated in 2020 (Siegel, Miller, & Jemal, 2020). Rates for new UC cases have been falling on average by 1.2% each year over the past 10 years, but death rates remained stable between 2007 and 2016. Early stages of disease (non–muscle invasive and muscle invasive) are often treated with intravesicular therapies, tumor resection, complete cystectomies, and/or neoadjuvant or adjuvant cisplatin-based chemotherapy (National Comprehensive Cancer Network [NCCN], 2020). Treatment selection is often dictated by stage, disease risk factors, performance status and comorbidities, and prior lines of therapy. Although approximately 5% of patients present with metastatic UC (mUC) at initial diagnosis, a large portion relapses or progresses to advanced stages following treatment for localized disease with a 5-year relative survival of 4.6% (NCCN, 2020; Siegel et al., 2020).

In recent years, a significant expansion in treatment options has been observed utilizing immunotherapies and targeted therapies for locally advanced or mUC (NCCN, 2020). In addition, several ongoing clinical trials are evaluating the role of immunotherapy in combination with chemotherapy for early, localized disease (Hanna, 2017, 2019). Most recently, pembrolizumab gained U.S. Food &

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Drug Administration (FDA) approval for bacillus Calmette-Guérin–unresponsive, high-risk, non–muscle invasive bladder cancer in patients who elect not to undergo cystectomy or are deemed ineligible based on findings from the KEYNOTE-057 trial (Merck & Co., Inc, 2020).

Despite numerous therapeutic advances, enrollment in a clinical trial is encouraged in all stages of advanced disease (NCCN, 2020). Given the poor outcomes in this setting, novel agents, such as enfortumab vedotin (Padcev), with alternative mechanisms of action, are needed. In this article, the role of enfortumab vedotin in the management of UC is reviewed.

MECHANISM OF ACTION

Enfortumab vedotin is an antibody-drug conjugate (ADC) comprised of a human IgG1 antibody directed against Nectin-4 linked to monomethyl auristatin E (MMAE), a microtubule-disrupting agent (Astellas Pharma US, Inc., 2019). The anticancer activity of enfortumab vedotin is due to the binding of the ADC to Nectin-4–expressing cells, followed by internalization of the ADC-Nectin-4 complex, and the release of MMAE via proteolytic cleavage. Monomethyl auristatin E activity induces cell cycle arrest and apoptotic cell death.

Nectins are immunoglobulin-like transmembrane proteins found in the adherens junctions of cells and mediate cell–cell adhesion via both homophilic and heterophilic interactions (Challita-Eid et al., 2016). In human tissue, 60% moderate-to-strong staining of Nectin-4 was observed in bladder tissue. An immunohistochemistry clinical trial assay was used in the EV-201 trial to assess patients with tumor tissue available, and detected Nectin-4 expression in all patients tested (Rosenberg et al., 2019a). As a result of uniform expression, testing for Nectin-4 expression is not required for utilizing enfortumab vedotin for mUC.

CLINICAL TRIALS/EFFICACY

The safety and efficacy of enfortumab vedotin were assessed in the EV-101 and EV-201 trials (Rosenberg et al., 2018, 2019a, 2019b). EV-101 evaluated the role of enfortumab vedotin in patients with mUC and other malignant solid tumors that express Nectin-4 in regard to pharmacokinetics, immunogenicity, safety, and antitumor activity (Rosenberg et al., 2019b). Tumor response was assessed as a secondary endpoint and defined as a complete response (CR) or partial response (PR) per Response Evaluation Criteria in Solid Tumors (RECIST) criteria (version 1.1). Subjects with mUC must have failed at least one prior chemotherapy regimen in the metastatic setting unless deemed cisplatin-ineligible, had availability of tumor tissue sampling for Nectin-4 expression, and no grade ≥ 2 motor neuropathy at baseline. The dose expansion cohort of this study established the maximum tolerated dose (MTD) of 1.25 mg/kg (Rosenberg et al., 2018).

At a median follow-up of 13.4 months, 112 patients with mUC had received enfortumab vedotin at 1.25 mg/kg on days 1, 8, and 15 every 28 days in EV-101 (Rosenberg et al., 2019b). Nearly all patients had prior exposure to platinum-based chemotherapy and 89 received a prior immune checkpoint inhibitor (ICI). Enfortumab vedotin resulted in an objective response rate (ORR) of 42% (CR, n = 5; PR, n = 42) in the intent-to-treat population, 42% (95% confidence interval [CI]= 31.2–52.5) in patients with prior ICI exposure, and 36% (95% CI = 20.4–54.9) in patients with liver metastasis. Overall survival (OS) at 1 year was 51.6% (95% CI = 40.3–61.8) in patients exposed to prior ICIs and 42% (95% CI = 25.0–58.0) in the liver metastasis group. The median OS was 12.2 months (95% CI = 8.5–17.1) and 10.4 months (95% CI = 6.4–14.1), and the median progression-free survival (PFS) was 5.4 months (95% CI = 5.1–6.3) and 3.5 months (95% CI = 1.6–6.6) in each group, respectively. The median duration of response (DoR) following ICI therapy was 7.4 months (95% CI = 4.2–9.4) and 7.7 months (95% CI = 3.7–NR) in the liver metastasis arm; 23.4% of responses were ongoing at a median follow-up of 11.3 months.

The FDA approval of enfortumab vedotin was based on the pivotal EV-201 trial, a global, phase II, two-cohort, single-arm study, which evaluated the role of enfortumab vedotin at 1.25 mg/kg on days 1, 8, and 15 of every 28-day cycle in patients with locally advanced or mUC who were previously treated with platinum-based chemotherapy and ICI therapy (Astellas Pharma US, Inc., 2019; Rosenberg et al., 2019a). Eligible subjects were adult patients 18 years or older, had an Eastern Cooperative Oncology Group Performance Status of

≤ 1, adequate organ function, and had no grade ≥ 2 neuropathy. The primary endpoint of EV-201 was ORR by an independent review facility per RECIST v1.1 criterion, and secondary endpoints included DoR, PFS, ORR by investigator, OS, safety, and tolerability.

A total of 128 patients were enrolled in cohort 1, and 125 patients received treatment (Rosenberg et al., 2019a). The median age was 69 years (range: 40–84 years), 70% were male, and 85% were Caucasian. Visceral metastases were present in 90% of patients and 40% had liver metastases. Nectin-4 expression was present in all patients tested (n = 120). The median number of prior systemic therapies was 3 (range: 1–6). Forty-six percent of patients received a prior PD-1 inhibitor, 42% received a prior PD-L1 inhibitor, and an additional 13% received both PD-1 and PD-L1 inhibitors. Sixty-six percent of patients received prior cisplatin-based regimens, 26% received prior carboplatin-based regimens, and an additional 8% received both cisplatin and carboplatin-based regimens. Confirmed ORR was 44% (95% CI = 35.1–53.2) by independent review, with a 12% CR rate and 32% PR rate. Similar responses were observed in prespecified subgroups, which included responses to prior immunotherapy (56% in responders and 41% in nonresponders) and in patients with poor prognostic characteristics, including liver metastases (38%) and three or more prior lines of therapy (41%). Stable disease was assessed in 28% of patients, 18% had progressive disease, and 10% were not evaluable. The median duration of response was 7.6 months (range: 0.95–11.30; 95% CI = 4.93–7.46).

ADVERSE EFFECTS

Three reports have been published at various time points demonstrating the safety profile from the EV-101 trial (Petrylak et al., 2019; Rosenberg et al., 2018, 2019). Petrylak and colagues (2019) reported on 68 patients with mUC who had received treatment. Treatment-related adverse events (TRAEs) were reported in 58 patients (85%); diarrhea, fatigue, nausea, and pruritus were reported in ≥ 25% of patients. Most TRAEs were grade ≤ 2 in severity; 19 patients (28%) experienced a TRAE of grade ≥ 3. The most common grade ≥ 3 TRAEs (occurring in ≥ 5 patients) regardless of attribution to treatment were urinary tract infection (10%) and hypophosphatemia (9%). No treatment-related deaths occurred.

Updates results by Rosenberg and colleagues (2018) of 112 patients who received therapy at the MTD demonstrated that enfortumab vedotin was generally well tolerated. Grade ≤ 2 fatigue (50%) was the most commonly reported TRAE. The most common grade ≥ 3 AEs regardless of attribution were anemia (7%), hyponatremia (6%), urinary tract infection (6%), and hyperglycemia (5%). Four patients experienced a fatal TRAE (respiratory failure, urinary tract obstruction, diabetic ketoacidosis, multiorgan failure). Rosenberg and colleagues (2019b) also reported mature results from EV-101 in 112 patients with mUC who received therapy with a median follow-up of 13.4 months. Fatigue (53%), alopecia (46%), and decreased appetite (42%) were the most commonly reported TRAEs. Anemia (8%), hyponatremia (7%), urinary tract infection (7%), and hyperglycemia (6%) were grade ≥ 3 AEs reported in ≥ 5% of patients regardless of attribution. Four fatal TRAEs were reported (respiratory failure, urinary tract obstruction, diabetic ketoacidosis, multiorgan failure).

In the EV-201 trial, the most common TRAEs were fatigue (50% all grade and 6% grade ≥ 3), alopecia (49% all grade), decreased appetite (44% all grade and 1% grade ≥ 3), dysgeusia (40% all grade and none grade ≥ 3), and peripheral sensory neuropathy (40% all grade and 2% grade ≥ 3; Rosenberg et al., 2019a). The most common grade ≥ 3 TRAEs were neutropenia (8%), anemia (7%), and fatigue (6%). Febrile neutropenia (4%) was the most common serious TRAEs. No routine growth factor was used. Most patients with neuropathy had resolution or ongoing grade 1 at last follow-up. No deaths were reported during the safety reporting period.

Peripheral neuropathy, rash, hyperglycemia, and infusion-related reactions were prespecified for analysis as composite terms. Treatment-related peripheral neuropathy occurred in 50% of patients, almost all (94%) of which were grade ≤ 2. Most patients (76%) with peripheral neuropathy had resolution or ongoing grade 1 peripheral neuropathy at last follow-up.

Treatment-related rash occurred in 48% of patients, most of which were low grade (75% grade

≤ 2) with onset in the first treatment cycle; 73% experienced complete resolution and 20% had some improvement at last follow-up. Three patients had infusion site extravasation, of which two cases were considered serious. All patients with extravasation recovered completely and were able to continue treatment.

Treatment-related hyperglycemia occurred in few patients (11%), regardless of known hyperglycemia at baseline; 57% achieved complete resolution and 14% experienced some improvement.

Adverse reactions leading to discontinuation occurred in 16% of patients. Peripheral neuropathy (6%) was the most common. Adverse reactions leading to dose interruption occurred in 64% of patients and were most commonly due to peripheral neuropathy (18%), rash (9%), and fatigue (6%). Adverse reactions leading to dose reduction occurred in 34% of patients and were most commonly due to peripheral neuropathy (12%), rash (6%), and fatigue (4%).

DOSING AND ADMINISTRATION

Enfotrumab vedotin is administered as a 30-minute intravenous infusion at a dose of 1.25 mg/kg (up to a maximum dose of 125 mg) on days 1, 8, and 15 of a 28-day cycle until disease progression or unacceptable toxicity (Astellas Pharma US, Inc., 2019). Enfortumab vedotin is compatible with 5% dextrose injection, 0.9% sodium chloride injection, or lactated Ringer's injection. No premedications are required for therapy.

Dose adjustments or delays for toxicities are highlighted in Table 1 for hyperglycemia, peripheral neuropathy, skin reactions, and hematologic and nonhematologic toxicities, and consists of three dosing levels of 1.0 mg/kg, 0.75 mg/kg, and 0.5 mg/kg (Astellas Pharma US, Inc., 2019). It is important to note that all patients should be capped at 100 kg in the event they exceed this weight; the final dose is capped per the dosing level (i.e., 1.0 mg/kg dose cap = 100 mg, 0.75 mg/kg dose cap = 75 mg, and 0.5 mg/kg dose cap = 50 mg). Enfortumab vedotin is available in vials of 20 mg and 30 mg. Dose rounding or dose capping should be considered for patients who are receiving the 125 mg and other doses, as this has been shown to reduce cost without impacting efficacy (Fahrenbruch, Kintzel, Bott, Gilmore, & Marckham, 2018).

No clinical studies evaluating the drug-drug interaction potential of enfortumab vedotin have been conducted (Astellas Pharma US, Inc., 2019). MMAE is metabolized via CYP3A4/5, and strong inhibitors or inducers may impact serum concentrations. There are no dose modifications recommended for drug-drug interactions with enfortumab vedotin. Enfortumab vedotin should be handled as a cytotoxic agent due to the pharmacological activity of MMAE.

PRACTICE IMPLICATIONS

The treatment landscape of UC continues to evolve, and numerous therapeutic advances have been observed over the past few years (Hanna., 2017, 2019). Urothelial carcinoma is a highly mutated tumor type with several agents and combination therapies under investigation in clinical trials (Cancer Genome Atlas Research Network, 2014). Sequencing of therapies is extremely important to optimize treatment outcomes, as numerous agents have demonstrated positive outcomes in early and advanced stages of disease.

Enrollment in a clinical trial is strongly encouraged for all patients with locally advanced or mUC (NCCN, 2020). Following platinum-based chemotherapy for advanced disease, pembrolizumab is the only category 1 recommendation at this time due to the OS benefit observed from the KEYNOTE-045 trial (Bellmunt et al., 2017; NCCN, 2020). However, despite effective second-line options with ICI and erdafitinib, many patients do not respond to immunotherapy, cannot tolerate targeted therapy, or progress. The recent FDA approval of pembrolizumab for non–muscle invasive bladder cancer may also limit the use of ICIs for metastatic disease due to early exposure of an ICI. In addition, the KEYNOTE-361 and IMvigor130 studies are currently ongoing and investigating the role of combination chemo-immunotherapy for front-line advanced disease (ClinicalTrials.gov identifiers NCT02853305 and NCT02807636). As a result, enfortumab vedotin may be used earlier than the third-line setting based on prior therapy selection.

Ongoing clinical trials will further refine the place in therapy of enfortumab vedotin. The EV-301 trial (NCT03474107), is an ongoing, phase III trial of enfortumab vedotin against investigator's

Table 1. Dose Modifications for Enfortumab Vedotin

Adverse reaction	Severity	Dose modification
Hyperglycemia	Blood glucose > 250 mg/dL	Withhold until ≤ 250 mg/dL, then resume at same dose
Peripheral neuropathy	Grade 2	First occurrence: Withhold until grade ≤ 1, then resume at same dose Subsequent occurrence(s): Withhold until grade ≤ 1, then reduce by one dose level
	Grade ≥ 3	Discontinue
Skin reactions	Grade 3	Withhold until grade ≤ 1, then resume at same dose or consider dose reduction by one dose level
	Grade 4 or recurrent grade 3	Discontinue
Hematologic toxicities	Grade 3 or grade 2 thrombocytopenia	Withhold until grade ≤ 1, then resume at same dose or consider dose reduction by one dose level
	Grade 4	Withhold until grade ≤ 1, then reduce dose by one dose level or discontinue
Nonhematologic toxicities	Grade 3	Withhold until grade ≤ 1, then resume at same dose or consider dose reduction by one dose level
	Grade 4	Discontinue

Note. Information from Astellas Pharma US, Inc. (2019).

choice of chemotherapy following progression on front- and second-line treatment with chemotherapy and immune checkpoint blockade. The primary endpoint of this trial is OS. Additionally, the EV-103 trial (NCT03288545), is a phase I, dose-escalation, dose-expansion trial looking at a broader use of enfortumab vedotin in combination with chemotherapy or immunotherapy in the front-line setting for locally advanced or mUC.

Supportive care measures, monitoring, and management of peripheral neuropathy, rash, and hyperglycemia should be in place prior to initiating therapy with enfortumab vedotin. Peripheral sensory neuropathy is more common than motor neuropathy, with a median time to onset of 2.43 months (range: 0.03–7.39; Rosenberg et al., 2019a). The median time to onset of grade ≥ 2 was 3.8 months (range: 0.6–9.2). Neuropathy led to treatment discontinuation in 6% of patients. At the time of their last evaluation, 19% had complete resolution and 26% had partial improvement.

The general management of neuropathy includes withholding therapy until recovery and/or dose reductions. Timely management of neuropathy is extremely important in this patient population, as some may have underlying neuropathy from prior platinum-based therapies. The median onset of treatment-related rash is 0.53 months (range: 0.03–7.39). This is often maculopapular and diffuse in appearance. Rash is primarily due to Nectin-4 expression in skin cells (Challita-Eid et al., 2016). Topical or systemic corticosteroids, oral antihistamines, or dose reductions and delays should be considered based on the severity of the rash. Hyperglycemia has a median onset of 0.58 months (range: 0.26–9.23; Rosenberg et al., 2019a). The etiology of hyperglycemia is unknown but is unlikely to be an on-target effect; close monitoring is warranted in patients on therapy. The dosing schema of enfortumab vedotin allows for frequent monitoring.

It is important to note that the most common adverse reactions (≥ 20%) included fatigue, peripheral neuropathy, decreased appetite, rash, alopecia, nausea, dysgeusia, diarrhea, dry eye, pruritus, and dry skin (Astellas Pharma US, Inc., 2019). Ocular disorders occurred in 46% of the 310 patients treated with enfortumab vedotin, and the majority of these events involved the cornea and included keratitis, blurred vision, limbal stem cell deficiency, and other events associated with dry eyes. Dry eye symptoms occurred in 36% of patients and blurred vision occurred in 14% of patients, with a median time to onset to symptomatic

ocular disorder of 1.9 months. Artificial tears for prophylaxis of dry eyes and ophthalmologic evaluation if ocular symptoms occur or do not resolve should be considered. Enfortumab vedotin should be avoided in the presence of moderate to severe hepatic impairment. Lastly, females and males of reproductive potential should utilize contraception for 2 months and 4 months, respectively, after the last dose of enfortumab vedotin.

SUMMARY

The treatment landscape for locally advanced and mUC has evolved significantly over the past several years. As a result, it is important for clinicians to remain abreast of novel therapeutic advances to optimally and safely manage patients. Enfortumab vedotin, a novel ADC, recently gained FDA approval for patients with locally advanced or mUC following progression on chemotherapy and ICI. Enfortumab vedotin has demonstrated unprecedented response rates of 44% in this difficult-to-treat population. Management of TRAEs is extremely important, as patients with advanced disease often present with numerous comorbidities. Peripheral neuropathy, rash, and hyperglycemia should be closely assessed and monitored in all patients. ●

Disclosure

Dr. Hanna has served as a speaker and consultant for Seattle Genetics and AbbVie and received advisory board funding from Astellas.

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