Review Article

Investig Clin Urol 2022;63:373-384.
https://doi.org/10.4111/icu.20220061
pISSN 2466-0493 • eISSN 2466-054X

INVESTIGATIVE AND CLINICAL UROLOGY
ICUROLOGY

A novel strategy for treatment of bladder cancer: Antibody-drug conjugates

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In the past, there was no second-line chemotherapeutic agent suitable for use when urothelial carcinoma (UC) progressed to platinum-resistant UC. However, recently, several new treatment options, such as immune checkpoint inhibitors or targeted therapy have shifted the treatment paradigm regarding second-line therapeutic modalities. A novel class of therapeutic agents includes an antibody-drug conjugate (ADC). ADCs consist of three characteristics: a monoclonal antibody, linker, and payload. The specificity of the monoclonal antibody facilitates the delivery of a linked cytotoxic drug directly into the target tumor cell. Although various ADCs have been developed and approved for use in treating several solid tumors, almost all ADCs for the treatment of UC are still in the testing phase. Here, we review the key points about ADCs and summarize the novel ADCs that are approved or are involved in ongoing studies in UC.

Keywords: Antibody-drug conjugate; Bladder cancer; Immunoconjugates; Immunotherapy; Urinary bladder neoplasms

INTRODUCTION

Urothelial carcinoma (UC) that included bladder cancer is the fifth frequently occurring malignant tumor in the world. Cisplatin-based chemotherapy is the established standard treatment that has demonstrated a survival benefit in patients with metastatic bladder cancer [1]. In patients with UC, the overall survival rate results fifteen months and 5-year survival rate is 15% [2]. The classical regimen of platinum-based chemotherapy for advanced UC was the combination of methotrexate, vinblastine, doxorubicin, and cisplatin that is called MVAC [3]. However, almost urologists generally preferred other cisplatin-based agents such as gemcitabine-cisplatin combination because of a MVAC toxicity. Platinum-based therapeutic regimens are related with considerable toxic effects, and 25% to 50% of patients with advanced UC cannot tolerate cisplatin-based therapy [4].

In the past, it was known that there was no second-line chemotherapy agent approved in the US for use when UC progressed to platinum-resistant urothelial carcinoma (PRUC). Recently, new therapeutic strategies with the potential to provide more durable remissions have appeared for second-line chemotherapy. Immune checkpoints is the term for cell-surface receptors that expressed by immune cells, but can also suppress the mechanism of tumor-associated immunity [5]. Several immune checkpoint inhibitors (ICIs) are approved therapeutic drugs for advanced UC after failure of chemotherapy [6-10]. The U.S. Food and Drug Administration (FDA) serially approved the ICIs such as atezolizumab, durvalumab, avelumab, pembrolizumab, and nivolumab from

Received: 12 February, 2022 • **Revised:** 25 March, 2022 • **Accepted:** 18 April, 2022 • **Published online:** 30 May, 2022
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2016 to 2017. Unfortunately, response rates of ICIs results approximately 20% in patients with advanced UC [11]. Furthermore, these ICIs have no predictable biomarkers, and it is unclear how to determine termination of treatment [12].

A novel therapeutic drugfor managing patients with chemotherapy resistant UC is antibody-drug conjugates (ADCs). ADCs targeting specific cell surface antigens represent a novel treatment option for PRUC [13]. The antitumor effect of ADCs was initially demonstrated in acute myeloid leukemia and breast cancer. FDA approved gemtuzumab ozogamicin for the treatment of AML in 2000. However, it was withdrawn in 2010 due to the low efficacy demonstrated in its post-market clinical trial [14]. Trastuzumab emtansine was approved for the treatment of patients with metastatic HER2-positive breast cancer in 2013 [15]. Subsequently, various ADCs have been developed and applied in the treatment of both solid and hematologic tumors. Furthermore, the challenges of combination treatment such as ICIs and traditional chemotherapeutic agents are currently being considered in diverse clinical studies.

Compared to these latest trends in cancer treatment, the application of ADCs in the field of urology is somewhat lagging. Over the past several years, the effort to apply ADCs has continued in urological cancers and many clinical trials have reported positive results. Recently, two ADCs, enfortumab vedotin (EV) and sacituzumab govitecan (SG), have been approved for patients with advanced or metastatic UC (mUC) following recurrence after platinum-based chemotherapy and ICIs [16]. This article introduces general information regarding ADCs and summarizes several promising results in patients with UC.

ANTIBODY-DRUG CONJUGATES

ADCs are a new therapeutic option containing an antibody attached to the cytotoxic drug [17]. ADCs comprise an antibody, a linker molecule, and an anti-cancer drug (payload) (Fig. 1). These were administered into cancer cells and exhibited a direct cytotoxic effect. The optimal target antigen is very highly expressed only in cancer cells. After the antibody binds to the specific antigen target of cancer, the conjugated cytotoxic drug is internalized by the cancer cells [18]. Unlike previous target therapy, ADCs can exert anti-cancer effects by targeting surface proteins that are not directly related with cellular growth or proliferation [19]. Despite the concise conceptual structure, many other factors should be considered when designing optimal ADCs, such as the selection of optimal target antigen and conjugation method.

Murine monoclonal antibodies are used in form of early ADCs. The antibodies are usually linked to cytotoxic drugs such as doxorubicin, vinblastine, or methotrexate. These ADCs, however, exhibited low success rates in clinical studies due to immunogenicity, low potency, inappropriate target selection, and decreased selectivity between tumors and normal tissues [20]. Recently, murine antibodies were replaced with human antibodies to prevent immunogenic incompatibility. Accurate target selection improved the efficacy of drug internalization. Therefore, we detail the aspects involved in creating the ADC in Table 1.

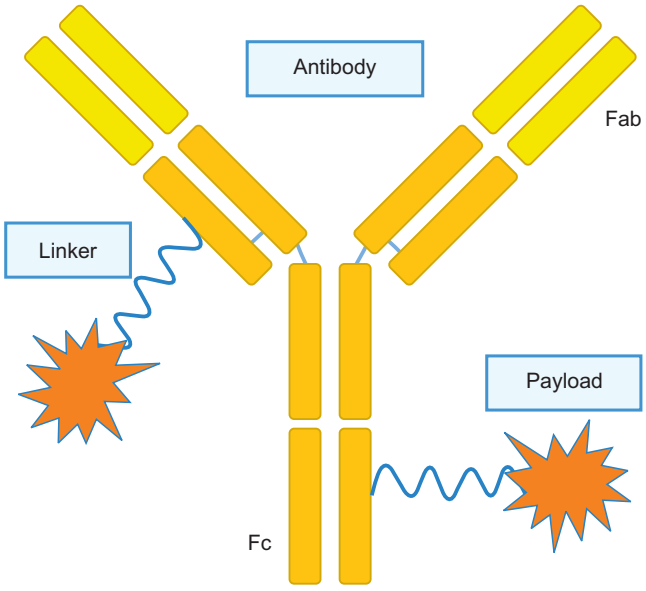

Fig. 1. Antibody-drug conjugate structure consisting of monoclonal antibody, linker, and cytotoxic payload. The antibody is specific to tumor cell surface proteins. The linker is the chemical connector that binds the drug to the antibody. The payload is a highly potent cytotoxic drug. Fab, fragment antigen binding; Fc, fragment crystallizable.

Following administration, the ADC undergoes several steps to produce cytotoxic effects in the cancer cells (Fig. 2) [21]. ADCs bind to specific antigens of the malignant cells. The ADC-antigen complex is internalized via the endocytosis [22]. After internalization mechanism, the ADCs' linkers are cleaved in the cancer cell. Then the cytotoxic payloads are activated. Released cytotoxic payloads show a cytotoxic effect through combining to the minor groove of deoxyribonucleic acid (DNA) or interacting with tubulin.

1. Antibody

The successful fabrication of an ADC depends on the optimal selection of a tumor-specific antigen and technology to deliver the ADC to the appropriate target. It is important to ensure that the antigen is specific and highly expressed in target cancer but is distinguished from normal cells [23]. Expression homogeneity of the antigen within cancers and

https://doi.org/10.4111/icu.20220061

Table 1. Considerations in antibody-drug conjugate design

Component	Description	Consideration
Target antigen	Cancer specific antigen that an antibody is directed	Target antigen should be highly expressed on tumor cells with low expression on normal tissues
Antibody	Targeted at a well-characterized antigen	Antibody should have high affinity for target antigen, long half-life, and high molecular weight
Linker	Covalent coupling of the cytotoxic drug and the antibody	Linker must maintain a stability in blood circulation and efficiently release the cytotoxic drug inside tumor cell
Conjugation	Specific method of attachment of the cytotoxic drug and linker to the antibody	The method of conjugation, number of drugs per antibody, and drug position influence the physical properties of the antibody-drug conjugate; aggregation, antigen binding, and clearance of the conjugation in the circulation
Payload	Cytotoxic drug that is expected for therapeutic effect	Payload should be highly potent because only a limited number of molecules can be attached to the antibody

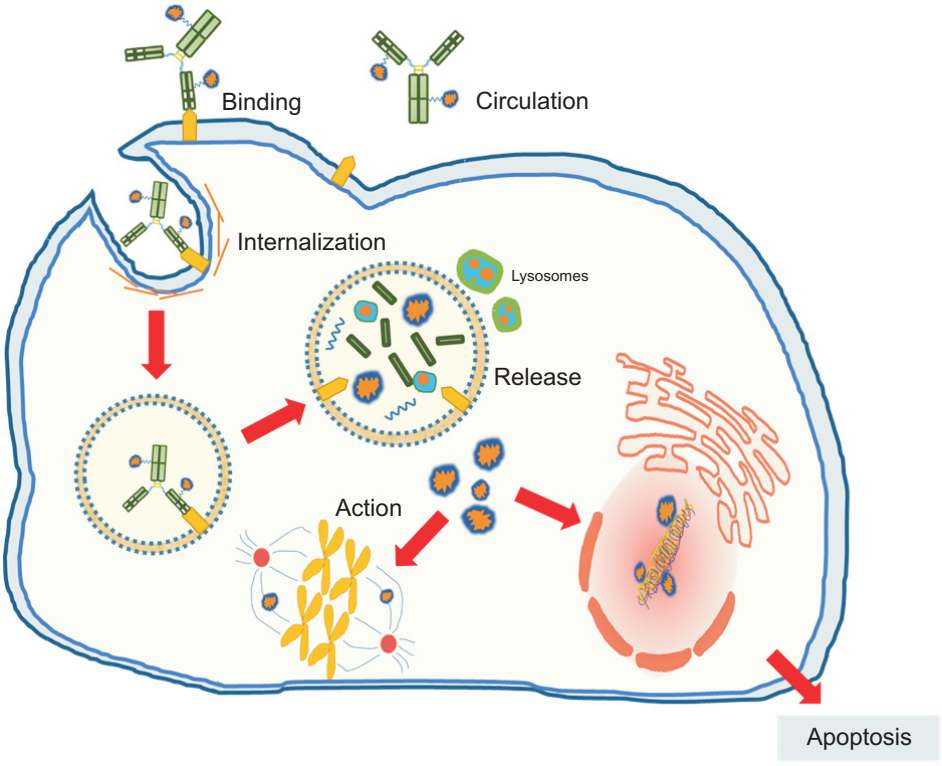

Fig. 2. Illustration of the mechanism of action of antibody-drug conjugates (ADCs). ADCs bind to the surface antigen on tumor cells. Subsequently, ADCs are internalized through receptor-mediated endocytosis. ADCs are processed through the endosome-lysosome pathway leading to release of the cytotoxic payload and induced tumor cell death by attacking DNA or affecting microtubule structure.

accessibility to the antigen from the blood circulation are critical to maximizing access of the ADC to the target [24]. If an expression of target antigen does not reach sufficient levels in tumor cells, ADC uptake will be low and the cytotoxic effect will be limited. It may induce drug accumulation in the extracellular space and lead to nonspecific toxicity in normal tissues. The antibody was developed considering the direct toxicity of the antibody in the past; nevertheless, the tumor-specific binding capacity of the antibody was more important than the cytotoxicity of the antibody. The most common type of antibody is known as human IgG isotypes, especially IgG1 [25].

2. Linker

The linker has an essential role in influencing the ADC's pharmacokinetics and drug efficacy [26]. The ideal linker should maintain stability in the bloodstream since the ADC should not release the cytotoxic drug before reaching its target and thereby cause off-target toxicity. In addition, the linker should readily release the drug after internalization [27]. From the viewpoint of intracellular stability and manner of degradation, linkers are divided as non-cleavable and cleavable [23]. Non-cleavable linkers are generally very stable in body fluids and solely depend on lysosomal degradation to release their payload. In contrast, cleavable linkers have instability under the low pH, protease-enriched environment of lysosomes, or high level of intracellular glutathione [15].

For this reason, cytotoxic substances affect nearby cells regardless of target antigen expression [18].

3. Payload

The payload means the cytotoxic drug that has an anticancer effect and concentrates high level in cancer cells. There are many payload drugs depending on the mechanism of cytotoxicity. Immunotherapeutic drugs loaded into the ADCs are able to play a very important role since they possess strong target-specific toxicity. The drugs commonly used in chemotherapy are difficult to apply to ADCs because of their systemic cytotoxicity and limitations of the dosage [28]. To overcome these limitations, the ideal payload drug should have an IC50 even at the concentration range of nM–pM and be able to avoid resistance by multidrug resistant protein 1 [29,30]. The cytotoxic drugs can be distinguished in two main groups: those damaging to DNA and those interfering with tubulin formation. For example, auristatins block tubulin assembly and cause G2/M phase cell cycle arrest; they are commonly used payloads in the form of monomethyl auristatin E (MMAE) [31-33]. Maytansinoids are known as another tubulin inhibitors used in ADC development such as trastuzumab emtansine (T-DM1) [34]. The DNA-damaging agents can act throughout the different cell cycle phases. Calicheamicin and duocarmycin are potent cytotoxic agents attacking the minor groove of DNA [35,36].

ANTIBODY-DRUG CONJUGATES IN UROTHELIAL CARCINOMA

After the FDA approval, EV and SG were included in the 2021 updated European Association of Urology guidelines on mUC [37]. Vicinium, trastuzumab emtansine, and tisotumab vedotin (TV) are emerging ADCs based on reliable clinical evidence. Table 2 provides a summary of the ADCs discussed in this article. Common adverse events (AEs) of ADCs are briefly indicated in Table 3.

1. Enfortumab vedotin

EV is composed of a Nectin-4-directed antibody and microtubule inhibitor. It is the first FDA-approved ADC in order to manage patients with mUC based on the phase II clinical trial [38]. Nectin-4 is a type 1 transmembrane protein and it is related with immunoglobulin-like adhesion molecules implicated in cell-to-cell adhesion [39]. Nectin-4 is overexpressed in UCs compared with other cancer cells or normal tissues and may contribute to tumor cell growth and proliferation. EV tends to bind Nectin-4 expressing cells with high affinity, facilitating the internalization and release of the microtubule-disrupting agent MMAE in target cells [3]. On December 18, 2019, the FDA notified accelerated approval to EV-ejfv (PADCEV®, Astellas and Seattle Genetics, Northbrook, IL, USA) for the treatment of patients with advanced or mUC who previously administered a PD-1/L1 inhibitor, and cisplatin-based chemotherapy [40].

1) Phase I study: EV-101

The phase I study about EV (EV-101) was published in 2020. This study designed a dose escalation and expansion study in patients with mUC who were treated by chemotherapy. EV demonstrated generally tolerable single-agent antitumor activity in patients with mUC regardless

Table 2. Molecular characteristics of novel antibody-drug conjugates (ADCs) in urothelial carcinoma

ADC	Target antigen	Cytotoxic compound	Development status
Enfortumab vedotin	Nectin-4	Monomethyl auristatin E (MMAE)	FDA-approval
Sacituzumab govitecan	TROP2	SN-38	FDA-approval
Oportuzumab monatox	EpCAM	*Pseudomonas* exotoxin A	Phase III
Trastuzumab emtansine	HER2	Derivative of maytansine (DM1)	Phase II
Tisotumab vedotin	Tissue factor (TF-011)	Monomethyl auristatin E (MMAE)	Phase II

FDA, U.S. Food and Drug Administration; EpCAM, epithelial cell adhesion molecule.

Table 3. Adverse events of antibody-drug conjugates (ADCs) in urothelial carcinoma

ADC	Enfortumab vedotin	Sacituzumab govitecan	Tisotumab vedotin
Clinical trial	NCT03474107	NCT03547973	NCT02001623
Treatment-related adverse events (Grade≥3)	Rash maculopapular (7%), fatigue (6%), neutrophil count decreased (6%), neutropenia (5%)	Neutropenia (34%), leukopenia (17%), anemia (14%), febrile neutropenia (10%)	Fatigue (10%), anemia (5%), abdominal pain (4%), hypokalemia (4%), conjunctivitis (3%)
Most common adverse events	Alopecia (45%), peripheral neuropathy (34%), pruritus (32%), fatigue (31%), decreased appetite (31%)	Diarrhea (65%), nausea (60%), fatigue (52%), alopecia (47%), neutropenia (46%), decreased appetite (36%)	Epistaxis (69%), fatigue (56%), nausea (52%), alopecia (44%), conjunctivitis (43%), decreased appetite (36%)

https://doi.org/10.4111/icu.20220061

of previous history of chemotherapy. An EV (1.25 mg/kg) resulted an encouraging and notable response rate of 43% in patients with mUC [41]. The median overall survival (OS) was 12.3 months for EV; OS for anti-PD-L1 therapy was up to 10.3 months in post-chemotherapy patients [6,7]. Common AEs included fatigue, alopecia, rash, peripheral neuropathy, decreased appetite, nausea, and diarrhea. Skin related events such as rash, alopecia, and pruritus are common because of mild to moderate expression of Nectin-4 on human skin keratinocytes and skin appendages. Peripheral neuropathy, which is associated with the microtubule inhibitor or MMAE, was observed in 49% of patients. Serious hyperglycemia was reported in 3.2% of patients with mUC.

2) Phase II study: EV-201

EV-201 is a multicenter, single-arm, phase II study of EV in patients with locally advanced or mUC previously administrated with PD-1 or PD-L1 inhibitors. EV was administered intravenously at a dose of 1.25 mg/kg on days 1, 8, and 15 of every 28-day cycle. Eighty-nine patients who received EV were included in this analysis. This study demonstrated that EV revealed a significant response rate (46 of 89 patients, 52%), with 18 of 89 patients (20%) achieving complete response, and a median duration of 10.9 months. Of the 80 patients with adequate tumor tissue for testing, 79 (99%) had Nectin-4 expression that was detectable by immunohistochemistry. Distribution of Nectin-4 expression was similar between responders and non-responders. Overall rates of AEs were similar to those of previous studies [38,41]. Skin reactions and hyperglycemia were observed within the first cycle of treatment. Additionally, peripheral neuropathy was reported in the end of the second cycle. It was demonstrated that patients treated with EV should be monitored for AEs in the early cycles of EV treatment. Dose modifications might be considered to reduce AEs.

3) Phase III study: EV-301

Preliminary outcomes of the randomized phase III study compared with EV monotherapy and single-agent chemotherapy in patients with previously treated by platinum and ICIs have been reported in a press release demonstrating a survival benefit [42]. Overall, 608 patients were randomized to EV (n=301) or chemotherapy (n=307). OS was prolonged with EV compared with chemotherapy (12.88 vs. 8.97 months, respectively). Progression-free survival was also longer in the EV group compared with the chemotherapy group (5.55 vs. 3.71 months, respectively). EV demonstrated superior efficacy over chemotherapy in patients with advanced UC previously treated with chemotherapeutic drugs and PD-1/L1 inhibitors. EV decreased the mortality rate by 30% compared with chemotherapy. The benefit of EV was observed across most subgroups, including patients with liver metastasis. Progression-free survival, overall response rates, and disease control rates were also superior for EV compared with chemotherapy. The overall incidence of treatment-related AEs was comparable between the groups. Skin reactions such as maculopapular rash are related to Nectin-4 expression in the skin [41]. Peripheral neuropathy occurred at a higher rate (49%–50%) with EV. Although the precise mechanism is unknown, hyperglycemia occurred more frequently in the group of EV. Because of a superior OS benefit, Phase III clinical trial (EV-301) was discontinued early. With recent data supporting maintenance treatment with the PD-L1 inhibitor avelumab after chemotherapy for advanced UC, EV may be considered at first relapse following maintenance immunotherapy [43].

2. Sacituzumab govitecan

Recently, the FDA approved SG as an ADC which contains an antibody against epithelial cell surface molecule. SG targets trophoblast antigen 2 (TROP2), a transmembrane glycoprotein that is usually expressed in trophoblasts, attached to SN-38 which is the active metabolite of irinotecan [44]. TROP2 protein is highly expressed in many epithelial cancers such as breast, cervical, and colorectal. It is known to exist in normal urothelium and in 83% of UCs. SN-38, a semi-synthetic camptothecin that is the active component of irinotecan, was selected as the optimal drug because irinotecan's clinical properties were well known [45].

The SG, a second-generation ADC, has reported high therapeutic effect and tolerable toxicity in several solid tumors [46]. This trial was designed as a phase I study with a dose of 8.0 mg/kg given weekly for 2 weeks in a 3-week cycle. Although 25 patients (age: 52–60 years, males: 10, females: 15) were enrolled; there was only one case of urinary bladder cancer. This study results that SG proved to be a successful drug in various solid tumors. Detailed data related with the efficacy and toxicity in the patient with bladder cancer were insufficient; however, this study revealed that the patient with urinary bladder cancer demonstrated a good response rate (30%) at an SG dose of 12 mg/kg. While more than half of the patients experienced fatigue (n=18, 72%), nausea (n=17, 68%), alopecia (n=13, 52%), diarrhea (n=13, 52%), and neutropenia (n=14, 56%), these were primarily grades 1 and 2. Severe AEs (grade 3 or 4) were mostly reported in patients with SG doses of 12 mg/kg and 18 mg/kg.

Ocean et al. [47] reported on the safety and pharmacokinetics of SG. Of the total 178 participants, 5 patients with

urinary bladder cancer were included: all males, 65 to 80 years old, who were administered doses of 8 mg/kg (n=3) and 10 mg/kg (n=2). The authors concluded that SG was safe and therapeutically active in metastatic solid cancers, even after several prior lines of therapy. They also proposed the optimal dose of SG with improved response and good therapeutic index at 10 mg/kg. In addition, Faltas et al. [48] reported that 3 patients exhibited a significant response from a total of 6 heavily pretreated patients with advanced PRUC. Progression-free survival was 6.7 to 8.2 months, and OS ranged from 7.5 to 11.4 months.

TROPHY-U-01 is a global, open-label, phase II study evaluating the clinical activity of SG in patients with advanced UC [49]. Cohort 1 included 113 patients who previous treated with platinum-based chemotherapy and ICIs. Patients received SG 10 mg/kg on days 1 and 8 of 21-day cycles. The results were an objective response rate of 27% (n=31, 95% confidence interval [CI], 19%–37%); progression-free survival of 5.4 months (95% CI, 3.5–6.9 months); OS of 10.5 months (8.2–12.3 months). The most common AEs were different from those observed with EV. Grade ≥3 treatment-related AEs reported neutropenia (35%), leukopenia (18%), anemia (14%), diarrhea (10%), nausea, and fatigue. Granulocyte colony stimulating factor usage was 30% and there was one treatment-related death due to sepsis [49].

A randomized phase III trial of SG compared with single-agent chemotherapy in patients with prior platinum and anti-PD-1/L1 therapy is now in progress (no. NCT04527991). The primary objective is to assess OS with SG in comparison with treatment of physician's choice (paclitaxel, docetaxel, or vinflunine) in participants with metastatic or locally advanced unresectable UC. In addition, combination therapy with SC and EV is to investigate the doses of SC and EV that can be safely combined in the treatment of mUC (no. NCT04724018).

3. Vicinium (Oportuzumab monatox, VB4-845)

Vicinium is a recombinant fusion protein comprising a humanized anti-epithelial cell adhesion molecule (EpCAM) single-chain antibody linked to a truncated form of *Pseudomonas* exotoxin A [50]. EpCAM is highly expressed in many epithelial tumors, especially high expression in UC [51]. Vicinium mediates cancer cell death by blocking protein synthesis. The toxicity of target therapies may be concerned with systemic administration due to normal tissue expression [52]. Moreover, repeated use of therapeutics consisting of foreign proteins is limited by their immunogenicity. It is desirable to develop therapies designed for local administration to minimize AEs. The Phase I study of oportuzumab monatox (OM) discussed safety, tolerability, pharmacokinetics, immunogenicity, and efficacy [53]. This study concluded that OM dosed on a weekly basis for 6 weeks was well tolerated at all doses. Although the maximum tolerated dose was not determined, OM demonstrated evidence of an antitumor effect that warrants further clinical investigation for the treatment of non-muscle invasive bladder cancer (NMIBC). AEs of OM were relatively mild and any AEs were not required the termination of treatment, even in the cohort of the highest dose.

A phase II study was evaluated the efficacy and tolerability of intravesical OM in patients with UC [54]. A total of 46 patients administered one induction cycle of 6 or 12 weekly intravesical OM instillations of 30 mg, followed by up to 3 maintenance cycles of 3 weekly administrations every 3 months. A complete response rate was observed in 39%–41% of patients at the 3-month evaluation. A total of 22 patients (44%) achieved a complete response. Seven patients (16%) remained disease-free. The most common AEs were related with reversible bladder irritative symptoms. The clinical trial concluded that OM was effective and tolerable in patients with Bacillus Calmette–Guérin (BCG) refractory bladder cancer. The results demonstrated the clinical benefit of OM and supported its possibility for the second line treatment of NMIBC.

Although many clinical trials demonstrated effectiveness of vicinium in NMIBC previously treated by BCG, the FDA did not approve vicinium in patients with BCG-unresponsive NMIBC. The FDA announced that it cannot approve the Biologics License Application for vicinium in its present form and recommended additional data and analyses. The determination was associated with a phase III clinical trial that has an estimated enrollment of 134 participants. In this study, the primary outcome was complete response rate up to 24 months. The 3-month complete response rate revealed 40%. The median duration of recurrence was 9.4 months (95% CI). Among patients who responded, 52% remained disease free for 12 months after treatment initiation. The 2-year OS rate was 96% (95% CI, 92%–100%).

However, some trials are continuing. A phase III follow-up trial, VISTA study (no. NCT02449239), is ongoing to analyze the efficacy and safety. It is a single-arm, open-label, multi-center study for BCG-unresponsive NMIBC, being conducted at centers around the US and Canada. Patients included high-grade Ta stage, or any T1 and carcinoma *in situ*. Patients were administered vicinium 30 mg in an intravesical instillation buffered in saline and held in the bladder for 2 hours. A primary endpoint was complete response rate and duration of response. A combination study

https://doi.org/10.4111/icu.20220061

involving durvalumab and vicinium is also being conducted (no. NCT03258593). This trial is to test whether the drugs durvalumab and vicinium used together are safe and effective to treat patients with UC that has not involved to the muscle layer.

4. Trastuzumab emtansine (T-DM1)

Ado-trastuzumab emtansine (T-DM1) is an ADC that is consisted of the monoclonal antibody trastuzumab linked to the microtubule poison emtansine (DM1). T-DM1 is already approved for the treatment of patients with progressed breast cancer [55]. Accumulating evidence from the testing of ADCs in several different tumor types has encouraged further research for exploration of new targets in UC [11]. Although HER2 has exhibited the highest expression in breast and lung cancer tissues, HER2 overexpression was markedly observed in UC tissue, commonly as a result of gene amplifications [56,57]. HER2 should be an appropriate target because the expression of HER2 is relatively low and even undetectable in normal urothelium but elevates in early staged UC and increases further based on disease progression [58].

Systemic therapy for advanced UC has not changed and mortality rates of UC is still high. The HER2 overexpression in UC has made HER2 a promising therapeutic target. Hayashi et al. [59] investigated the effect of T-DM1 compared to trastuzumab in two different models of HER2 overexpressing UC. They demonstrated that T-DM1 showed higher growth inhibition compared with trastuzumab in RT4V6 which was the highest HER2 expressing bladder cancer cell line. They concluded that T-DM1 has promising antitumor effects in preclinical models of HER2 overexpressing bladder cancer.

Although a clinical trial only for patients with UC does not exist, there are two ongoing phase II trials evaluating effectiveness of the drug in patients with HER2-overexpressing UC (no. NCT02999672, NCT02675829). In NCT02999672 study, thirteen patients with locally advanced or mUC were included. The first six patients administered T-DM1 at a dose of 2.4 mg/kg weekly followed by dose escalation (3.6 mg/kg for 3 weeks). It will evaluate the efficacy, safety, and pharmacokinetics of T-DM1. Participants will receive an intravenous infusion of T-DM1 until unacceptable toxicity, withdrawal of consent, disease progression, or death. The NCT02675829 study is still recruiting patients with bladder cancer. The purpose is to determine the effects of a drug called TE in patients and the impact on their cancers which are believed to be controlled by the abnormal *HER2* gene. This study is recruiting 135 participants who have lung, colorectal, endometrial, salivary gland, and other solid cancers. The treatment strategy is that T-DM1 is administered intravenously at dose of 3.6 mg/kg every 21 days until disease progression or severe toxicity. However, it is not known how many patients with bladder cancer participated until the study completion date estimated to be in February 2022.

5. Tisotumab vedotin

TV is a first-in-human ADC that is directed against tissue factor (TF) expressed on the cell surface of tumor cells [60]. TV is composed of a human monoclonal antibody specific for TF conjugated to the microtubule-disrupting agent MMAE via a protease-cleavable valine-citrulline linker. TF is a transmembrane glycoprotein that functions as the nitiator of the TF in coagulation pathway [61]. It plays a key role in cancer growth, metastasis, and angiogenesis. In UC, TF is positively expressed in high percentages (77.6%) of tumors [62]. The expression of TF supposed to predict disease-specific survival, risk of disease progression, and benefit of adjuvant chemotherapy. In 2019, de Bono et al. [63] performed phase I/II clinical trial using TV in patients with bladder cancer. Seventeen patients with bladder cancer of a total of 174 participants were enrolled. In the dose escalation arm (phase I study), one group received TV at a dose of 0.3 mg/kg and the other received TV at 1.5 mg/kg. Fifteen patients with bladder cancer received TB at a dose of 2.0 mg/kg in the dose expansion arm (phase II study). The primary outcome was the safety and tolerability of TV, assessed by the frequency of AEs, serious AEs, infusion-related AEs, grade 3 or worse AEs, and study drug-related AEs. Although the study did not report disease-specific rate of AEs, antitumor activity in the dose-expansion phase was eventually demonstrated. According to the Response Evaluation Criteria in Solid Tumors (version 1.1), four patients (26.7%) with bladder cancer achieved a confirmed objective response. This study was not intended to assess therapeutic effect; however, encouraging preliminary antitumor activity for TV was reported in a wide spectrum of solid tumors including bladder cancer.

FUTURE OF ANTIBODY-DRUG CONJUGATES: ONGOING TRIALS

ADCs have a possibility of the emerging standard in cases of progression after chemotherapy or immunotherapy [64]. Searching the optimal sequence of novel agents and suitable combinations are the subject of many ongoing trials. These trials are investigating the expansion of therapeutic indications and combination strategies. A number of ongoing tri-

als are exploring combination setting in patients with BCG refractory NMIBC. This will expand the therapeutic indications of ADCs. Another future direction presents the investigation of the synergic effect of ACD with other drugs such as ICIs. For instance, the EV-302 clinical study is an ongoing phase III study evaluating the efficacy of EV with pembrolizumab. The other efforts are directed toward searching new ADCs that has highly efficacious, or less resistant with low toxicity; several agents are aimed at a diversity of targets such as epidermal growth factor receptor (EGFR), integrin β6, B7-H3, or CD25.

After the FDA approval of EV (PADCEV®) for the treatment of patients with locally advanced or mUC, many other ADCs are being studied in advanced phases of clinical research and have displayed reliable evidence about tolerability and activity [40]. Through the website of ClinicalTrials.gov, we searched ongoing clinical studies using some keywords; antibody-drug conjugate AND/OR bladder cancer. Nine ongoing clinical studies were matched. Six studies have resulted, and another three studies are attempting to enroll patients with UC. In addition, we briefly summarized other ongoing trials in Table 4.

On the other hand, there is a negative view of ADCs to date. Drug-antibody-ratio (DAR) may be another consideration [65]. The conjugation process of ADCs results in a heterogeneity with multiple DARs. Beyond target and payload drug, uneven DARs will affect drug efficacy and toxicity [66]. The effort to decrease the DAR heterogeneity of ADCs may result in improved clinical outcomes.

1. NCT02529553

The main purpose of this phase I study was to evaluate the safety of the drug known as LY3076226 in participants with advanced or metastatic cancer [67]. LY3076226 is an ADC being developed by Eli Lilly Oncology, composed of human IgG1 monoclonal antibody against the human fibroblast growth factor receptor 3 attached with a cleavable linker to the maytansine derivative DM4. Fibroblast growth factor and their receptors are known to control a wide range of biological functions, regulating cellular proliferation, survival, migration, or differentiation. This study revealed acceptable safety and tolerability of LY3076226 up to a dose of 5.0 mg/kg.

2. NCT02552121 and NCT02001623

These phase I/II studies are briefly summarized; the primary objective is to evaluate the safety, tolerability, and efficacy of SG as a single dose administered in 21-day treatment cycles in previously treated participants with advanced epithelial cancer such as cervical, colorectal, endometrial, ovarian, esophageal, gastric adenocarcinoma, and metastatic urothelial cancer. These two studies had a similar study protocol, but the enrolled numbers of participants (33 vs. 195), included disease categories, treatment cycles (28-day vs. 21-day) were different. The studies of SG in urothelial cancer reported promising results [48,49].

Table 4. Clinical trials on recruiting status of antibody-drug conjugates (ADCs) in urothelial carcinoma

ADC	Trial	Design	Description	Primary endpoint
Enfortumab vedotin	NCT05014139	Phase I	Intravesical treatment in NMIBC	AEs, DLTs
	NCT04223856	Phase III	Combination therapy	Progression-free survival, OS
	NCT04995419	Phase II	Therapeutic effect in Chinese patients	ORR, pharmacokinetic
	NCT03288545	Phase I/II	Monotherapy vs. Combination therapy	Safety, ORR
	NCT04960709	Phase III	Durvalumab Combination with/without Tremelimumab	Efficacy, safety
	NCT04878029	Phase I	Combination with Cabozantinib	AEs
	NCT04963153	Phase I	Combination with Erdafitinib	AEs, MTD
	NCT04700124	Phase III	Combination with Pembrolizumab, perioperatively (EV-304)	pCRR, EFS
	NCT03924895	Phase III	Neoadjuvant with Pembrolizumab (EV-303)	pCRR, EFS
	NCT04724018	Phase I	Sacituzumab govitecan	MTD, DLTs
	NCT03606174	Phase II	Combination with PD-(L)1 checkpoint inhibitors	ORR
Sacituzumab govitecan	NCT04863885	Phase I/II	Combination with Ipilimumab plus Nivolumab	MTD, ORR
	NCT04527991	Phase III	Compared to Paclitaxel, Docetaxel, or Vinflunine (TROPiCS-04)	OS
	NCT03547973	Phase II	Combination therapy (TROPHY U-01)	ORR
Oportuzumab monatox	NCT03258593	Phase I	Combination with Durvalumab in NMIBC	Safety, tolerability
Trastuzumab emtansine	NCT02675829	Phase II	Bladder cancer with abnormal *HER2* gene	ORR

NMIBC, non-muscle invasive bladder cancer; AEs, adverse events; DLTs, dose limiting toxicities; OS, overall survival; ORR, objective response rate; MTD, maximally tolerable dose; pCRR, pathologic complete response rate; EFS, event-free survival; PD-(L)1, programmed cell death protein-(ligand)1.

https://doi.org/10.4111/icu.20220061

3. NCT01631552

This study was to investigate the tolerability of TF-ADC (TV) in patients with specified solid tumors such as ovarian, bladder, prostate, esophageal, and lung cancers. The study was conducted in two phases. In the dose escalation portion of the trial, participants were enrolled into cohorts at increasing dose levels of TV in 21-day treatment cycles. TV is targeted to the TF, coagulation factor III (thromboplastin also known as CD142), a protein encoded by the *F3* gene present in subendothelial tissue, and leukocytes. TV demonstrated an acceptable safety outcome and anti-cancer effect in patients with recurrent or metastatic cervical cancer [68]. On September 20, 2021, the FDA approved TV-tftv (TIVDAK®, Seagen, Bothell, WA, USA), a TF-directed antibody and microtubule inhibitor conjugate, for adult patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy. The study of the effectiveness of TV in patients with bladder cancer is still ongoing.

4. Recruiting studies

A study is currently recruiting patients with bladder cancer and is designed to evaluate the effect of SG and EV combination therapy in patients with mUC (no. NCT04724018). This research will assess which doses of SG and EV can be safely combined in the treatment of mUC. Another study being conducted is a clinical trial comparing the therapeutic effects of EV monotherapy and combination therapy in patients with UC (no. NCT03288545). This study will test an EV alone and with different combinations (pembrolizumab, cisplatin, carboplatin, and gemcitabine) of anticancer therapy. It will assess the side effects of the drugs and determine if the cancer reduces with the different combinations. In addition, a multicenter study was underway to compare the therapeutic effects of ICIs and ADC (EV) in patients with bladder cancer (no. NCT03606174). The study will evaluate the clinical activity of a PD-1 or PD-L1 checkpoint inhibitor regimens combined with the investigational agent sitravatinib in patients with advanced or mUC.

CONCLUSIONS

ADCs are emerging as novel therapeutic agents that have begun to demonstrate efficacy in the treatment of a variety of cancers, including leukemia, lymphoma, breast cancer, and UC. Recently, various ADCs have been approved or are in the process of approval by the FDA based on the high response rate of patients with mUC refractory to platinum-based chemotherapy and ICIs. In future clinical trials, we believe that the optimal combination therapy of ADCs, ICIs, and platinum-based chemotherapy can be determined. Additionally, we are supposed to study decreasing toxicity, improving safety, and overcoming resistance of ADCs in order to become ideal anticancer drugs.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

FUNDING

This research was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology, Republic of Korea (NRF-2021R1A2C1004307 and NRF-2021M3E5E6037643).

AUTHORS' CONTRIBUTIONS

Research conception and design: In Ho Chang. Data acquisition: Jung Hoon Kim. Statistical analysis: Jung Hoon Kim. Data analysis and interpretation: all authors. Drafting of the manuscript: Jung Hoon Kim. Critical revision of the manuscript: In Ho Chang. Obtaining funding: In Ho Chang. Administrative, technical, or material support: all authors. Supervision: In Ho Chang. Approval of the final manuscript: all authors.

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