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Review Article

Molecular targets in urinary bladder cancer

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ABSTRACT

Molecular classification of urothelial carcinoma of the bladder has revealed high mutation rates and a heterogenous variety of mutations. *FGFR3* mutations are commonly detected in the Luminal-papillary subtype. Molecular targeted therapy for urothelial carcinoma is now the standard of care after disease progression on platinum/immune checkpoint inhibitor therapy. Enfortumab vedotin is preferred as there is level 1 evidence available to support its use. Erdafitinib is the first approved gene-targeted therapy for patients with *FGFR3/2* alterations. Sacituzumab govitecan shows promise in early phase trials. Further results from phase 3 trials are eagerly anticipated.

Keywords: Targeted therapy, Immunotherapy, Urinary bladder, Precision medicine

INTRODUCTION

Cancer of the urinary bladder is the 10th most common cancer diagnosed worldwide with approximately 573,000 new cases and 213,000 deaths recorded in 2020. It is 4 times more common in men than women, with the highest incidence rates noted in the western hemisphere in Southern/Western Europe and North America. (GLOBOCAN 2020).[1] These patterns reflect the prevalence of tobacco smoking which is attributed to almost half of all bladder cancer cases diagnosed globally.[2]

The fourth edition of the 2016 WHO classification of bladder cancers identifies more than 40 different histological types of bladder cancers, with >90% identified as urothelial carcinomas.[3] This review focuses on the recent advances in molecular taxonomy and the role of molecularly targeted therapy in this histological subtype.

MOLECULAR CLASSIFICATION

A 2017 TCGA analysis of 412 muscle-invasive bladder cancers (MIBC) revealed that bladder cancers tend to have high mutation rates, similar to melanoma, and non-small cell lung cancers. These mutations are principally due to an endogenous mutagenic enzyme called APOBEC cytidine deaminase (apolipoprotein B mRNA editing catalytic polypeptide-like) which is also implicated in cervical, breast, head, neck, and lung cancers. Cancers with a high mutation burden showed an exceptional 75% 5-year survival probability whereas the "neuronal" subtype which behaves clinically like neuroendocrine tumors showed the poorest survival.[4] A more recent 2020 consensus molecular classification has identified six molecular classes of MIBC. These have possible therapeutic implications, with *FGFR3* mutations identified in a significant subset of

Luminal papillary tumors and immune checkpoint markers in the basal-squamous subtype[5] [Table 1].

These molecular classifications have provided a framework for future prospective trials to establish how these classes can best be used clinically. As of now, there are very few established biomarkers and approved targeted therapies for advanced bladder cancers. Before delving into the clinical data supporting these molecular targets, a summary of current systemic therapy for advanced urothelial cancers is discussed.

Table 1: Molecular classification of muscle-invasive bladder carcinoma.

2017 TCGA classification (*n*=412)[4]	**2020 classification (*n*=1750)[5]**
1. Luminal-papillary (35%) - FGFR3-44% - Retained SHH signalling - Develops from precursor NMIBC	1. Luminal papillary (24%) - FGFR3-40% - CDKN2A deletion- 33% - Chr. 9 deletion
2. Luminal-infiltrated (19%) - Wild type p53 signature - Chemo-resistant - Lymphocytic infiltrates, increased PD-1/PD-L1 expression	2. Luminal non-specified (8%) - PPARG- 76% - ELF3-35%
3. Luminal (6%) - The highest expression of Uroplakin genes - Umbrella cell phenotype	3. Luminal unstable (15%) - PPARG-89%, E2F3/SOX4-76% - ERBB2 amplification-39% - TP53 mutation-76% - Highest somatic mutation load
4. Basal-squamous (35%) - TP53 mutations - Strongest immune expression signature	4. Stroma-rich (15%)
5. Neuronal (5%) - TP53/RB1 mutations	5. Basal-squamous (35%) - TP53 mutation-58%, RB1-20% - 3p14.2 deletion-49% 6. NE-like (3%) - TP53/RB1 mutations-94%

CURRENT SYSTEMIC THERAPY FOR ADVANCED UROTHELIAL CANCERS

Cisplatin-based combination chemotherapy is the preferred initial therapy for advanced urothelial cancers. Gemcitabine-cisplatin is preferred over methotrexate-vinblastine-doxorubicin-cisplatin as it has similar efficacy and is less toxic. The prognosis of these patients is poor, as only 50% achieve any response to therapy and have a median survival of 14 months with a 5-year survival rate of only 13%.[6,7] Maintenance therapy with avelumab, an immune checkpoint inhibitor (ICPi), in patients who do not have progression after four to six cycles of chemotherapy in the randomized phase III JAVELIN Bladder 100 trial resulted in an improvement in median overall survival (OS) from 14.3 to 21.4 months (HR 0.69, $P = 0.001$) and represents a breakthrough in the first-line systemic therapy for advanced bladder cancers.[8]

The ICPi's pembrolizumab and atezolizumab are approved as first-line treatment options for patients who are ineligible for platinum-based chemotherapy based on single-arm Phase II trials.[9,10] Long-term data for pembrolizumab were presented at the 2021 ASCO meeting, where an objective response rate of 29% and a 3-year OS of 22% were reported.[11] Second-line immunotherapy is approved in those who have progressed after platinum-based chemotherapy; however, after the approval of maintenance avelumab in the first-line setting, their current role in the second-line setting remains limited. Moreover, only pembrolizumab has Phase III data to support its use in the second-line setting (2 year OS 26.9% vs. 14.3% with physician's choice of chemotherapy) whereas only Phase I/II data exist to support the use of nivolumab and avelumab in this setting.[12-15]

MOLECULAR TARGETED THERAPY

NECTIN-4 - Enfortumab vedotin (EV)

Nectin-4 is a type I transmembrane protein and belongs to a family of cell-adhesion molecules that have been identified as a potential target in epithelial cancers. Moderate to strong staining has been observed in more than 60% of bladder tumor specimens.[16] EV is a novel antibody-drug conjugate (ADC) comprising the human anti-nectin4 antibody linked to a microtubule inhibitor (monomethyl auristatin E). Based on encouraging data from Phase I and II trials (EV-101 and EV-201, respectively),[17,18] EV (1.25 mg/kg intravenously D1/D8/D15 every 28 days) was evaluated in the Phase III EV-301 study in patients who had progressed after platinum-based chemotherapy and a ICPi. Nectin-4 expression was not required for enrolment in the trial. The control arm consisted of the physician's choice of chemotherapy (either paclitaxel/docetaxel/vinflunine). The trial achieved its primary endpoint, with OS being significantly longer in the experimental arm (median OS 12.8 vs. 8.9 months, HR 0.70, $P = 0.001$). Overall response rate (ORR) was also better with EV (40.6% vs. 17.9%, $P < 0.001$). The unique side effects attributable to EV were skin rashes (Grade1-2-30% and Grade 3-14%) and peripheral sensory neuropathy (Grade 1-2-40% and Grade 3-3.7%).[19]

EV was approved on July 9, 2021, by the US Food and Drug Administration (FDA) in patients with locally advanced or metastatic urothelial cancers who have progressed on both platinum-based chemotherapy and ICPi therapy.[20]

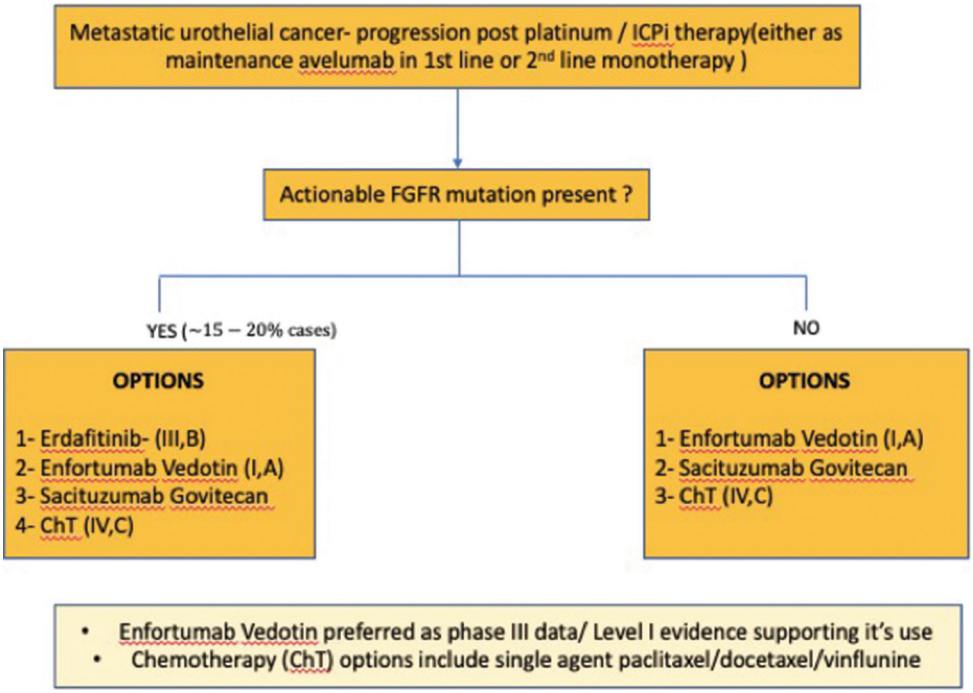

Figure 1: Treatment algorithm for targeted therapy in urothelial carcinoma.

Table 2: Select ongoing phase 3 trials of targeted therapies in urothelial carcinoma.

Trial ID	Standard arm	Experimental arm	Planned target (n)	Primary endpoint	Study completion date
NCT04527991 (TROPICS-04)	Physician's choice of chemotherapy*	Sacituzumab govitecan	600	OS	January 2024
NCT03390504	Arm 1B-** Arm 2B- Pembrolizumab	Arm 1A/2A- Erdafitinib	631	OS	April 2024
NCT04223856 (EV-302) 1st line setting	Gemcitabine+Cisplatin/ Carboplatin	Pembrolizumab+EV	860	PFS, OS	November 2023
NCT03924895 (Cisplatin ineligible -postoperative)	Surgery (Radical cystectomy +pelvic lymph node dissection)	Arm 1- Pembrolizumab+Surgery Arm 2- Pembrolizumab +EV+Surgery	863	pCR (pathological Complete response) EFS	May 2027

*Paclitaxel/Docetaxel/Vinflunine. **Docetaxel/Vinflunine. OS: Overall survival, EV: Enfortumab vedotin

FGFR3/FGFR2 - Erdafitinib

Erdafitinib is an oral pan-fibroblast growth factor receptor (FGFR) tyrosine kinase inhibitor. Erdafitinib was studied in advanced urothelial cancers in the single arm phase 2 BLC2001 trial. FGFR3 gene mutations (R248Cs, S249C, G370C, and Y373C) or FGFR2/3 gene fusions (FGFR3-TACC3, FGFR3 BAIAP2L1, FGFR2-BICC1, and FGFR2-CASP7) were required for study entry. FGFR alterations were tested by a RNA-based RT-PCR assay. Out of 2214 patients screened for the study, only 417 had a detectable FGFR alteration and ultimately 99 patients were enrolled to receive 8 mg/day of continuous oral erdafitinib. In the initial publication, an ORR of 40% and a median progression-free survival (PFS) of 5.5 months was noted in this heavily pre-treated population. ≥Grade 3 toxicities noted were hyponatremia (11%), stomatitis (14%), and asthenia (8%). Hyperphosphatemia, a known class effect of FGFR inhibitors, was noted in 78% of patients. About 3% of patients discontinued treatment due to central serous retinopathy.[21]

Based on these results, the US FDA granted accelerated approval to erdafitinib on April 12, 2019, for patients with locally advanced or metastatic urothelial cancers with

FGFR3/2 alterations who had progressed on platinum-based chemotherapy. The FDA has also approved a companion diagnostic RT-PCR assay to detect FGFR alterations (*therascreen* FGFR kit, QIAGEN N.V). This marked the 1st time that a gene-targeted therapy was approved for bladder cancer [Figure 1].[22] Long-term follow-up data of the BLC2001 trial were recently published which confirmed the initial findings and did not report any new safety signals.[23]

Trophoblast cell surface antigen 2 (Trop-2) - Sacituzumab govitecan (SG)

Trop-2 is a transmembrane glycoprotein that acts on cell proliferation, adhesion, and migration by acting on many intracellular signaling pathways.[24] Elevated Trop-2 expression correlates with aggressiveness and poor prognosis in many epithelial cancers including metastatic urothelial cancers.[25] SG is a Trop-2 directed ADC comprising the anti-Trop-2 humanized monoclonal antibody linked to SN-38 (an active metabolite of irinotecan, a Type 1 Topoisomerase inhibitor). SG was dosed at 10 mg/kg intravenously Day 1 and 8 every 21 days in the single-arm Phase II TROPHY-U-01 study (n = 113). After a median of 6 cycles of SG, an ORR of 27.4% was achieved with a median PFS of 5.4 months. Neutropenia was among the most common adverse reactions leading to dose interruption (≥Grade 3–35%). Other significant side effects were anemia (≥Grade 3–14%), and diarrhea (≥Grade 3–10%). Patients with homozygous *UGT1A1 *28/*28* genotype are more prone to neutropenia and should be monitored more closely.[26]

Based on these results, the US FDA granted accelerated approval to SG on April 13, 2021. However, this approval remains contingent on further randomized data confirming the survival benefit and toxicity profile of this agent [Table 2].[27]

CONCLUSION

Platinum-based chemotherapy is still the backbone of systemic therapy for advanced urothelial carcinomas. Immune checkpoint inhibition has also become a standard of care in these cancers, both as maintenance in 1st line therapy and as monotherapy in 2nd line setting. However, durable responses are obtained in a minority of patients and the overall prognosis remains poor. Molecularly targeted therapy has become the standard of care after the progression of immune checkpoint inhibition. Investigational agents in early phase clinical trials include anti-HER2 ADCs, EZH2 inhibitors, and adoptive cell therapy.

The explosion of knowledge generated by advances in genotyping and transcriptional profiling has now set the stage for a future clinical trial design that should use carefully selected biomarkers and identify the best targets for pharmacological inhibition as well as inform prognosis.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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