Review

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Emerging Novel Therapies toTreat Urothelial Carcinoma

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Simple Summary: Urothelial cell carcinoma (UCC) is the ninth most common cancer worldwide and in the US the fourth most common cancer with ~82,000 new cases (62,000 men) diagnosed annually leading to ~ 17000 deaths/year (~12,000 men). While early-stage cases exhibit more favorable outcomes, the emergence of drug resistance and distant metastasis reduces median overall survival (OS) to 12-15 months. The development of modern genetic and molecular assays to detect high risk mutations have improved the detection of high-risk disease. Recently, immune therapies have been developed and demonstrate markedly improve OS rates compared to treatment with chemotherapy alone. However, challenges persist and there remains an urgent, unmet need to develop and advance novel molecular and therapeutic strategies that prevent or overcome drug resistance and improve patient outcome. Here, we provide a comprehensive overview of the etiology, diagnostic approach and emerging therapeutic strategies to improve UCC patient quality of life and OS.

Abstract: Urothelial cell carcinoma (UCC, bladder cancer) remains a difficult to treat malignancy with rising incidence worldwide. In the U.S., UCC is the sixth most incident neoplasm and ~90% of diagnoses are made in those >55 years of age, ~four times more commonly observed in men than women. The most important risk factor for developing bladder cancer is tobacco smoking, which accounts for ~50% of cases followed by occupational exposure to aromatic amines and ionizing radiation. The standard of care for advanced UCC includes platinum-based chemotherapy and programmed cell death (PD-1) or programmed cell death ligand 1 (PD-L1) inhibitors, administered as frontline, second-line, or maintenance therapy. UCC is highly aggressive and remains generally incurable since these cancers are associated with intrinsic and acquired drug resistance. UCC is highly lethal in the metastatic state and characterized by genomic instability, high PD-L1 expression, DNA damage-response mutations, and high tumor mutational burden. Although immune checkpoint inhibitors (ICIs) achieve long-term durable responses in other cancers, their ability to achieve similar results with metastatic UCC (mUCC) is not as well-defined. Here, we discuss the novel therapies to improve the management of mUCC.

Keywords: urothelial cell cancer; metastasis; drug resistance; immunotherapy; immune checkpoint inhibitors; tumorigenesis; antibody–drug conjugate

1. Introduction

1.1. Overview

Urothelial cell carcinoma (UCC, formerly known as transitional cell carcinoma,) is the most common neoplasm of the urinary system. UCC is the most common histologic type of bladder cancer and accounts for ~90% of all bladder cancers [1]. A number of histologic variants of UCC have been

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identifed including micropapillary, microcystic, nested, lymphoepithelioma-like, plasmacytoid, sarcomatoid, giant cell, poorly differentiated, lipid rich, clear cell and urothelial carcinoma with divergent differentiation. UCC is defined as the invasion of the cancer cells basement membrane or *lamina propria* or deeper by neoplastic cells of urothelial origin. Invasion is defined as 'micro invasion' when the depth of invasion is 2 mm or less [2]. The World Health Organization (WHO) classifies bladder cancers based on differentiation as low grade (grade 1 and 2) or high grade (grade 3) [1]. The distinction between low-grade and high-grade urothelial disease has implications related to risk stratification and patient's management and treatment outcome.

Urothelial tumors arise and evolve through divergent genetic and phenotypic pathways [3]. Some tumors progress from urothelial hyperplasia to low-grade, non-invasive superficial papillary tumours. More aggressive variants arise from flat, high-grade carcinoma *in situ* and progress to invasive tumors or arise *de novo* as invasive tumors [4]. These two distinct phenotypic variants of urothelial tumors exhibit drastically different biological behavior, response to treatment and prognosis for patients. The low-grade papillary variant is often multifocal and tends to recur, and infrequently progresses to the muscle invasive stage. In contrast, most of invasive variants develop into incurable metastases despite radical cystectomy (RC) and different modalities. It is evident that the UCC variants harbor distinctive genetic defects that impact growth control and metastatic potential Table 1, ref. [5]. Low-grade, non-invasive papillary tumors are frequently characterized by activating mutations in *HRAS* and *fibroblast growth factor receptor 3 gene* (FGFR3) [6]. High-grade invasive tumours are characterized by structural and functional defects in the *p53* and retinoblastoma protein *(Rb)* tumor-suppressor pathways [7].

Table 1. Frequency of selected gene alterations associated with MIBC tumors.

Gene	Cytogenic location	Alteration	Frequency of alteration
Chromosome			
	9p	Deletion	21–30 %
	9q	Deletion	17 %
Oncogenes			
HRAS	11p15	Activating mutation	10–15 %
FGFR3	4p16	Activating mutation	~50 % overexpression 15 % Mutation
PIK3CA	3q26	Activating mutation	25 %
MDM2	12q13	Overexpression	4 % overexpression
Tumor suppressor genes			
TP53	17p13	Deletion or mutation	70 %
RB1	13q14	Deletion or mutation	37 %
PTEN	10q23	Homozygous deletion or mutation	LOH 30–35 % Mutation 17 %
CDKN2A	9p21	Homozygous deletion or methylation or mutation	HD 20–30 % LOH ~60 %
PTCH	9q22	Deletion or mutation	LOH ~60 % Mutations are rare
DBC1	9q32-33	Deletion or methylation	LOH ~60 %
TSC1	9q34	Deletion or mutation	LOH ~60 % Mutation ~15 %

Table 2. Clinical trials that evaluated the efficacy of novel therapies to treat UCC/ mUCC.

Trial	Patient Characteristics	Regimen	Primary, Secondary End points	Most Common Adverse Events	Results
BLC2001 Phase 2 study in mUCC patients	99 patients with FGFR alteration who had progressed on chemotherapy or immunotherapy	Erdafitinib 8 mg in either an intermittent or continuous regimen.	Primary end point was ORR. Secondary end points were PFS, OS and duration of response.	Hyperphosphatemia, stomatitis and diarrhea.	ORR was 40%.

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KEYNOTE-045 Phase 3 trial in mUCC	542 patients who recurred or progressed after platinum-based chemotherapy	Pembrolizumab at 200 mg every 3 weeks or the investigator's choice of chemotherapy with paclitaxel, docetaxel, or vinflunine	Co-primary endpoints were OS and PFS, among all patients and among patients who had a PD-L1 CPS of 10% or more.	Pruritus, fatigue, and nausea	OS was 8 vs. 5.2 mos. PFS did not demonstrate a significant difference.
JAVELIN Bladder-100 Phase 3 trial in unresectable locally advanced and mUCC	700 patients who completed 1st line chemotherapy without progression.	Maintenance avelumab 10 mg/kg IV q2 weekly vs. best supportive care	Primary end point was OS. Secondary end points included PFS and safety.	Fatigue, pruritus and urinary tract infections.	OS at 1 year was 71.3 compared to 58.4%. Median PFS was 3.7 vs 2.0 mos.
***CheckMate-274* Phase 3 trial with MIBC.**	709 in patients with MIBC who had undergone radical cystectomy. Neoadjuvant cisplatin-based chemotherapy before trial entry was allowed.	Adjuvant nivolumab 240 mg IV or placebo q2 weeks for up to 1 year vs. placebo.	Primary endpoint was DFS. Secondary end point was survival free from recurrence outside the urothelial tract.	Pruritus, fatigue, and diarrhea	DFS was 20.8 mos with nivolumab and 10.8 mos with placebo. Patients who were free from recurrence outside the urothelial tract at 6 mos was 77 vs 63%.
***EV-301* Phase 3 trial in locally advanced or mUCC**	608 patients who had previously received platinum-containing CHT and had disease progression during or after treatment with a PD-1 or PD-L1 inhibitor	enfortumab vedotin 1.25 mg/kg on days 1,8,15 of a 28-day cycle or investigator-choice CHT on day 1 of a 21-day cycle.	Primary endpoint was OS.	Alopecia, peripheral sensory neuropathy, pruritus.	Median OS was 12.8 vs. 8.9 mos.
TROPHY-U-01 Phase II in mUCC	113 patients who previously received platinum-containing CHT and had disease progression during or after treatment with a PD-1 or PD-L1 inhibitor.	Sacituzumab govitecan 10 mg/kg on days 1 and 8 of 21-day cycles	The primary outcome was centrally reviewed ORR; secondary outcomes were PFS, OS, duration of response, and safety.	Key grade ≥ 3 treatment-related adverse events included neutropenia (35%), leukopenia (18%), anemia (14%), diarrhea (10%), and febrile neutropenia (10%), with 6% discontinuing treatment because of treatment-related adverse events.	At median follow-up of 9.1 mos, ORR was 27% (31 of 113; 19.5 to 36.6); 77% had measurable disease reduction. Median duration of response was 7.2 mos (4.7 to 8.6 months), with median PFS and OS of 5.4 mos (3.5 to 7.2 mos) and 10.9 mos (9.0 to 13.8 mos).

1.2. Environmental and Hereditary Risk factors for Urothelial Cancers

The risk factors for UCC are largely environmental, with smoking by far the most important. Smoking is a major risk factor for bladder cancer and is estimated to account for ~50% of cases in both men and women. Current smokers are 4-5 times more likely to develop bladder cancer than non-smokers [8]. Other environmental risk factors include occupational exposures, radiation, contaminants in drinking water, and chronic bladder infections [9]. These factors all contribute to an increased risk of developing bladder cancer, highlighting the importance of preventative measures, e.g., smoking cessation and minimizing exposure to harmful substances.

The consequences of these risk factors and ex[posures leads to field changes within the urothelial tract that predispose individuals to the development of recurrent tumors, occurring in new locations in the urothelial tract. This phenomenon is referred to as polychronotropism [10]. In addition to environmental factors, genetics have also been implicated in an individual's susceptibility to

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urothelial bladder cancer. Studies have found that individuals with a family history of UCC have a higher relative risk of developing the disease. However, this increased risk cannot be entirely attributed to shared environmental exposures, indicating that genetic factors may play a role in the development of bladder cancer [11]. Hereditary non-polyposis colon cancer syndrome (HNPCC) is caused by mutations in DNA mismatch repair genes. HNPCC can be identified through microsatellite instability or the absence of the corresponding protein via immunostaining and is linked to a greater risk of developing bladder and upper urinary tract/urothelial cancers [12].

2. Divergent Mechanisms Underlying Urothelial Tumorigenesis

2.1. Invasive and non-invasive UCC

Noninvasive UCC are further subcategorized into exophytic papillary and carcinom*a in situ* (CIS) based upon distinct molecular alterations [13]. Exophytic papillary tumors, or Ta tumors, which are a type of noninvasive urothelial cancer, can have varying genetic mutations and are classified as either high or low grade. Low-grade Ta tumors are often associated with mutations involving receptor tyrosine kinase-*Ras* activation, specifically either *HRAS* or *FGFR3* mutations [14–16], while high-grade Ta tumors are typically linked with *p16INK4a* homozygous deletion and a lower frequency of *FGFR3* mutations [17]. In contrast, CIS and invasive tumors have alterations in *Tp53* and *Rb* [18]. Muscle-invasive tumors, on the other hand, are characterized by changes in vascular endothelial growth factors (VEGF), cadherins, and matrix metalloproteinases (MMPs) [19]. Gene expression profiling (GEP) has identified novel UCC subtypes. The Bladder Cancer Molecular Taxonomy Group identified six distinct subtypes of muscle-invasive urothelial tumors which include: 1) luminal papillary, 2) luminal non-specified, 3) luminal unstable, 4) stroma-rich, 5) basal/squamous, and 6) neuroendocrine-like. Each subtype is associated with unique biologic, histologic and genetic characteristics. Hence, treatment strategies are guided by oncogenic mechanisms, immune and stromal cell infiltration, and histologic and clinical features [20,21].

2.2. Cell cycle alterations

UCC is characterized by alterations in specific molecular pathways that result in uncontrolled cellular proliferation. These genetic alterations may be pharmacologically targeted by therapeutic interventions [22–25]. The most well-characterized pathways in UCC are those regulating the cell cycle, particularly the *p53* and *RB* mechanisms, which interact with mediators of apoptosis and gene regulation [26]. *TP53* is encoded on chromosome 17p13.1 and inhibits cell-cycle progression by transcriptionally activating *p21WAF1/CIP1* [27]. *TP53* mutations result in p53 inactivation and the rate of *p53* alterations in primary tumors increases progressively from normal urothelium to non-muscle-invasive tumors to muscle-invasive disease and metastatic nodes [28]. *p53* as a prognostic marker is not clinically established, but it has been shown to predict recurrence and cancer-specific mortality in muscle-invasive disease [29].

p21 is a cyclin-dependent kinase (CDK) inhibitor that is transcriptionally regulated by p53 [30]. Loss of *p21* expression can predict disease progression, and its maintenance can abrogate the effects of altered *p53* [31–33]. Mdm2, which participates in an autoregulatory feedback loop with *p53*, is frequently amplified in bladder cancer [34]. *Rb* is a cell-cycle regulatory protein that interacts with CDKs and E2F, leading to transcription of genes required for DNA synthesis [35]. Inactivating *Rb* mutations have been confirmed in bladder tumors [36,37]. CDK inhibitors, e.g., p21, p16, and p27 negatively regulate CDKs, acting as tumor suppressors is a complex process that involves multiple pathways leading to programmed cell death. Low expression of caspase-3 has been associated with a worse prognosis [38,39], while survivin, which blocks caspase activity and inhibits apoptosis, is overexpressed in >60% of bladder cancers [40]. Bcl-2, an antiapoptotic member of the Bcl-2 family of proteins, is associated with poor prognosis in bladder cancer patients treated with radiotherapy or chemotherapy [41,42]. Conversely, Bax, a pro-apoptotic member of the Bcl-2 family [43], is a favorable prognosticator in invasive disease [44,45].

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2.3. Intricate relationship between cell signaling and gene regulation

Cell signalling and gene regulation are linked processes and when these processes are dysregulated it can result in abnormal cell growth and cancer. One of the main causes of this dysregulation is abnormalities in cell-surface receptors, which play a role in modulating external signals to the cell nucleus and controlling gene expression. For example, activating *FGFR3* mutations are common in low-grade papillary Ta tumors and bladder cancer, leading to activation of the Ras-mitogen-activated protein kinase *(MAPK*) pathway [46,47] Additionally, members of the *MAPK* pathway, e.g., *HRAS* and *MAP4K3*, have been associated with non-invasive cancer recurrence and high-risk bladder cancer, respectively [48].

Other factors that impact cell signalling and gene regulation in bladder cancer include the sex hormone receptors, Janus kinase family members, and meiotic recombination 11 *(MRE11*) . Reduced expression of the estrogen receptor-β (ER-) has been linked to better progression-free survival (PFS) rates in patients with non-invasive bladder cancer [49], while higher levels have been associated with more advanced tumors [50]. Androgen receptor (AR) expression has been inversely correlated with pathologic stage and grade [51,52]. Janus kinase family members, such as *STAT3,* can predict recurrence and survival in bladder cancer patients [53]. Finally, *MRE11* expression has been associated with both better and worse outcomes in different contexts, highlighting the complex interplay of factors involved in bladder cancer development and progression [54]

2.4. Immune dysregulation and cytokine signaling

Cancer can evade the immune system, allowing it to progress. Certain proteins such as IL-6, NF-B, CRP, and PD-L1 play a role in immune modulation and have been associated with more aggressive features of bladder cancer, advanced stage, and higher cancer-specific mortality [55,56]. PD-L1 is a checkpoint protein that can impede immune function, allowing tumor cells to grow and proliferate unregulated [57]. Tumor PD-L1 expression has been linked to advanced stage and grade, disease progression, and worse OS after cystectomy [58]. Checkpoint inhibitors have been approved to treat advanced or metastatic and Bacillus Calmette-Guerin (BCG) unresponsive bladder cancer.

2.5. Influence of angiogenesis on UCC invasion and metastasis

Angiogenesis is influenced by factors secreted from tumor cells that interact with endothelial cells in the stroma.VEGFs, urokinase-type plasminogen activator (uPA), and thrombospondin 1 (TSP-1) all play a role in angiogenesis and UCC progression. Elevated levels of VEGFs and uPA have been associated with poor clinical outcomes [59–61], while TSP-1 acts as an inhibitor of angiogenesis and under expression is linked to reduced OS [62]. Microvessel density, a measure of angiogenesis, also has prognostic value in bladder cancer [63]. The cadherins, particularly E-cadherin, play a significant role in epithelial cell-cell adhesion. Reduced expression of E-cadherin has been linked to tumor recurrence and disease progression, and poor OS in bladder cancer patients [64]. Several protease families, including matrix metalloproteinases (MMPs), can also modulate the tumor's ability to disrupt the extracellular matrix and invade neighboring tissue. Overexpression of *MMP-2* and *MMP-9* is associated with advanced-stage bladder cancer and worse OS [65]. Intercellular adhesion molecule 1 (ICAM1) is another mediator of cell adhesion that correlates with the grade, size, and nodal status of bladder tumors [66]. Lastly, carbohydrate antigen (CA) 19-9 and carcinoembryonic antigen (CEA), are involved in cell adhesion and have been reported to predict higher rates of bladder cancer recurrence and worse PFS after surgery [67].

3. Screening, Diagnostic Approach and Staging of Urothelial Carcinoma

In 2011, the United States Preventive Services Task Force (USPSTF) determined that there was not enough evidence to provide a recommendation for bladder cancer screening [68]. Hematuria is the most common symptom in patients with urothelial cancer. Irritative voiding symptoms, such as dysuria, may indicate carcinoma *in situ* (CIS) or a bladder tumor in patients with risk factors such as

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tobacco use. Patients are risk stratified and intermediate and high-risk patients are recommended to undergo cystoscopy [69]. The diagnosis is confirmed through cystoscopy and biopsy.

Staging of UCC presents a major challenge as the depth of invasion determined by cystoscopy and Transurethral Resection of Bladder Tumor (TURBT) only correlates with cystectomy results in ~50-60% of cases. Although a TURBT specimen can confirm the presence of muscle invasive (T2) disease, it cannot provide information on more advanced invasion due to the risk of bladder perforation. TURBT specimen should contain *muscularis propria*, but if absent, a repeated TURBT is often recommended. CT or non-invasive MRI can detect extravesical or nodal disease and is more reliable if performed with a distended bladder before transurethral resection. FDG-PET/CT imaging may aid in the staging of muscle-invasive disease and detecting metastatic bladder cancer [70]. However, its usefulness in local staging is limited by the urinary excretion of FDG [71]. For non-muscle-invasive tumors, the histologic grading system of low grade and high grade is more relevant since almost all muscle-invasive neoplasms are high grade. Although there is increasing interest in utilizing molecular detection of circulating tumor cell (CTCs) in patients with UCC ,the reported diagnostic effectiveness of these methods has been inconsistent. CTC detection assays for urothelial cancers have a low diagnostic sensitivity, as they are unable to identify around two-thirds of patients. However, CTC detection displays a high specificity for the diagnosis of urothelial cancers. Therefore, it may not be useful as the initial screening or diagnostic testing, but may be valuable in diagnositc confirmation. The timing of disease assessment is a crucial consideration in CTC detection since surgical interventions may result in a temporary dissemination of CTCs in the bloodstream, while chemotherapy and other systemic treatments may destroy CTCs or reduce the expression of markers, leading to a conversion of CTC-positive patients to CTC-negative [72]. Nonetheless, additional studies are needed to standardize techniques and determine the best marker combinations for detecting CTCs in UCC and bladder cancer patients.

4. Standard of care therapy for UCC

4.1. Initial treatment

The iitial treatment and prognosis of UCC patients depends on several key factors including the anatomical site, extent (stage), and histological grade of the disease. Non-muscle-invasive bladder UCC (NMIBC), with the exception of carcinoma *in situ* (CIS), can be treated by transurethral resection leading to excellent survival outcomes. One successful way of treating NMIBCs is using BCG vaccine intravesical immunotherapy, which decreased the risk of recurrence and progression of NMIBCs [73] Intrauterine injection of BCG causes extensive inflammation in the bladder wall which targets tumor cells, but BCG intravesical immunotherapy may have short-term immune-stimulating effects [74]. Muscle-invasive bladder UCC (MIBC) and upper urinary tract UC (UTUC) often require RC and/or nephroureterectomy (RNU) [75]. Systemic chemotherapy, that consists of a cisplatin-based regimen for mUCC, generally does not achieve durable responses. Therefore, treatment outcome of the patients with mUCC has been exceedingly poor with an OS rate of ~15%. Cisplatin-based neoadjuvant chemotherapy (NAC) is the standard treatment for MIBC, with benefits including downstaging and elimination of micro-metastatic disease before RC [76,77]. However, patient eligibility for cisplatin-based NAC is limited by a range of factors, e.g., ECOG, creatinine clearance with hearing loss, neuropathy, and heart failure [78,79]. Tri-modality treatment therapy (TMT) involving TURBT, radiation therapy, and concurrent chemotherapy, is a commonly used alternative. In clinical trials, TMT has demonstrated 5-year OS rates comparable to NAC with RC which yields rates of 48-65% [80]. MIBC is associated with a higher incidence of distant metastasis compared with NMIBC.

4.2. Bladder preservation in UCC

Bladder preservation therapies, e.g., partial cystectomy TMT, are worth considering for MIBC patients unfit for RC, ineligible for chemotherapy, or hesitant to undergo the procedure due to concerns over complications and urinary diversion [81]. TMT has demonstrated safety and efficacy

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in multiple studies [82–84]. Recent studies have shown that TMT may have better cancer-specific survival and OS than RC [85,86]

Studies are ongoing to explore bladder preservation options for non-muscle-invasive disease (pT2 or lower) and in patients that achieve a complete response (CR) to NAC. Tumor genomic profiling technology may help to identify biomarkers that can predict response to NAC and provide treatment guidelines[87,88]. Clinical trials, e.g., RETAIN, are exploring active surveillance and non-surgical local therapy options for MIBC patients with specific genetic alterations and <cT1 disease on restaging TURBT [89,90].

5. Emerging strategies to improve the treatment of UCC

5.1. Surgical

Management of UCC relies heavily on surgical intervention, particularly for early-stage disease. TURBT is the most frequently employed surgical technique for NMIBC and for patients eligible for bladder preservation therapy [91]. In more advanced cases, RC may be required [92]. Recent advances in surgical methods have given rise to minimally-invasive approaches, e.g., robotic-assisted surgery [93,94]. Moreover, ongoing research efforts aim to develop novel surgical modalities, such as photodynamic therapy, which employs light to activate a photosensitizing agent and selectively destroy malignant cells while sparing healthy tissue [95].

5.2. Single agent and combination chemotherapy

Patients with mUCC can benefit from a variety of chemotherapy combinations, e.g., MVAC and gemcitabine plus cisplatin [96,97]. In certain cases where combination chemotherapy is not suitable or prior treatment has failed, single agent chemotherapy options, e.g., platinum compounds (cisplatin, carboplatin), gemcitabine, vinca alkaloids (vinblastine, vinflunine), anthracyclines (doxorubicin, epirubicin), methotrexate, taxanes (paclitaxel, docetaxel, and nanoparticle albumin-bound paclitaxel - nabpaclitaxel), and ifosfamide may be used [98,99]. However, the response to single-agent chemotherapy is typically brief, and there is no consistent evidence showing improvement in survival with first-line therapy.

5.3. Targeting FGFR

Erdafitinib is a potent FGFR1-4 tyrosine kinase inhibitor. *FGFRs* are essential in regulating cell proliferation, migration, differentiation, and survival [100]. As many as 20% of patients with advanced UCC have *FGFR* alterations, and such mutations are even more frequent (37%) in patients with upper tract urothelial carcinoma. Thus, FGFR inhibition may be particularly appropriate in patients with luminal I subtype disease, in which immunotherapeutic approaches may be less effective[101]. Among patients with locally advanced and unresectable or mUCC with specific FGFR alterations, erdafitinib has demonstrated a noteworthy antitumor activity. In a open-label, phase 2 study, 99 patients with locally advanced or mUCC and *FGFR* alterations who had disease progression after previous chemotherapy were enrolled. Patients were randomly assigned to receive erdafitinib in either an intermittent or a continuous regimen receiving a median of 5 cycles. The confirmed response rate was 40%, with a median duration of PFS of 5.5 months and OS of 13.8 months. Responses were prompt and not influenced by the number or type of prior treatments, the location of the tumor, or the presence of visceral metastasis Treatment-related adverse events of grade 3 or higher were reported in 46% of patients, with 13% discontinuing treatment due to adverse events. Common side effects included diarrhea, nausea, vomiting, fatigue, and skin rash. Treatment was also associated with more serious adverse events, e.g., hyperphosphatemia and detachment of retinal pigment epithelium.

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5.4. Immune checkpoint inhibitors

Immunotherapy and targeted treatments to address situations where BCG is unsuccessful and for cancers who have progressed following cisplatin-based therapies [102]. High tumor mutational burden, DNA damage-response mutations, the presence of genomic instability and high expression of PD-L1 protein makes UCC suitable for immunotherapy. The treatment landscape for patients with advanced UCC has been significantly changed with the approval of ICIs, e.g., atezolizumab, pembrolizumab, avelumab, and durvalumab. These approvals have opened new treatment options for patients with disease progression after platinum-based chemotherapy, those who are not eligible for first-line cisplatin-based therapy and have PD-L1-positive tumors, and those who are not suitable candidates for platinum-based therapy [103,104]. In 2017, pembrolizumab, a humanized monoclonal antibody targeting PD-1, was approved for patients with advanced UCC who had progressed after cisplatin-based therapy. A phase 3 randomized, controlled trial that included 542 patients with advanced UCC randomly assigned to receive pembrolizumab or investigator's choice of chemotherapy. The co-primary end points were OS and PFS. Results showed that pembrolizumab improved OS compared to chemotherapy, with a median OS of 10.3 months in the pembrolizumab group vs. 7.4 months in the chemotherapy group. The study also found fewer treatment-related adverse events of any grade in the pembrolizumab group than the chemotherapy group [105]. Interestingly, patients benefited from pembrolizumab regardless of PD-L1 expression, which was measured as the combined positive score (CPS), defined as the proportion of PD-L1-expressing tumor and infiltrating immune cells relative to the total number of tumor cells. PD-L1 positivity was defined as having a CPS $\geq$10%.

Avelumab, another ICI, received approval in 2020 as maintenance therapy for patients with locally advanced or mUCC who did not progress after first-line platinum-based chemotherapy. The results of a phase 3 trial showed that the addition of maintenance avelumab, an anti-programmed death-ligand 1 (PD-L1) monoclonal antibody, to best supportive care prolonged OS in patients with unresectable locally advanced or mUCC who did not have disease progression with first-line chemotherapy. The study enrolled 700 patients, and OS at 1 year was significantly better in the avelumab group compared to the control group. Avelumab also significantly prolonged OS and PFS in the PD-L1-positive population. The incidence of adverse events was higher in the avelumab group but generally manageable[106].Following the demonstration of its efficacy, avelumab has since been incorporated as a treatment option for patients with advanced urothelial carcinoma.

After the success of ICIs in treating mUCC, they have been introduced as adjuvant therapy. In June 2021, the FDA approved nivolumab for patients who have undergone complete resection and have high-risk UCC, defined as residual cancer of ≥pT2 or pN+ after receiving neoadjuvant cisplatin-based chemotherapy or ≥pT3 or pN+ without prior chemotherapy. A phase 3, multicenter, double-blind, randomized, controlled trial that compared the efficacy of nivolumab vs. placebo in 709 patients with muscle-invasive UCC who had undergone radical surgery. The study showed that nivolumab significantly improved disease-free survival and survival free from recurrence outside the urothelial tract, particularly in patients with a tumor PDL-1 expression level of $\geq$1% [107]. Atezolizumab, previously used in the treatment of mUCC [108], has been discontinued recently based on phase III trial which demonstrated that although the addition of atezolizumab to platinum-based chemotherapy resulted in improved PFS, but did not lead to any OS advantages. Consequently, the FDA revoked its regulatory approval and it is no longer used.

5.5. Antibody-drug conjugates

To date, two antobody-drug conjugates (ADCs) have been approved for the treatment of bladder cancer: Enfortumab vedotin was evaluated in a global, open-label, phase 3 trial. The study enrolled 608 patients who had previously received platinum-containing chemotherapy and PD-1/PD-L1 inhibitors. Patients were randomly assigned to receive either enfortumab vedotin or chemotherapy. The results showed that OS was longer in the enfortumab vedotin group than in the chemotherapy group, with a median OS of 12.9 vs. 9.0 months, respectively. Additionally, PFS was longer in the enfortumab vedotin group, with a median PFS of 5.6 months compared to 3.7 months in the

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chemotherapy group. The incidence of treatment-related adverse events was similar in both groups. Subsequently it was approved by the FDA in December 2019 [109] enfortumab vedotin targets Nectin-4, which is overexpressed in numerous bladder cancers and is linked to a microtubule inhibitor conjugate known as monomethyl auristatin E. Although skin reactions, peripheral neuropathy, and hyperglycemia are common side effects, they are mostly mild to moderate in severity [110,111]. Sacituzumab govitecan is a new type of ADC that targets Trop-2 through an anti-Trop-2 humanized monoclonal antibody hRS7 IgG1κ combined with SN-38, which is the active metabolite of the topoisomerase 1 inhibitor irinotecan. It is recognized for its distinctive toxicity profile that may lead to diarrhea, nausea, vomiting, fatigue, neutropenia, and even severe or life-threatening infusion reactions [112]. The approval of enfortumab vedotin and sacituzumab govitecan was a significant milestone in the treatment of UCC.

5.6. Cellular vaccines and oncolytic viruses

Vaccine therapy activates the immune system to target cancer cells using various methods, such as synthetic peptides and viral vectors. PANVAC-VF is an example of vaccine therapy that has shown positive results in clinical trials[113], but further research is needed to optimize its dosing and effectiveness in combination with other treatments. Oncolytic viruses selectively replicate within tumor cells, resulting in their destruction and the release of additional oncolytic viruses and tumor antigens. CG0070 is an example of an oncolytic virus that specifically targets cells with RB gene mutations, which are common in UCC [114]. Despite showing promising results, the efficacy of vaccine therapy and oncolytic viruses in combination with other therapies needs further investigation [115].

5.7. CAR-T therapy

CAR-T therapy is an emerging immunotherapy approach that involves genetically modifying a patient's T-cells to target and attack cancer cells. In UCC, CAR-T therapy is being investigated as a potential treatment for patients with advanced or metastatic disease who have failed traditional therapies [116]. While still in early clinical trials, CAR-T therapy has shown improving responses in some patients with UCC. However, more research is needed to optimize the therapy and determine its long-term safety and efficacy [117].

5.8. Antiangiogenics

There is currently no established role for antiangiogenic agents in the treatment of advanced or metastatic bladder cancer. Ramucirumab and bevacizumab, both *VEGF* pathway inhibitors, have shown improved PFS but not OS in clinical trials [118,119]. Cabozantinib, a multi-kinase inhibitor including VEGF receptors, is an investigational agent for platinum-refractory mUCC as a single agent or in combination with ICIs, with promising objective response rates in clinical trials [120].

6. Conclusions

Despite advances in diagnostic and therapeutic strategies, mUCC remains a significant challenge in the field of medical oncology. Early diagnosis is crucial to improve patient outcomes and current treatments offer a range of options for managing UCC and mUCC. However, personalized treatment approaches based on individual patient characteristics and tumor characteristics hold promise to improve patient quality-of-life and OS whilereducing treatment-related toxicities. The treatment of mUCC has shifted dramatially following the introduction of ICIs (121–123). Importantly, the JAVELIN Bladder 100 trial convincingly demonstrated PFS and OS benefit upon the administration of avelumab for patients that achieve stable disease or response to chemotherapy. Current recommendations include the first-line use of pembrolizumab for platinum-ineligible patients. Avelumab is recommended as maintenance therapy for patients that did not progression with first-line chemotherapy (121–123).

7. Future Directions

Further exploration of prevention strategies, e.g., lifestyle modifications, smoking cessation, and chemoprevention, has the potential to reduce the incidence and improve the management and outcome of UCC. ICIs have recently been FDA-approved as first-line therapy for cisplatin-ineligible patients or as second-line therapy for mUCC patients. Collectively, recent trials indicate that ~30% of mUCC patients demonstrate a response to ICIs immunotherapy. Future studies that explore the utility of ICIs in the adjuvant or neoadjuvant setting, or in combination with chemotherapy or other novel agents, may identify therapeutic strategies to enhance patient response. In addition, clinically useful biomarkers are needed to identify high-risk disease and to optimize and personalize ICIs treatment for UCC.

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