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REVIEW

Current and Emerging Treatments for Urothelial Carcinoma: A Focus on Enfortumab Vedotin

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Abstract: Urothelial carcinoma is a common malignancy that affects the urinary system, with bladder cancer being the most prevalent form. Although the management of early-stage disease has seen significant improvements, the treatment of locally advanced and metastatic urothelial carcinoma remains challenging. Over the past decade, there has been an explosion in the number of therapies available for the treatment of advanced disease, with immune checkpoint inhibitors and antibody-drug conjugates leading the way. Enfortumab vedotin is an antibody-drug conjugate that targets Nectin-4, a protein that is overexpressed in urothelial carcinoma cells. In clinical trials, it has shown promising outcomes for the treatment of advanced urothelial carcinoma that has progressed after chemotherapy or immunotherapy. The US Food and Drug Administration has granted expedited approval for enfortumab vedotin in the treatment of advanced urothelial carcinoma. This review provides an overview of the current and emerging treatments for urothelial carcinoma, with a particular focus on enfortumab vedotin. We discuss the mechanisms of action, clinical efficacy, safety, and ongoing research of enfortumab vedotin, along with the current landscape of other approved therapies and promising agents in development. The aim of this review is to provide a comprehensive and up-to-date summary of the available treatment options for urothelial carcinoma, including their limitations and future prospects.

Keywords: urothelial carcinoma, enfortumab vedotin, erdafitinib

Introduction

The sixth most frequent cancer in the US population, urothelial carcinoma accounts for around 2.9% of global mortality.[1] Urothelial bladder cancer (UBC) is a form of cancer that begins in the bladder lining. Noninvasive UBCs, which represent around 75% of newly diagnosed cases, have a high risk of recurrence and development, despite localized therapy. Invasive UBCs, which account for the remaining 25%, need major surgery or radiation and may have poor results even with systemic treatment.[2,3]

In this piece of writing, we will clarify the factors that contribute to the risk of urothelial carcinoma and discuss the progress that has been made in its treatment over time. Ultimately, our focus will be on highlighting the significance of a highly promising medication called "enfortumab vedotin" and examining its trials and outcomes in detail, particularly for the treatment of advanced urothelial carcinoma affecting the bladder.

Risk Factors

Other than nonmodifiable risk factors such as genetics, age, male gender, birth defects, race, and ethnicity, smoking is the biggest modifiable risk factor for developing bladder cancer.[4] Around 10% of cases of Bladder Cancer are caused by occupational exposure to aromatic amines, polycyclic aromatic hydrocarbons, and chlorinated hydrocarbons. This kind of exposure is prevalent in industrial plants that handle paint, dye, metal, and petroleum products.[5,6] Exposure to potentially carcinogenic trihalomethanes resulting from the chlorination of drinking water and to arsenic in drinking water can also raise the risk of Bladder Ca.[7] Ionizing radiation exposure is also associated with increased risk, while weak links were

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suggested for cyclophosphamide and pioglitazone. Schistosomiasis, which is caused by repeated infection with a parasitic trematode, is another cause of Bladder Ca.

Genetics and Urothelial Cancer

In the current modern era, changes in DNA have been reported from time to time which is proven to be a main culprit for causing Bladder Carcinoma.[8,9] In a recent study, A high expression of NRP2 has been proven to be associated with a poor prognosis of Bladder Urothelial Carcinoma.[10] From previous trials and studies, it is now a well-established conclusion that non-muscle invasive urothelial carcinoma has been associated with FGFR3 mutations but it usually does not progress aggressively with a 5-year survival of almost 90%.[11] However, muscle-invasive bladder carcinoma has been frequently associated with the tp53 mutations with a 5-year survival of <50%.[12]

Old and Current Treatment Guidelines

The treatment guidelines for the Non-invasive type of urothelial carcinoma seem to be pretty much loud and clear.

Bacillus Calmette–Guerin (BCG)

Intravesical Bacillus Calmette–Guerin (BCG) immunotherapy for urothelial carcinoma of the bladder has remained a first-line option due to its safer adverse effects profile although it has shown efficacy of 50%.[13] New findings have indicated that neutrophils and TNF-related apoptosis-inducing ligands (TRAIL) may play a part in the inflammatory response that combats tumor growth.[14,15]

The typical dosage regimen for BCG therapy entails providing six weekly doses of BCG as an induction course after transurethral resection of the bladder tumor (TURBT).[16] Patients with carcinoma in situ (CIS) and high-risk superficial tumors, on the other hand, benefit from extra doses of BCG given at regular intervals following the initial induction course, known as maintenance BCG therapy. The purpose of maintenance treatment is to keep cancer from returning and to enhance long-term outcomes for these patients.[17] The particular dose schedule and length of maintenance BCG treatment may vary based on the condition and reaction of the individual patient.

Due to the potential risks involved, patients with a history of BCG sepsis, immunosuppression, extensive hematuria or traumatic catheterization, and current urinary tract infection are not ideal candidates for BCG instillation treatment.[18] Mild cystitis, shown as urgency, frequency, low-grade fever, and malaise, is a common adverse effect of intravesical BCG. These symptoms may be experienced by up to 90% of individuals.[19–21]

Sacituzumab Govitecan

Sacituzumab govitecan is an antibody-drug conjugate that specifically targets the protein Trop-2 found on cancer cells. By binding to Trop-2, it releases the chemotherapy drug SN-38 inside the cancer cells, leading to cell death and inhibiting tumor growth.[22] Initially approved for metastatic triple-negative breast cancer (mTNBC) in patients who have undergone prior therapies,[23] it has shown promising results with an objective response rate of 27% in the TROPHY-U-01 Phase II trial.[24] The drug has also received accelerated approval for locally advanced or metastatic urothelial cancer in patients previously treated with platinum-based chemotherapy and a programmed cell death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor.[25]

However, the clinical use of sacituzumab govitecan is limited due to its adverse effects. Common side effects include diarrhea, nausea, fatigue, alopecia, and neutropenia.[26,27] Grade ≥ 3 treatment-related adverse events such as neutropenia, leukopenia, anemia, diarrhea, and febrile neutropenia have been observed. Although these effects can be effectively managed with supportive care, they present challenges in practical application and management.[28,29]

Therefore, a careful assessment of the overall benefit-risk profile is necessary when considering the use of sacituzumab govitecan in clinical practice, particularly in light of its observed adverse effects. Ongoing studies are exploring the potential of using sacituzumab govitecan as a single agent or in combination with other therapies for urothelial cancers.

Surgical Options

Current guidelines had also described surgical interventions like TUR of the Bladder where there is a possibility of muscle invasion and complications. A proper transurethral resection (TUR) of a bladder tumor is an important first step in controlling and assessing the illness. Inadequate excision of the primary tumor or insufficient sample of the muscularis propria might result in disease recurrence or incorrect staging.[30,31] Furthermore, failure to discover tumors such as carcinoma in situ (CIS) during the first resection might lead to incorrect disease staging. As a result, it is critical to do a thorough TUR to guarantee total tumor removal, and accurate staging, and to reduce the chance of recurrence.[32] Re-TUR can also be indicated for reassurance and to repeat staging for further planning of the treatment.[33] Radical cystectomy is indicated in advanced cases of urothelial carcinoma where the eligibility criteria are met and where there is a high chance of muscle invasion.[34,35]

Immunotherapies and Targeted Medicines

Immunotherapies and targeted medicines have made considerable advances in the treatment of locally progressed and metastatic urothelial carcinoma (UC) in recent years.[36] However, for suitable patients, cisplatin-based chemotherapy remains the mainstay of treatment. The US Food and Drug Administration has approved erdafitinib, a pan-fibroblast growth factor receptor (FGFR) inhibitor, as a second-line therapeutic option for patients with sensitive FGFR2 or FGFR3 mutations after platinum-based chemotherapy.[37] It is crucial to emphasize that FGFR mutations are found in only a small fraction (10–20%) of people with metastatic UC.

Checkpoint proteins that inhibit anti-tumor T-cell responses include programmed death-1 (PD-1), programmed death ligand-1 (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). In practice, many solid tumors, including non-small cell lung cancer, malignant melanoma, and urothelial carcinoma, utilize immune-evasion strategies to elude identification and elimination by the immune system. Anti-tumor T-cell responses can be suppressed by programmed death-1 (PD-1), programmed death ligand-1 (PD-L1), or cytotoxic T-lymphocyte-associated protein 4 (CTLA-4).[38,39] Enhancement of these checkpoint proteins is a typical immune-evasion approach used by a variety of solid cancers, including non-small cell lung cancer (NSCLC), malignant melanoma, and urothelial carcinoma.[40,41] Though FDA approved certain drugs of this class for trials Recent evidence suggests that relying solely on PD-L1 as a predictive biomarker for immune checkpoint blockade (ICB in advanced urothelial carcinoma (UC) may not be sufficient. To achieve optimal personalized patient selection, a combination of PD-L1 with other new biomarkers will be required.[42]

How Enfortumab Vedotin Works?

A completely humanized monoclonal antibody (AGS-22M6) called enfortumab vedotin targets nectin-4 and is coupled to the microtubule-disrupting compound monomethyl auristatin E (MMAE).[43] Nectin-4 is overexpressed in urothelial, breast, lung, and pancreatic malignancies and is correlated with disease progression and a poor prognosis. Nectins are transmembrane proteins that participate in Ca2+-independent cell-cell adhesion through homophilic and heterophilic interactions. Nectin-4 staining was seen at moderate to high levels in 60% of the analyzed bladder tissues in human tissue microarrays.[44] Enfortumab vedotin attaches to nectin-4, penetrates the cell, and after being cleaved by proteolytic enzymes releases MMAE, which destroys the cellular microtubule network and causes cell death by causing cell cycle arrest during the G2/M phase.

Enfortumab vedotin is a completely humanized monoclonal antibody (AGS-22M6) that targets nectin-4, a transmembrane protein involved in cell-cell adhesion through homophilic and heterophilic interactions. This antibody is coupled with the microtubule-disrupting compound monomethyl auristatin E (MMAE) (7). Nectin-4 is often over-expressed in several malignancies, including urothelial, breast, lung, and pancreatic cancer, and is correlated with disease progression and poor prognosis. Studies have shown moderate to high levels of nectin-4 staining in 60% of analyzed bladder tissues in human tissue microarrays (8). This innovative therapy shows great promise in treating urothelial carcinoma and other malignancies associated with nectin-4 overexpression.

Previous Trials

Enfortumab vedotin (EV) was the subject of the first substantial trial in this series, EV-101, which evaluated EV's safety, tolerability, and antitumor efficacy.[45] Enfortumab vedotin's pharmacokinetics, immunogenicity, safety, and anticancer activity in patients with metastatic urothelial carcinoma (mUC) or other malignant solid tumors that express nectin-4 will be examined in the Phase I study known as EV-101. The three adverse drug reactions (ADRs) with the highest reported frequency were decreased appetite (42%), weakness (53%), and alopecia (46%).

In the EV-201 trial, the safety and effectiveness of intravenous enfortumab vedotin at a dose of 1.25 mg/kg on days 1, 8, and 15 of a 28-day cycle in patients with locally advanced or metastatic urothelial carcinoma (UC) had previously received platinum-based chemotherapy and a checkpoint inhibitor were examined, this was a two-cohort, single-arm study.[46] Cohort 1 included 128 patients, with 125 getting the medicines. Patients who had had both platinum-based chemotherapy and immunotherapy were deliberately recruited. The findings were encouraging, especially in cisplatin-ineligible UC patients. Fatigue (50%), baldness (49%), reduced appetite (44%), dysgeusia (40%), and peripheral sensory neuropathy (40% were the most prevalent grade 1 adverse drug reactions (ADRs). Neutropenia was the most common grade 3 adverse event.

The objective of EV-301, the third and last research in this series, was to determine enfortumab vedotin's survival advantage. A total of 608 individuals were randomized at random, with 307 receiving chemotherapy and 301 receiving enfortumab vedotin.[47] With a hazard ratio for mortality of 0.70 (95% CI, 0.56 to 0.89; P=0.001), the enfortumab vedotin group had a longer median overall survival (12.88 months vs 8.97 months) than the chemotherapy group. Both groups experienced similar rates of treatment-related side effects (93.9% in the enfortumab vedotin group and 91.8% in the chemotherapy group). Patients with locally advanced or metastatic urothelial cancer who had previously had platinum-based therapy with a PD-1 or PD-L1 inhibitor showed a significant extension of survival after receiving formal vedotin.[48] This trial shows that Enfortumab vedotin treatment was well tolerated, with verified responses reported in 52% of cisplatin-ineligible patients with locally advanced or metastatic urothelial carcinoma who had previously been treated with PD-1 or PD-L1 inhibitors.[49]

Nct0307099

The study is a Phase 1 clinical trial in Japanese patients with locally advanced/metastatic urothelial carcinoma, evaluating the safety, tolerability, and pharmacokinetics of enfortumab vedotin (EV) post-chemotherapy or in cisplatin-ineligible patients.[50] On Days 1, 8, and 15 of a 28-day cycle, patients were randomized 1:1 to receive EV at 1.0 mg/kg (Arm A) or 1.25 mg/kg (Arm B). Pharmacokinetics and safety were the main goals, whereas anticancer activity was a secondary goal. Seventeen patients (9 in Arm A, and 8 in Arm B) were treated. One patient achieved a complete response, and five achieved partial responses (3 in Arm A, and 2 in Arm B). The objective response rate was 35.3% and the disease control rate was 76.5%.

Ongoing Trials

Ev-302

The goal of this study is to evaluate the efficacy of enfortumab vedotin + pembrolizumab to the conventional treatment of gemcitabine + platinum-containing chemotherapy in patients with locally advanced or metastatic urothelial carcinoma who have never been treated before.[51] Patients will be randomly assigned in the clinical trial to receive either EV + pembrolizumab or conventional chemotherapy, with stratification determined by the presence of liver metastases, PD-L1 expression, and eligibility for cisplatin. The control arm will get gemcitabine (1000 mg/m2) and cisplatin/carboplatin (based on AUC) on a 3-week cycle, while the combination arm will receive EV (1.25 mg/kg) and pembrolizumab (200 mg) on certain days.

Mk-3475-905/Keynote-905/Ev-303 (Nct03924895)

This research investigates the use of pembrolizumab or enfortumab vedotin in combination with pembrolizumab in patients with muscle-invasive bladder cancer (MIBC) who are unable to receive cisplatin or decline cisplatin as part of their perioperative treatment plan, with the aim of determining their effectiveness.[52] A total of 836 patients will be enrolled in this study and randomly assigned in a 1:1:1 ratio to three different treatment arms. The first arm will receive three cycles of neoadjuvant pembrolizumab, followed by radical cystectomy (RC) and pelvic lymph node dissection (PLND), and then 14 cycles of adjuvant pembrolizumab. The second arm will receive three cycles of neoadjuvant

enfortumab vedotin (EV) in combination with pembrolizumab, followed by RC+PLND, and then six cycles of adjuvant EV and pembrolizumab, followed by eight cycles of adjuvant pembrolizumab. The third arm will receive RC+PLND alone. Neoadjuvant or adjuvant pembrolizumab will be administered intravenously at a dose of 200 mg every 3 weeks (Q3W), while neoadjuvant or adjuvant EV will be administered at a dose of 1.25 mg/kg on days 1 and 8 Q3W.

MORPHEUS mUC (NCT03869190)

In addition, the goal of this clinical research is to determine if pembrolizumab or enfortumab vedotin combination with pembrolizumab can be used as perioperative therapy for patients with muscle-invasive bladder cancer (MIBC) who are ineligible for or refuse to receive cisplatin.[53]

There are two stages to the MORPHEUS-mUC study (NCT03869190). In Stage 1, atezolizumab monotherapy or experimental combinations will be given to 130–305 patients with locally progressed or metastatic urothelial cancer. Atezolizumab in combination with enfortumab vedotin or linagliptin will be the main focus of Stage 2 unless these combinations exhibit no effect in Stage 1. We will keep a tight eye on safety for any possible overlapping toxicities. Brief summary of trials is presented in Table 1

Adverse Effects Profile

Fatigue, baldness, reduced appetite, and peripheral neuropathy are some of the most frequently reported side effects of enfortumab vedotin. At the most recent follow-up, of the patients who had a rash, 73% had it completely resolved and 20% had some improvement.[43] Aside from these, there have also been reports of increased glucose levels, elevated aspartate aminotransferase levels, rash, decreased lymphocyte counts, elevated creatinine levels, peripheral neuropathy, increased glucose levels, increased lipase levels, decreased albumin levels, diarrhea, pruritus, nausea, dysgeusia,

Table 1 Summary of Clinical Trials

Trial	Objective	Patient Population	Key Findings
EV-101 n= 112	Phase I study evaluating safety and efficacy	Patients with metastatic urothelial carcinoma (mUC)	Objective Response Rate = 42% Common ADRs: decreased appetite, weakness, alopecia
EV-201 n= 125	Safety and efficacy evaluation	Locally advanced or metastatic urothelial carcinoma	Objective Response rate = 44% Common ADRs: fatigue, baldness, reduced appetite, dysgeusia, peripheral sensory neuropathy
EV-301 n= 608	Overall survival comparison	Locally advanced or metastatic urothelial cancer	Longer median overall survival in the enfortumab vedotin group compared to the chemotherapy group
NCT03070990 n= 26	Safety and pharmacokinetics evaluation	Japanese patients with urothelial carcinoma	Objective response rate: 35.3%
EV-302	Comparison of enfortumab vedotin + pembrolizumab	Locally advanced or metastatic urothelial carcinoma	Ongoing trial
MK-3475-905/ KEYNOTE-905/EV-303	Effectiveness of pembrolizumab or enfortumab vedotin combination	Muscle-invasive bladder cancer (MIBC)	Ongoing trial
MORPHEUS mUC	Evaluation of pembrolizumab or enfortumab vedotin combination	Muscle-invasive bladder cancer (MIBC)	Ongoing trial

Abbreviations: ADRs, Adverse Reactions; mUC, Patients with metastatic urothelial carcinoma (mUC); MIBC, Muscle-invasive bladder cancer.

decreased phosphate levels, decreased weight, and decreased potassium levels. Please take note that "decreased potassium" appeared twice in the original text; thus, it appears only once in the updated text to prevent repetition.

Conclusion

Enfortumab vedotin has demonstrated a safe and successful treatment profile in clinical studies, especially in a challenging-to-treat population of individuals with locally advanced or metastatic urothelial carcinoma (UC). This novel treatment has shown promising benefits in individuals who have previously taken chemotherapy, immunotherapy, or erdafitinib. For advanced bladder cancer patients who have progressed on these medicines, there is currently no universally approved standard-of-care choice, making enfortumab vedotin a prospective breakthrough in the treatment of UC. Despite these considerable therapeutic advances, UC remains an aggressive illness that is now incurable in the majority of patients. More research and the development of innovative therapeutic techniques are required to enhance outcomes for UC patients.

Disclosure

The authors report no conflicts of interest regarding the research, authorship, and publication of this article.

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