Current Trends in Internal Medicine
Jain A, et al. Curr Trends Intern Med 8: 233.
www.doi.org/10.29011/2638-003X.100133
www.gavinpublishers.com

Review Article

Targeted Precision: Antibody-Drug Conjugates Revolutionize Urothelial Carcinoma Therapy

Arpit Jain[1], Varun Goel[1*], Satyajeet Soni[1], Satya Narayan[1], Pallavi Redhu[1], Dharmishtha Ashis Basu[1], Pankaj Goyal[1], Akanksha Jaju[2], Nivedita Patnaik[3], Vineet Talwar[1]

[1]Department of Medical Oncology, Rajiv Gandhi Cancer Institute and Research Centre, New Delhi, 110085, India

[2]Department of Pathology, ESIC Hospital, Basaidarapur, Delhi

[3]Consultant, Department of Pathology, BLK-Max Super Speciality Hospital, Delhi.

[*]**Corresponding author:** Varun Goel, Consultant, Department of Medical Oncology, Rajiv Gandhi Cancer Institute and Research Centre, New Delhi, 110085, India

Citation: Jain A, Goel V, Soni S, Narayan S, Redhu P, et al. (2024) Targeted Precision: Antibody-Drug Conjugates Revolutionize Urothelial Carcinoma Therapy. Intern Med 8: 233. DOI: 10.29011/2638-003X.100133

Received Date: 08 June 2024; **Accepted Date:** 18 June 2024; **Published Date:** 21 June 2024

Abstract

Despite advancements with immune checkpoint inhibitors, Urothelial carcinoma remains a formidable challenge due to aggressive progression and limited treatment options. However, recent advancements in targeted therapy have provided promising avenues for improved outcomes. Antibody-Drug Conjugates (ADCs) represent a novel approach that combines the specificity of monoclonal antibodies with the cytotoxicity of chemotherapeutic agents, thereby enhancing efficacy while minimizing systemic toxicity. This review explores the role of ADCs in the management of urothelial carcinoma, elucidating their mechanisms of action, clinical efficacy, and future directions in precision oncology.

Keywords: Urothelial Carcinoma; Antibody-Drug Conjugates; Targeted Therapy; Chemotherapy; Monoclonal Antibodies

Introduction

Urothelial carcinoma, encompassing tumours arising from the bladder, ureters, and renal pelvis, ranks among the most prevalent malignancies worldwide. Despite advances in treatment modalities, the prognosis for patients with advanced or metastatic disease remains poor, necessitating the exploration of novel therapeutic strategies [1]. In recent years, the emergence of targeted therapies has offered a promising avenue for improved outcomes in UC. Among these, Antibody-Drug Conjugates (ADCs) have garnered considerable attention for their ability to deliver potent cytotoxic payloads selectively to cancer cells while sparing healthy tissues [2]. By harnessing the specificity of monoclonal antibodies and the cytotoxicity of chemotherapeutic agents, ADCs represent a paradigm shift in precision oncology. This review presents a comprehensive examination of mechanisms of action, clinical applications, and ongoing advancements of ADCs in the management of UC.

Antibody-Drug Conjugates

Antibody-Drug Conjugates (ADCs) represent a novel therapeutic approach in cancer treatment, coupling monoclonal antibodies (mAbs) with small molecule anticancer agents. This innovative strategy targets specific antigens selectively expressed on tumor surfaces, facilitating the localized and targeted delivery of cytotoxic payloads to tumor cells [3]. ADCs typically comprise three components: a target-specific antibody, a connecting linker, and a cytotoxic payload, with variations in these components depending on the specific ADC.

The cornerstone of ADC structure is characterized by immunoglobulin G (IgG), particularly IgG1, due to its ability to stimulate immune effector function and high serum stability. Ideal mAb selection emphasizes the identification of highly expressed antigens on malignant cells, limited antigen immunogenicity, and strong binding affinity toward the target antigen. The linker plays a crucial role in ADC stability and drug delivery [4]. Cleavable linkers, which break down in the tumor microenvironment, and non-cleavable linkers, which degrade the entire antibody-linker construct to release the payload, are two major subclasses.

The cytotoxic payloads of ADCs are heavily toxic molecules that require carrier antibodies for targeted delivery. These payloads encompass agents that destabilize microtubules, generate DNA damage, and act as protein toxins. Microtubule destabilizers, DNA-damaging agents, and protein toxins exhibit distinct mechanisms of action, targeting various cellular processes to induce apoptosis and inhibit tumor growth.

Clinical Efficacy

Metastatic Setting

Enfortumab Vedotin

Enfortumab vedotin is an Antibody-Drug Conjugate (ADC) engineered to specifically target nectin-4, linked to monomethyl auristatin E (MMAE) via a protease-cleavable linker. Nectin-4, encoded by the NECTIN4 gene, is a transmembrane polypeptide frequently associated with poor prognosis in metastatic urothelial carcinoma (UC) [5]. While nectin-4 is predominantly found in placental and embryonic tissues, its expression diminishes in adult life. However, elevated levels are observed in various cancers, including bladder, breast, lung, and ovarian cancer. Studies indicate that nectin-4 plays a crucial role in promoting metastasis through signaling pathways such as WNT beta-catenin and PI3K-AKT-mTOR, and interaction with the ERBB2 receptor.

Enfortumab Vedotin (EV) was initially evaluated in patients with metastatic UC who had previously received chemotherapy. The phase I study, EV101, demonstrated promising results, leading to the initiation of a phase II study testing a dose of 1.25 mg/kg administered on days 1, 8, and 15 of a 28-day cycle. Among the 155 patients enrolled in the EV-101 study, those who received the recommended dose exhibited an overall response rate (ORR) of 43%, with a median Progression-Free Survival (PFS) of 5.4 months and median Overall Survival (OS) of 12.3 months [6]. The most common Adverse Events (AEs) included fatigue, alopecia, loss of appetite, dysgeusia, and peripheral neuropathy. Grade 3 and 4 toxicities were infrequent.

In the subsequent phase II trial (EV-201), EV was investigated in patients previously treated with immunotherapy. Cohort 1 included platinum-treated patients, while cohort 2 enrolled platinum-ineligible patients. The ORR in cohort 1 was 44%, with a median duration of response (mDOR) of 7.6 months, and median PFS and OS of 5.8 and 11.7 months, respectively. Notably, responses were observed across all subgroups, including patients unresponsive to immunotherapy [7].

The EV-301 study, a phase III trial, compared EV to investigator-choice chemotherapy in patients progressing after platinum and immunotherapy. EV demonstrated superior median OS (12.9 vs. 9.0 months) and PFS (5.5 vs. 3.7 months), leading to FDA and EMA approvals for previously treated patients [8].

The EV-302/KEYNOTE-A39 trial compared enfortumab vedotin plus pembrolizumab (EV+P) with chemotherapy in first-line treatment for locally advanced metastatic urothelial carcinoma (la/mUC). EV+P significantly extended Progression-Free Survival (PFS) by 55% and overall survival (OS) by 53%, with a median PFS of 12.5 months and a median OS of 31.5 months compared to 6.3 months and 16.1 months, respectively, with chemotherapy [9]. Additionally, EV+P achieved a higher Overall Response Rate (ORR) of 67.7% compared to 44.4% with chemotherapy, indicating its superior efficacy in la/mUC treatment.

Despite its efficacy, EV has been associated with several adverse reactions, including severe skin reactions, pneumonia, hyperglycemia, pneumonitis, neuropathy, ocular disorders, infusion-site reactions, and embryofetal toxicity.

Sacituzumab Govitecan

Sacituzumab Govitecan (SG) is another ADC designed to target Trop-2, a glycoprotein overexpressed in various epithelial tumors, including UC. SG consists of a monoclonal antibody against Trop-2 linked to SN-38, an irinotecan metabolite, via a hydrolysable linker. Initial trials demonstrated acceptable toxicity profiles and promising efficacy in metastatic UC patients who progressed after prior therapies.

In phase I/II studies, SG showed an ORR of 31%, with a clinical benefit rate of 47%, and a median duration of response (DOR) of 12.6 months. Median PFS and OS were 7.3 and 18.9 months, respectively. Notable adverse events included neutropenia, anemia, hypophosphatemia, diarrhea, fatigue, and febrile neutropenia. Preliminary data from the TROPHY-U-01 trial supported accelerated approval of SG in this patient population [10].

Sirtratumab Vedotin (ASG15-ME)

Sirtratumab vedotin (SV) is an ADC targeting SLITRK6, a transmembrane protein overexpressed in various tumors, including UC. SV consists of a human gamma 2 antibody conjugated to MMAE via a protease-cleavable linker. Initial trials demonstrated an ORR of 33% in metastatic UC patients, with a median DOR of 15 weeks and median PFS of 16 weeks. Fatigue and reversible ocular toxicities were the most common adverse events. However, there are currently no ongoing trials evaluating SV efficacy in metastatic UC [11].

Targeting HER-2 in Bladder Cancer

HER-2, a member of the EGFR family, is overexpressed in a subset of UC tumors, particularly luminal variants. Several ADCs targeting HER-2 have been evaluated in metastatic UC:

Trastuzumab emtansine (TDM-1) and Trastuzumab deruxtecan (DS-8201a) showed promising results in breast cancer but failed to demonstrate significant activity in UC.

Disitamab vedotin (RC-48), a novel ADC targeting HER-2, demonstrated an ORR of 51% in HER-2+ metastatic UC patients previously treated with platinum-based chemotherapy [12].

Additionally, Peptide-Drug Conjugates (PDCs) represent a novel approach to target HER-2, with potential diagnostic and therapeutic implications. PDCs selectively deliver payloads via sequence-specific peptides, offering advantages such as reduced immunogenicity and biodegradability.

Activity of ADC in Localized Bladder Cancer

Oportuzumab Monatox (OM), a recombinant fusion protein targeting EpCAM, has shown promising results in patients with Non-Muscle-Invasive Bladder Cancer (NMIBC) refractory to intravesical Bacillus Calmette-Guérin (BCG) therapy. OM induces apoptosis by releasing exotoxin upon internalization after binding to EpCAM. Phase I and II trials demonstrated high complete response rates in BCG-refractory NMIBC patients, leading to ongoing investigations, including combination trials with durvalumab [13].

These ADCs represent promising therapeutic options for both metastatic and localized bladder cancer, offering targeted approaches with manageable toxicity profiles.

Drug Name	Target	Cytotoxic Payload	Study Trial Phase	Treatment	**Patient Population**	**Sample Size**	**ORR (%)**	**Median PFS (m) (95% CI)**	**Median OS (m) (95% CI)**	**Median DOR (m)**	**Adverse Events (G3–G4)**
Enfortumab Vedotin	Nectin-4	MMAE	EV-101 Phase I(6)	EV	Metastatic UC post-chemotherapy	155	43	5.4 (5.1–6.3)	12.3 (9.3–15.3)	7	34%
			EV-201 Phase II(7)	EV	Platinum-treated metastatic UC	125	44	5.8 (4.9–7.5)	11.7 (9.1-not reached)	8	54% (cohort 1), 55% (cohort 2)
			EV-301 Phase III(8)	EV vs. Chemotherapy	Progressed after platinum-containing chemo & ICI	608	40.6 vs. 17.9	5.5 vs. 3.7 (HR: 0.62; 0.51–0.75; p < 0.001)	12.8 vs. 8.9 (HR: 0.70; 0.56–0.89; p = 0.001)	5	51% vs. 48%
			EV-302 Phase III(9)	EV + Pembrolizumab vs. Chemotherapy	First-line la/Muc		First-line la/mUC	-	12.5 months (EV+P) 6.3 months (Chemo)	31.5 months (EV+P) 16.1 months (Chemo)	

Sacitu-zumab Govitecan	Trop-2	SN-38	Phase I/II	SG	Meta-static UC post-prior systemic therapy	45	29	6.8 (3.6–9.7)	16.8 (9.0–21.9)	13	59%
			TRO-PHY-U-01 Cohort 1(10)			113	27	5.4 (3.5–7.2)	10.9 (9.0–13.8)	7	Not evalu-able
Sirtra-tumab Ve-dotin(11)	SLI TRK-6	MMAE	Phase I	SV	Metastatic UC	51	33	4	4	N/A	50%
Disitamab Vedo-tin(12)	HER-2	MMAE	Phase II	DS-8201a	Metastatic UC	43	51.20%	6.9 (5.6–8.9)	13.9 (9.1–NE)	7	58%
(Note: ORR = Overall Response Rate, PFS = Progression-Free Survival, OS = Overall Survival, DOR = Duration of Response, G3–G4 = Grade 3–4)											

Table 1: Clinical Evidence of ADCs in Urothelial Carcinoma.

Several ADCs targeting various antigens have shown promising results in clinical trials for urothelial carcinoma. Enfortumab vedotin, an ADC targeting Nectin-4, demonstrated significant activity in patients with locally advanced or metastatic disease who had previously received platinum-based chemotherapy and immune checkpoint inhibitors. The FDA approval of enfortumab vedotin in 2019 marked a milestone in the treatment landscape for urothelial carcinoma, providing a new therapeutic option for patients with limited alternatives.

Future Directions

The success of enfortumab vedotin has sparked interest in further exploring ADCs as a therapeutic strategy for urothelial carcinoma. Ongoing clinical trials are evaluating novel ADCs targeting different antigens, including HER2, EGFR, and FGFR3, either as monotherapy or in combination with other agents. Additionally, efforts are underway to optimize the design of ADCs by enhancing antibody specificity, payload potency, and linker stability to maximize therapeutic efficacy and minimize resistance mechanisms.

Conclusion

Antibody-drug conjugates represent a promising addition to the armamentarium of targeted therapies for urothelial carcinoma, offering improved efficacy and tolerability compared to conventional chemotherapy. With ongoing research and clinical trials, the role of ADCs in the management of urothelial carcinoma is likely to expand, providing new hope for patients with this challenging disease.

Conflict of interests: None

Funding: None

References

1. Rouprêt M, Babjuk M, Compérat E, Zigeuner R, Sylvester RJ, Burger M, et al. (2018) European Association of Urology Guidelines on Upper Urinary Tract Urothelial Carcinoma: 2017 Update. Eur Urol 73: 111–22.
2. Iacovelli R, Cicala CM, Ciccarese C, Sacco E, Racioppi M, Bassi PF, et al. (2023) Management of metastatic urothelial carcinoma: Current approach, emerging agents, and future perspectives. Urol J 90: 3–10.
3. Fu Z, Li S, Han S, Shi C, Zhang Y (2022) Antibody drug conjugate: the "biological missile" for targeted cancer therapy. Signal Transduct Target Ther 7: 1–25.
4. Criscitiello C, Morganti S, Curigliano G (2021) Antibody–drug conjugates in solid tumors: a look into novel targets. J Hematol OncolJ Hematol Oncol 14: 20.
5. Halford Z, Anderson MK, Clark MD (2021) Enfortumab Vedotin-ejfv: A First-in-Class Anti–Nectin-4 Antibody-Drug Conjugate for the Management of Urothelial Carcinoma. Ann Pharmacother 55: 772–82.
6. Rosenberg J, Sridhar SS, Zhang J, Smith D, Ruether D, Flaig TW, et al. (2020) EV-101: A Phase I Study of Single-Agent Enfortumab

Vedotin in Patients With Nectin-4–Positive Solid Tumors, Including Metastatic Urothelial Carcinoma. J Clin Oncol 38: 1041–9.

7. Yu EY, Petrylak DP, O'Donnell PH, Lee JL, Heijden MS van der, Loriot Y, et al. (2021) Enfortumab vedotin after PD-1 or PD-L1 inhibitors in cisplatin-ineligible patients with advanced urothelial carcinoma (EV-201): a multicentre, single-arm, phase 2 trial. Lancet Oncol 22: 872–82.

8. Thomas P, Jonathan ER, Guru PS, Yohann L, Ignacio D, Jae-Lyun L, et al. (2021) Enfortumab Vedotin in Previously Treated Advanced Urothelial Carcinoma. N Engl J Med 384: 1125–35.

9. Powles TB, Valderrama BP, Gupta S, Bedke J, Kikuchi E, Hoffman-Censits J, et al. (2023) LBA6 EV-302/KEYNOTE-A39: Open-label, randomized phase III study of enfortumab vedotin in combination with pembrolizumab (EV+P) vs chemotherapy (Chemo) in previously untreated locally advanced metastatic urothelial carcinoma (la/mUC). Ann Oncol 34: S1340.

10. Loriot Y, Petrylak DP, Kalebasty AR, Fléchon A, Jain RK, Gupta S, et al. (2024) TROPHY-U-01, a phase II open-label study of sacituzumab govitecan in patients with metastatic urothelial carcinoma progressing after platinum-based chemotherapy and checkpoint inhibitors: updated safety and efficacy outcomes. Ann Oncol 35: 392–401.

11. Petrylak D, Heath E, Sonpavde G, George S, Morgans AK, Eigl BJ, et al. (2016) Interim analysis of a phase I dose escalation trial of the antibody drug conjugate (ADC) AGS15E (ASG-15ME) in patients (Pts) with metastatic urothelial cancer (mUC). Ann Oncol 27: vi269.

12. Karasseva NG, Glinsky VV, Chen NX, Komatireddy R, Quinn TP (2002) Identification and Characterization of Peptides That Bind Human ErbB-2 Selected from a Bacteriophage Display Library. J Protein Chem 21: 287–96.

13. Kowalski M, Entwistle J, Cizeau J, Niforos D, Loewen S, Chapman W, et al. (2010) A Phase I study of an intravesically administered immunotoxin targeting EpCAM for the treatment of nonmuscle-invasive bladder cancer in BCGrefractory and BCG-intolerant patients. Drug Des Devel Ther 4: 313–20.