Research Review™
PRODUCT REVIEW

Enfortumab vedotin (PADCEV™) for the treatment of locally advanced or metastatic urothelial cancer

Making Education Easy 2023

Independent expert commentary provided by Associate Professor Andrew Weickhardt

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Abbreviations used in this review:

BMI = body mass index
BSA = body surface area
eGFR = estimated glomerular filtration rate
EV = enfortumab vedotin
FGFR = fibroblast growth factor receptor
HR = hazard ratio
IV = intravenous
MMAE = monomethyl auristatin E
ORR = overall response rate
OS = overall survival
PD-1 = programmed cell death protein
PD-L1 = programmed cell death ligand
QoL = quality of life
SJS = Stevens-Johnson syndrome
TEN = toxic epidermal necrolysis
TRAE = treatment-related adverse effects

This publication discusses the evidence supporting the use of enfortumab vedotin (PADCEV™) for the treatment of urothelial cancer. Enfortumab vedotin is a novel antibody-drug conjugate given by IV infusion that is indicated for adult patients with locally advanced or metastatic urothelial carcinoma who have previously received platinum-containing chemotherapy and a PD-1 or PDL-1 inhibitor.

Background

Bladder cancer is the tenth most frequently diagnosed cancer globally and the most prevalent cancer of the urinary system.[1,2] In Australia, there were estimated to be 3,219 new cases of bladder cancer diagnosed in 2022 (2,470 male, 749 female).[3] Bladder cancer was responsible for an estimated 1,043 deaths in Australia in 2022, equating to 2.1% of all cancer deaths.[3] Following a diagnosis of bladder cancer, the 5-year survival rate in Australia was 56% from 2014-2018.[3] The median age of diagnosis for bladder cancer is 73 years in the United States.[4]

Urothelial carcinoma, also referred to as transitional cell carcinoma, is the most common histological subtype of bladder cancer, accounting for approximately 90% of bladder cancer cases.[1,5] Direct exposure of the urothelium to carcinogens in tobacco smoke or environmental or occupational carcinogens is the primary cause of most bladder cancer and exposure to these toxins is thought to explain why the incidence is approximately four times higher in males, for whom it is the sixth most common cancer.[1,2] Additional risk factors for the development of bladder cancer include increasing age, Caucasian ancestry, a personal or family history of bladder cancer, pelvic radiation, chronic infection or irritation of the urinary tract, obesity and diabetes.[4]

Management

Bladder cancer is a spectrum of disease that can be divided into three categories that differ in their prognosis, management and goals of care:[4]

1. Non-muscle-invasive disease – treatment aims to reduce recurrence and prevent progression.
2. Muscle-invasive disease – the aim of treatment is to determine if the bladder should be removed or if it can be retained without reducing survival. Patients at a high risk of distant spread may require systemic therapy to increase the chance of curative treatment.
3. Metastatic disease – treatment aims to prolong survival and maintain QoL with agents selected to achieve the best outcome.

Approximately 75% of newly diagnosed bladder cancer is non-muscle-invasive disease that is generally treated with transurethral resection followed by either adjuvant intravesical bacillus Calmette–Guérin immunotherapy or intravesical chemotherapy.[4–6] Despite treatment, 70% of non-muscle-invasive tumours reoccur and 20% of these will progress to muscle-invasive disease with a high risk of progression or metastasis.[5] Invasion of the carcinoma beyond the mucosa into deeper layers of the bladder wall is associated with a substantial decline in survivability with the reported 5-year survival rates for regional and metastatic disease being 36% and 4-5% respectively.[1,5] Approximately 5% of patients with bladder cancer have metastatic disease when they are diagnosed.[4]

Treating advanced urothelial cancer

Locally advanced or metastatic urothelial carcinoma is typically aggressive and the prognosis for most patients is currently poor.[7] Platinum-based chemotherapy remains the first-line treatment for unresectable locally advanced or metastatic urothelial carcinoma.[8] Maintenance therapy with the PD-L1 inhibitor avelumab is a standard of care for patients with stable disease or disease refractory to platinum-based chemotherapy, with significant improvements in OS compared to the alternative strategy of waiting for later progression.[4] The PD-1 inhibitor pembrolizumab is a second-line therapy for patients who do not receive maintenance avelumab or who progress within 12 months of chemotherapy, which is sometimes witnessed post-neoadjuvant chemotherapy/cystectomy.[4] Despite these recent advances, studies indicate that the response rate remains relatively low at approximately 13-24% with immune checkpoint inhibitors as second-line therapy and although the response is often durable in those who do respond, the median OS is only 10-11 months.[8–10]

In general, the prognosis for patients with metastatic urothelial carcinoma is described as dismal and there is an unmet need for additional treatments for patients with urothelial carcinoma that is refractory to platinum-based and immune check point therapies.[11] More recently, the novel antibody-drug conjugate enfortumab vedotin and the pan-EGFR inhibitor erdafitinib have emerged as a third-line option following platinum-based therapy and immunotherapy.[4]

Expert comment

Despite advances in the treatment of locally advanced and metastatic urothelial cancer brought about by the introduction of immunotherapy, many patients still die of progressive disease within 2 years of their diagnosis. Enfortumab vedotin has a novel mechanism of action as an antibody-drug conjugate with a potent payload that can lead to responses and disease control in patients who have progressed or are intolerant of immunotherapy. Responses have been documented in patients with visceral and bone metastases, often a site of life-limiting progression.

Enfortumab vedotin

Enfortumab vedotin (EV) is a novel antibody-drug conjugate that delivers the microtubule-disrupting chemical monomethyl auristatin E (MMAE) into cells expressing the cell surface nectin-4 receptor.[11] Nectin-4 is an immunoglobulin-like cell adhesion molecule that is mainly expressed in the embryo, placenta and skin.[7,11] Nectins are believed to be involved in the mediation of cell-cell adhesions in tight junctions, adherens junctions and synaptic junctions, as well as helping to regulate anti-apoptosis signalling and assisting in cellular motility and proliferation.[7,12] Significantly, almost all advanced urothelial carcinomas express nectin-4 on their surface, meaning that a biomarker is not required to identify patients who are likely to respond to treatment.[5,8] The EV complex comprises a fully human IgG1 kappa antibody conjugated to MMAE with a protease-cleavable linker (**Figure 1**).[13]

Following administration, EV is thought to undergo catabolism into small peptides, amino acids and unconjugated MMAE and related catabolites.[13] According to *in vitro* studies, unconjugated MMAE is metabolised via CYP3A4 and is expected to be mostly excreted in the faeces with smaller amounts recoverable in the urine.[13]

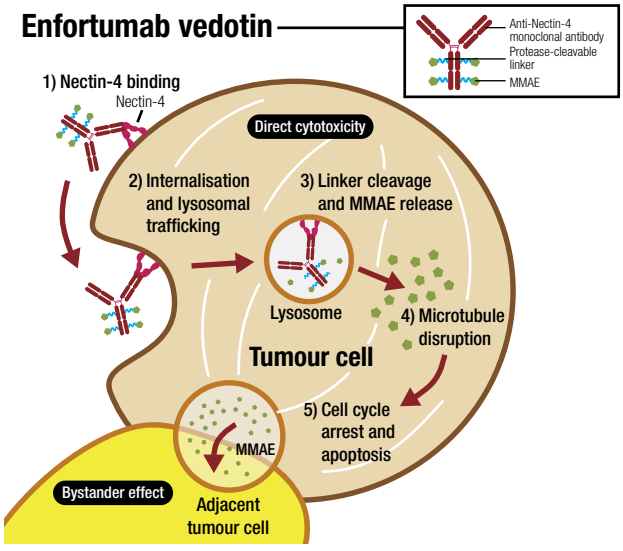

Figure 1. Enfortumab vedotin (insert) and its proposed anti-tumour mechanism. Adapted from Lacouture *et al* (2022).[7]

In late 2019, the U.S. Food and Drug Administration granted accelerated approval for EV (PADCEV™) for the treatment of adult patients with locally advanced or metastatic urothelial cancer who had received a PD-1 or PD-L1 inhibitor, and a platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced or metastatic setting.[14]

In 2023, EV was listed on the PBS in Australia.

Indications

In Australia, PADCEV™ is indicated as monotherapy for adults with locally advanced or metastatic urothelial carcinoma who have previously received platinum-containing chemotherapy and a PD-1 or PDL-1 inhibitor.[13]

PADCEV™ should be initiated and supervised by clinicians experienced in the management of cancer patients.[13]

Dosage and administration

The recommended dose of PADCEV™ is 1.25 mg/kg (to a maximum of 125 mg) given as an IV infusion over 30 minutes on days 1, 8 and 15 of a 28-day cycle until disease progression or unacceptable toxicity.[13] Dose reductions are not required for patients aged ≥65 years, patients with mild or severe renal impairment or those with mild hepatic dysfunction.[13] There is no data available on the use of PADCEV™ in patients with end-stage renal disease or moderate or severe hepatic dysfunction.[13]

A dose reduction schedule is provided to assist in the management of the adverse effects associated with PADCEV™ (**Table 1**).[13]

Treatment with PADCEV™ is contraindicated by known hypersensitivity to EV or to any of its excipients.[13] The safety and efficacy of PADCEV™ has not been established in paediatric patients.[13]

Table 1. Recommended dose reduction schedule for the management of PADCEV™-related adverse effects.[13]

Dose level	Dose
Starting dose	1.25 mg/kg to a maximum of 125 mg
First dose reduction	1 mg/kg to a maximum of 100 mg
Second dose reduction	0.75 mg/kg to a maximum of 75 mg
Third dose reduction	0.5 mg/kg to a maximum of 50 mg

Adverse effects

EV is subject to additional monitoring in Australia to facilitate the rapid reporting of relevant safety information. Healthcare professionals are requested to report any suspected adverse events at: www.tga.gov.au/reporting-problems.[13]

Due to the expression of nectin-4 on the skin, dermatological reactions are expected in some patients following the initiation of EV.[7] In patients treated with PADCEV™, most skin reactions have been a mild to moderate maculopapular rash, although severe cutaneous adverse events including SJS and TEN resulting in death have been reported, typically in the first cycle of treatment.[13]

Patients beginning PADCEV™ should be monitored for skin reactions throughout treatment, particularly during the first cycle (see: "Managing adverse dermatological effects").[13] Topical corticosteroids and antihistamines may be appropriate for mild to moderate dermatological reactions, such as Grade 1 or first instance of Grade 2 reactions (rash covering 10-30% of BSA regardless of symptoms or >30% with only mild symptoms).[13] For worsening Grade 2 cutaneous reactions, withhold PADCEV™ until the reaction is Grade ≤1 (**Table 2**) and a dose reduction should be considered if there are any further episodes of Grade ≥2 cutaneous reactions. For more severe dermatological reactions (Grade ≥3, rash 30% of BSA with moderate or severe symptoms) or suspected SJS or TEN, withhold PADCEV™ and consider referral to a relevant specialist.[13] Withhold PADCEV™ until the reaction is Grade <1 and dose reductions should be considered. PADCEV™ should be permanently discontinued in patients with confirmed SJS or TEN, Grade 4 or recurrent Grade 3 cutaneous reactions.[13]

Skin and soft tissue injury has been reported following extravasation when administering PADCEV™.[13] Adequate venous access should be confirmed prior to initiating treatment and the patient monitored for infusion site extravasation while administration occurs.[13]

Additional adverse effects

Hyperglycaemia and diabetic ketoacidosis (including fatal events) have been observed following treatment with PADCEV™ in patients with and without pre-existing diabetes.[13] Hyperglycaemia is more frequent in patients with a BMI ≥30 kg/m^2 or those with pre-existing hyperglycaemia.[13] Patients should have an HbA1c test before starting PADCEV™ and blood glucose levels should be regularly monitored in patients with diabetes or those with risk factors for diabetes or hyperglycaemia.[13] PADCEV™ should be withheld if the patient's blood glucose is >13.9 mmol/L.[13]

Pneumonitis, including fatal events, has been reported in patients taking PADCEV™.[13] Patients should be monitored for symptoms and signs suggestive of pneumonitis and interstitial lung disease such as cough, dyspnoea, hypoxia or interstitial infiltrates on radiography.[13] PADCEV™ should be withheld and a dose reduction considered for patients with Grade 2 pneumonitis/interstitial lung disease and treatment should be permanently discontinued in patients with Grade 3 or 4 disease.[13]

Peripheral neuropathy may develop in some patients treated with PADCEV™.[13] Depending on the severity, it may be appropriate to pause treatment, reduce the dose or discontinue the medicine.[13] Patients taking PADCEV™ should also be monitored for ophthalmological complications, e.g. dry eye, with referral for assessment if symptoms do not resolve.

Table 2. Dose interruption, reduction and discontinuation recommendations for patients with adverse reactions to PADCEV™[13]

Adverse event	Severity*	Recommendation
Cutaneous reactions	Grade 2 worsening	Consider withholding PADCEV™ until Grade ≤1
	Grade 3 (severe)	Withhold until Grade ≤1 then resume at same dose or consider dose reduction by 1 level
	Suspected SJS or TEN	Immediately withdraw PADCEV™ until diagnosis is established. Manage as Grade 3 if SJS or TEN are ruled-out.
	Confirmed SJS or TEN, Grade 4 or recurrent Grade 3	Permanently discontinue
Hyperglycaemia	Blood glucose >13.9 mmol/L	Withhold until blood glucose ≤13.9 mmol/L and resume treatment at the same dose
Pneumonitis/ interstitial lung disease	Grade 2	Withhold until Grade ≤1 then resume at same dose or consider dose reduction by 1 level
	Grade ≥3	Permanently discontinue
Peripheral neuropathy	Grade 2	Withhold until Grade ≤1. For first occurrence, resume at same dose. For a recurrence, withhold until Grade ≤1, then resume with treatment reduced by 1 level.
	Grade ≥3	Permanently discontinue

*Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = life-threatening

Preconception, pregnancy and lactation

The effect of PADCEV™ on human fertility in both males and females is unknown, although data from rats indicates the potential for EV to reduce male fertility.[13] Male patients with female partners of reproductive potential should use effective contraception during treatment and for 6 months after finishing PADCEV™.[13] Women who could become pregnant should take a pregnancy test within 7 days of beginning treatment with PADCEV™ and use effective contraception during and for 7 months after completing treatment.[13]

PADCEV™ is contraindicated during pregnancy.[13] Breastfeeding should be halted during treatment with PADCEV™ and for 6 months after completing treatment.[13]

Managing adverse dermatological effects

The dermatological adverse effects associated with EV treatment may vary in locality, distribution, severity and symptomology, although onset is typically within the first treatment cycle.[7] The most common presentation is erythematous, scaly, pruritic papules in intertriginous, flexural, and acral areas with possible truncal involvement.[7] A schematic of select dermatological adverse effects is shown in **Figure 2**. Risk factors for the onset of dermatological reactions have not been firmly established, however, patients who have had previous cutaneous reactions to other medicines are more at risk, as are patients with family or personal histories of skin conditions, patients with skin damaged due to sunlight or therapeutic radiation, older patients and those with renal and/or hepatic dysfunction.[7]

Skin assessments should be routinely performed in patients treated with EV, beginning early in the first cycle of treatment.[7] The patient and any caregivers should be informed about the possibility of adverse dermatological reactions and understand the need to immediately notify a health professional following new or worsening reactions.[7]

Preventative strategies may include the use of moisturisers containing zinc and sunscreen.[7] Mild-to-moderate cutaneous events may be managed with supportive care and the appropriate use of topical corticosteroids, antihistamines and antibiotics.[7]

Red flags that may be consistent with a serious cutaneous adverse reaction include:[7]

- Fever ≥38°C
- Malaise
- Mucosal involvement (conjunctivitis, oral, genital)
- Skin pain or cutaneous burning, numbness or tingling

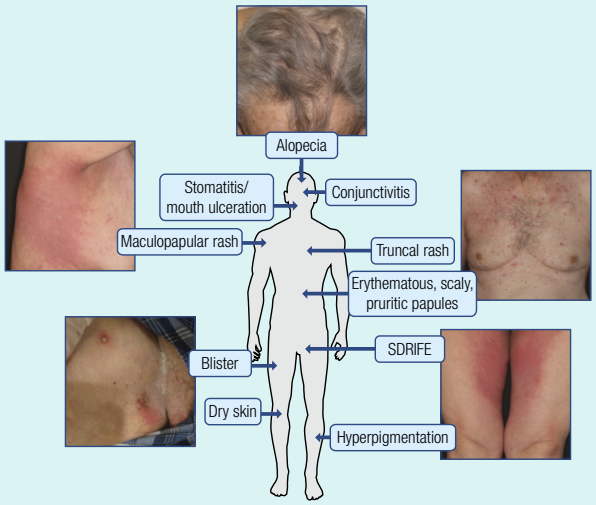

Figure 2. Schematic illustration of select adverse dermatological effects associated with enfortumab vedotin treatment. Adapted from Lacouture *et al* (2022).[7]

Expert comment

The cyotoxic payload of enfortumab vedotin leads to a range of side effects that need to be monitored carefully. These side effects can be divided into early and late adverse events. After commencing treatment, clinicians need to monitor patients carefully for the development of cutaneous rashes that often emerge within weeks of starting therapy. Despite being highly effective in some patients, enfortumab vedotin has a propensity to cause symptomatic rash in 55% of patients, and this can progress if the appropriate management is not instituted rapidly. This often involves withholding dosing and consideration of dose reductions if the rash is moderately severe (**Table 2**). Clinicians also need to be aware of the risk of hyperglycaemia – I often perform fasting blood sugar tests and check patient's HbA1c prior to starting therapy. The most significant longer-term issue that limits the treatment duration of enfortumab vedotin is the development of peripheral neuropathy.

Studies on safety and efficacy

Enfortumab vedotin received accelerated approval from the United States FDA for the treatment of locally advanced or metastatic urothelial cancer in patients who have previously received a PD-1 or programmed PD-L1 inhibitor, and a platinum-containing chemotherapy, following the results of the EV-201 clinical trial.[14] This pivotal, single-arm phase 2 trial of 125 patients with metastatic urothelial carcinoma reported an objective response rate of 44%, including a complete response rate of 12%, and a median duration of response of 7.6 months.[15] Following these results, the phase 3 EV-301 trial was conducted.

EV-301

EV-301 was a global, open-label, phase 3 trial of patients aged ≥18 years with locally advanced or metastatic urothelial carcinoma who had been previously treated with platinum-containing chemotherapy and had disease progression during or following PD-1 or PD-L1 inhibitor treatment.[16] The study was designed to determine if there was a clinical benefit associated with EV compared to standard chemotherapy selected prior to randomisation.[16] The primary end-point of the study was OS. Key secondary endpoints included PFS, clinical response and safety. QoL and patient-reported outcomes were recorded and are likely to be published elsewhere.[16]

Study inclusion criteria for EV-301 were an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 or 1, and for patients who had undergone platinum chemotherapy as neoadjuvant or adjuvant therapy, progression needed to have occurred within 12 months of completing treatment.[16] Exclusion criteria were pre-existing Grade ≥2 sensory or motor neuropathy or persistent clinically significant adverse effects from prior treatment, active central nervous system metastases, uncontrolled diabetes, active keratitis or corneal ulcerations, or prior treatment with multiple chemotherapy regimens for locally advanced or metastatic urothelial carcinoma, including neoadjuvant or adjuvant treatment.[16]

The study randomised 301 patients to EV 1.25 mg per kilogram of body weight on days 1, 8 and 15 of a 28-day cycle and 307 patients were randomised to investigator-chosen chemotherapy (standard docetaxel, paclitaxel, or vinflunine) on day 1 of a 21-day cycle.[16] Prespecified dose modifications and regimen interruptions were permitted to manage adverse effects.[16] Within the standard chemotherapy arm, 117 patients were treated with docetaxel, 112 with paclitaxel and 78 received vinflunine.[16] There were 5 patients in the EV arm and 16 in the chemotherapy arm who did not receive any amount of study medicine.[16]

The median age of enrolled patients was 68 years and 77.3% were men. The baseline characteristics of the study arms were generally well balanced. Visceral disease was confirmed in 77.7% of the EV arm and 81.7% in the chemotherapy arm.[16] At the data cutoff point, the median treatment durations were 5 months in the EV arm and 3.5 months in the chemotherapy arm.[16]

Results

EV-301 was stopped early due to a superior OS at the planned interim analysis.[16] The median OS was 12.88 months (95% CI, 10.58 to 15.21) in the EV arm and 8.97 months (CI 8.05 to 10.74) in the chemotherapy arm (**Figure 3**).[16] Between randomisation and data cutoff, there were 134 deaths in the EV arm and 167 deaths in the chemotherapy arm.[16] The mortality risk in the EV arm was 30% lower than the chemotherapy arm at a median of 11.1 months of follow-up (hazard ratio 0.70; 95% CI, 0.56 to 0.89; p=0.001).[16] At 12 months, 51.5% of the EV arm were estimated to be alive compared to 39.2% in the chemotherapy arm.[16]

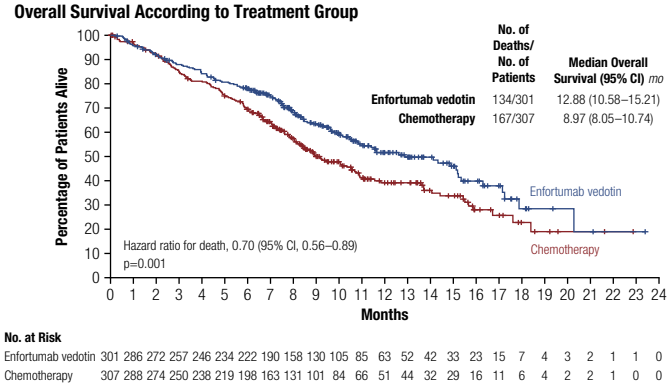

Figure 3. Kaplan-Meier estimates of overall survival of patients with locally advanced or metastatic urothelial carcinoma treated with enfortumab vedotin or standard chemotherapy. Adapted from Powels *et al* (2021).[16]

The median PFS was 5.55 months (95% CI, 5.32 to 5.82) in the EV arm and 3.71 months (CI 3.52 to 3.94) in the chemotherapy arm (**Figure 4**).[16] The risk of disease progression or death was 38% lower for patients in the EV arm compared to standard chemotherapy (HR 0.62; CI 0.51 to 0.75; p<0.001).[16] The PFS benefit associated with EV treatment was also seen across multiple subgroups.[16]

The confirmed overall response in the EV arm was 40.6% vs 17.9% in the standard chemotherapy arm (p<0.001) and this was consistent when subgroup analyses were performed.[16] A complete response was seen in 4.9% of the EV arm and 2.7% of the chemotherapy arm and disease control was 71.9% and 53.4% respectively (p<0.001).[16]

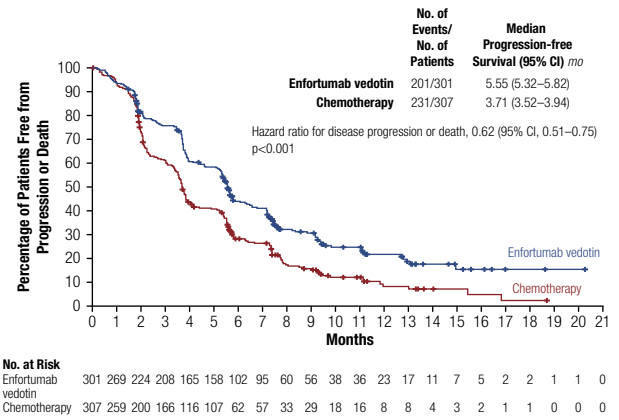

Figure 4. Kaplan-Meier estimates of progression-free survival of patients with locally advanced or metastatic urothelial carcinoma treated with enfortumab vedotin or standard chemotherapy. Adapted from Powels *et al* (2021).[16]

TRAE were experienced by 93.9% of patients in the EV group and 91.8% in the standard chemotherapy arm, while the respective rates of Grade ≥3 TRAE were 51.4% and 49.8%.[16] Following exposure adjustment, this equated to 2.4 and 4.3 TRAE per patient-year respectively.[16] Skin reactions and peripheral neuropathy were the most common TRAE of special interest associated with EV.[16] A treatment-related rash was recorded in 43.9% of patients receiving EV (Grade 1, 13.9%; Grade 2, 15.5%; Grade 3, 14.2%; Grade 4, 0.3%) and in 9.6% of patients receiving chemotherapy (Grade 1, 7.2%; Grade 2, 2.1%; Grade 3, 0.3%).[16] Treatment-related peripheral neuropathy was generally experienced as sensory events and occurred in 46.3% of the EV arm and 30.6% in the chemotherapy arm.[16] Peripheral sensory neuropathy was the most frequent TRAE in the EV arm requiring a dose reduction (7.1%), treatment interruption (15.5%) or treatment withdrawal (2.4%).[16]

Treatment-related hyperglycaemia occurred in 6.4% of patients receiving EV and 0.3% of patients receiving chemotherapy.[16] In the EV arm, Grade 1 or 2 hyperglycaemia occurred in 7 patients, Grade 3 hyperglycaemia occurred in 11 patients and 1 patient died.[16] Investigator-assessed TRAE resulting in death occurred in 7 patients in the EV arm (multiorgan dysfunction syndrome [2 patients], and 1 case each of hepatic dysfunction, hyperglycaemia, pelvic abscess, pneumonia, and septic shock).[16] In the chemotherapy arm, 3 patients died of investigator-assessed TRAE (neutropenic sepsis, sepsis, and pancytopenia).[16]

Conclusion

The investigators concluded that compared to standard chemotherapy, EV significantly prolonged survival with a 30% lower mortality risk in patients with locally advanced or metastatic urothelial carcinoma who had been previously treated with platinum-based therapy and a PD-1 or PD-L1 inhibitor.[16] PFS, OR and disease control were also superior in the EV arm of the trial.[16] The overall incidence of TRAE was similar between the two treatment arms, however, skin reactions, peripheral neuropathy and hyperglycaemia that were often mild-to-moderate in severity were more frequent in the EV arm.[16]

Subgroup analysis of EV-301

To further analyse the efficacy and safety of EV in patients with urothelial carcinoma, a subgroup analysis of 86 Japanese patients from EV-301 was conducted.[17] Within the cohort, 36 patients received EV and 50 received standard chemotherapy.[17] The median age of patients in the EV group was 70 years and the median age was 66.5 years in the chemotherapy group.[17] The baseline characteristics were generally similar between the Japanese cohort and the EV-301 population.[17] Overall, the Japanese patient cohort was 74.4% male.[17]

The median OS for the EV arm was 15.18 months and 10.55 months for the standard chemotherapy arm (HR 0.437; 95% CI: 0.209 to 0.914).[17] The median PFS for the EV arm was 6.47 months and 5.39 months for the chemotherapy arm.[17] After 12 months, the EV arm OS was 67.4% compared to 30.9% in the chemotherapy arm.[17] The confirmed ORR was 34.4% in the EV arm and 21.3% in the chemotherapy arm.[17]

Within the EV arm, 91.7% of patients experienced TRAE as did 97.9% of patients taking standard chemotherapy.[17] Grade ≥3 TRAE occurred in 63.9% of patients in the EV arm and in 75% of those receiving chemotherapy.[17] Following adjustment for treatment exposure, this equated to 3.5 Grade ≥3 events per patient-year in the EV arm and 11.9 events per patient-year in the chemotherapy arm.[17] There were no new safety signals detected.[17]

It was concluded that the results in this Japanese subgroup with locally advanced or metastatic urothelial carcinoma were consistent with the EV-301 cohort, with EV appearing to be safe and efficacious.[17] It is important to be mindful, however, that the effects of randomisation are not preserved in subgroups, therefore a cautious interpretation of these results is recommended.

Real-world data

As patients in the real world often have poorer health than those included in clinical trials, two real-world studies have been conducted to determine the efficacy and safety of EV in patients with previously treated advanced/metastatic urothelial carcinoma.

One study used retrospective data from 23 facilities to identify 125 patients with metastatic and previously treated urothelial cancer. The median patient age was 66 years and 76% had an ECOG performance score of 0-1, 13.6% had an ECOG score of 2-4 and the ECOG score was unknown in 10.4%.[18] Within the group, 19.2% of patients were aged ≥75 years when EV was initiated.[18] The administration of EV was a fourth-line or later treatment for 44.8% of patients.[18]

The ORR was 41.6% with 39.2% of patients experiencing a partial response and 2.4% experiencing a complete response.[18] The median OS was 10 months (95% CI 7.2 to 12.80) and the median PFS was 5 months (CI 4.34 to 5.67).[18] In patients with an ECOG performance score of 0-1, the median OS was 14 months and was comparable with the prospective data from EV-301.[18] In the 17 patients with an ECOG performance score of 2-4, the outcome was poor with a median OS of 3 months (CI 1.26 to 4.74), indicating that initiating EV requires careful consideration in patients with poor performance scores.[18]

The most frequent adverse events were peripheral sensory neuropathy followed by skin toxicity.[18] Adverse events Grade ≥3 were experienced by 30.4% of patients, which was lower than in EV-301, perhaps because all TRAE were not captured by the retrospective analysis.[18] Permanent discontinuation of treatment due to intolerable toxicity occurred in 10.4% of patients.[18] Pneumonia or pneumonitis resulted in 3 deaths.[18]

The Urothelial Cancer Network to Investigate Therapeutic Experiences (UNITE) study was a retrospective investigation designed to assess the outcomes for subsets of patients with advanced urothelial cancer who were treated with EV but had not been previously included in clinical trials.[19] Among 260 patients with advanced urothelial cancer treated with EV monotherapy, the observed response rate was 52% and was >40% in all reported subsets of interest, including patients with eGFR <30 mL/min, diabetes, neuropathy and with fibroblast growth factor receptor 3 (FGFR3) alterations.[19] The median PFS of the study group was 6.8 months and the median OS was 14.4 months.[19] Safety and toxicity data for the UNITE study were not included in this report.[19]

Collectively, these real-world retrospective analyses of patients with previously treated and advanced urothelial cancer are broadly in agreement with the prospective data from the EV-201 and EV-301 trials. Both retrospective studies support the safety and efficacy of EV treatment in patients with advanced or metastatic urothelial cancer, including in patients with significant comorbidities.

Expert comment

A multitude of studies and real-world data support the use of enfortumab vedotin for patients with urothelial carcinoma. Early trials such as EV-103 and later larger randomised trials such as EV-301 have reported encouraging high response rates in pretreated patients, with response duration greater than conventional chemotherapy. Randomised data such as from EV-301 shows the superiority of enfortumab vedotin over chemotherapy. Real world data has shown similar outcomes and a reasonable safety profile in patients treated off trial. Clinicians are encouraged to review the safety profile of PADCEV™ and familiarise themselves with the management of the more common side effects such as rash.

Take-home messages

- Locally advanced or metastatic urothelial carcinoma is typically aggressive and the prognosis for most patients is currently poor.
- Enfortumab vedotin (EV) is a novel antibody-drug conjugate that delivers a microtubule-disrupting chemical into cells expressing the nectin-4 receptor that is present on almost all advanced urothelial carcinomas.
- PADCEV™ (EV) is indicated as monotherapy for adult patients with locally advanced or metastatic urothelial carcinoma who have previously received platinum-containing chemotherapy and a PD-1 or PDL-1 inhibitor.
- The recommended dose of PADCEV™ is 1.25 mg/kg (to a maximum of 125 mg) given as an IV infusion on days 1, 8 and 15 of a 28-day cycle until disease progression or unacceptable toxicity.
- Cutaneous reactions are expected in patients receiving PADCEV™, typically in the first cycle of treatment. In a small number of cases, these reactions can be severe and patient education and careful monitoring is required.
- EV is associated with a 30% lower mortality risk compared to standard chemotherapy in patients with locally advanced or metastatic urothelial carcinoma who have been previously treated with platinum-based therapy and a PD-1 or PD-L1 inhibitor.
- Overall, the rate of TRAE is comparable between patients treated with EV or standard chemotherapy, however, treatment-related cutaneous reactions, peripheral neuropathy and hyperglycaemia are more common in EV-treated patients.
- Real-world data support the safety and efficacy of EV in patients with previously treated advanced or metastatic urothelial cancer.

Expert's concluding comments

The introduction of enfortumab vedotin heralds the arrival of a new class of potent antibody-drug conjugates for the treatment of urothelial carcinoma. Patients with disease progression despite chemotherapy and immunotherapy have a new treatment agent to control their cancer, with a surprisingly high response rate of 45% in this setting, even in patients with visceral or bony metastatic disease. Current trials are investigating the use of enfortumab vedotin in the first-line setting in combination with immunotherapy, as well as muscle invasive bladder cancer.

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