New Agents for the Treatment of Advanced Bladder Cancer

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This article will review select novel targets and approaches relevant to urothelial cancer.

Introduction

At diagnosis, 25% to 30% of bladder cancer patients will present with muscle-invasive bladder cancer (MIBC), with approximately 25% of those patients already harboring occult lymph node metastases. Approximately 5% will present with distant metastatic urothelial carcinoma (MUC).[1] Unfortunately, the 5-year survival rate in patients with locally advanced or metastatic disease is only around 15%.[2] Cisplatin-based chemotherapy has a proven survival benefit, both in patients who are treated neoadjuvantly for locally advanced disease and in those with metastases. Standard first-line regimens for locally advanced/metastatic disease include combination chemotherapy with methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC), and doublet therapy with gemcitabine plus cisplatin (GC). Despite an overall objective response rate (ORR) of greater than 50% to cisplatin-based therapy, the duration of response is approximately 7 months and the median survival time is 15 months.[3] Toxicity can be significant in this population of patients. Patients who do not respond to initial cisplatin-based therapy, or who develop a relapse after initial chemotherapy, respond poorly to subsequent treatments. The median survival time in these refractory patients is approximately 9 months.[4]

A clearer understanding of molecular targets and immunologic characteristics of urothelial tumor cells has resulted in new therapeutic leads that may help optimize first- and second-line therapy, evaluate new combination approaches, and elucidate the role of maintenance therapy after initial response. This article will review select novel targets and approaches relevant to urothelial cancer.

Therapeutic Leads: The Cancer Genome Atlas

The Cancer Genome Atlas (TCGA) Research Network is a multi-institutional, comprehensive, widespread effort developed by the National Cancer Institute to collect specimens of a broad range of cancer types, in the hope of analyzing the genetics and molecular biology of tumor subtypes, in order to identify common mutations and targets for treatment. Upon initiation of the project in 2006, researchers sought to identify genomic changes in more than 20 different types of human cancer, including bladder cancer. A decade later, many targeted drugs are being used to treat other types of cancer. Similarly, the focus of research in advanced urothelial cancer is now shifting away from chemotherapy and toward targeted therapies.

TCGA recently published a comprehensive integrated study of 131 chemotherapy-naive high-grade MIBCs.[5] Mutations in 32 genes have now been identified and found to be statistically significant in the development and disease course of bladder cancer. These genomic alterations—including changes impacting the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) and receptor tyrosine kinase (RTK)/RAS pathways, ERBB2 (human epidermal growth factor receptor 2 [HER2]), ERBB3, and fibroblast growth factor receptor 3 (FGFR3)—have potential therapeutic implications.[6] Using data from the International Genomics Consortium to identify specific topics in need of future study may prove beneficial in constructing new trials involving agents that target these genes. Summarized in this article are studies that have evaluated therapeutic agents aimed at targets identified by TCGA. (Table 1 lists select clinical trials of targeted therapy agents in advanced bladder cancer, and Table 2 highlights some studies of checkpoint inhibitors in this disease setting.)

Anti–PI3K/AKT/mTOR Therapy

The serine/threonine protein kinase mTOR is part of the PI3K/AKT/mTOR pathway, which plays a
critical role in cell growth, angiogenesis, protein synthesis, and cell survival. Mutations, copy number alterations, and RNA expression changes affecting the PI3K/AKT/mTOR pathway are commonly found in various malignancies, including bladder cancer.[7] Data from Memorial Sloan Kettering Cancer Center showed mutations or copy number gains/losses of genes in the PI3K/AKT/mTOR pathway, including PIK3CA, PIK3R1, TSC1, PTEN, and the AKT3 isoforms in 26 of 95 patients (27%) with high-grade MIBC. These genetic alterations were associated with a trend toward longer time to recurrence (hazard ratio [HR], 0.53; P = .08).[8] In a single-arm, nonrandomized, phase II trial, treatment with the oral mTOR inhibitor everolimus yielded two partial responses (PRs) and a median survival time of 8.3 months in patients with MUC refractory to up to four cytotoxic chemotherapy regimens.[9] In another single-institution phase II study, everolimus showed antitumor activity in only a small number of patients with advanced bladder cancer.[10] In these studies, patients were unselected. However, enrichment of the patient population with genetic alterations, such as a TSC1 mutation[11] or mTOR-activating mutations (E2419K and E2014K),[12] may increase the observed levels of sensitivity to mTOR inhibitors. In a phase I trial of pazopanib combined with everolimus, a complete response (CR) of 14 months was observed for a patient who had mutations of both E2419K and E2014K.[12] Several trials of the mTOR inhibitors sirolimus, temsirolimus, and everolimus are currently accruing patients with advanced bladder cancer in order to assess these agents either in combination with a standard chemotherapy regimen or as monotherapy.

**Agents Targeting Epidermal Growth Factor Receptor (EGFR)**

The 170-kDa transmembrane receptor tyrosine kinase EGFR is a member of the ErbB family of type-1 receptor tyrosine kinases. In addition to EGFR, this receptor family includes the human epidermal growth factor receptor receptors HER2 (ERBB2), HER3 (ERBB3), and HER4 (ERBB4). EGFR is expressed in a variety of human epithelial tumors, including lung and bladder cancer. EGFR signaling has been shown to regulate the cell proliferation, apoptosis, angiogenesis, invasion, and tumor metastasis observed in preclinical models of transitional cell carcinoma (TCC) of the bladder.[13] This signaling pathway is expressed in about two-thirds of specimens of nonmetastatic MIBC; correlates with primary tumor stage; and is associated in some studies with tumor recurrence, progression, and patient survival.[14] Strong EGFR immunostaining patterns were observed in the majority of bladder cancer metastases (13 of 20) in one study.[15] Higher levels of EGFR appear to correlate with the basal-like histologic subgroup of bladder cancer. Therefore, the EGFR pathway represents a potential therapeutic target in urothelial carcinoma, either through antibodies that bind to the receptor or by the use of small molecules that target the tyrosine kinase.

**Gefitinib**

The rationale for the investigation of gefitinib in bladder cancer was based on the investigation of EGFR targeting by cetuximab (C225) in the early 2000s; cetuximab inhibited angiogenesis in mouse models of TCC, and this activity was enhanced by paclitaxel.[16] Gefitinib, an orally active selective EGFR tyrosine kinase inhibitor (TKI), has demonstrated antitumor activity synergistic with that of platinum and other chemotherapeutic agents in a variety of cell lines and human tumor xenograft models. In multiple studies, antitumor activity has been seen at all levels of EGFR expression, but has been greatest against tumors with the highest degree of EGFR expression. In EGFR-expressing human bladder cancer cell lines, gefitinib has inhibited extracellular signal-regulated kinase and AKT phosphorylation, as well as EGFR phosphorylation.

The Southwest Oncology Group evaluated gefitinib administered as a single agent in patients with MUC in whom prior platinum-based chemotherapy had failed.[17] Among the 31 patients treated, 1 patient demonstrated a PR in a lung metastasis and 2 patients had stable disease. At first evaluation, 81% of patients demonstrated progressive disease. The median survival time was 3 months. A phase II trial (Cancer and Leukemia Group B 90102) sought to determine the efficacy of GC and gefitinib in patients with advanced urothelial carcinoma.[18] Patients with previously untreated measurable disease were treated with cisplatin at a dosage of 70 mg/m^2 on day 1 and gemcitabine at 1,000 mg/m^2 on days 1 and 8, given every 3 weeks concurrent with gefitinib at 500 mg/day orally for 6 cycles. Maintenance gefitinib at 500 mg/day was continued for patients with responding or stable disease. A total of 54 of 58 patients were assessable. There were 12 patients (22%) with node-only disease, and 25 (46%) had an Eastern Cooperative Oncology Group performance status of 0. There were 23 objective responses, for an ORR of 42.6% (95% CI, 29.2%–56.8%). The median survival time was 15.1 months (95% CI, 11.1–21.7 months) and the median time to progression was 7.4 months (95% CI, 5.6–9.2 months). However, the addition of gefitinib did not appear to improve...
the response rate or survival outcomes in comparison with historical controls of patients treated just with cisplatin plus gemcitabine.

**Erlotinib**

Treatment with the EGFR TKI erlotinib has been studied in a variety of tumor types. In a phase II open-label trial of this agent given prior to radical cystectomy for MIBC, 20 patients were treated with 4 weeks of adjuvant erlotinib; 60% were downstaged to pT1 or less, suggesting single-agent activity with EGFR inhibitors in this disease setting.[19] A similar trial at the University of Texas MD Anderson Cancer Center is assessing the rate of complete pathologic response after 3 to 5 weeks of erlotinib therapy in patients with MIBC.[20] Despite high levels of expression of EGFR in patients with MUC, the aforementioned results with the TKIs have been disappointing, and may be related to the paucity of EGFR mutations in bladder cancer specimens. In patients treated with EGFR TKIs for advanced lung cancer, point mutations at exons 19 and 21 of the EGFR gene’s ATP-dependent tyrosine kinase domain are associated with response. Chaux et al[21] found that mutations of these exons were not detected in micro-dissected paraffin sections obtained from 19 urothelial tumors, despite immunohistochemical expression in 74% of the examined cases. Thus, alterations associated with TKI response have not been detected in urothelial carcinoma.

**Cetuximab**

The anti-EGFR monoclonal antibody cetuximab is approved for treatment of non–small-cell lung cancer (NSCLC), head and neck cancer, and colorectal cancers. Cetuximab monotherapy has preclinical activity in bladder tumor models. Although it has modest antitumor effects when used as a single agent in this setting, enhanced tumor effects were revealed when cetuximab was combined with the second-line agent paclitaxel.[16] A randomized, noncomparative, phase II study aimed to evaluate the efficacy of cetuximab with or without paclitaxel in the second-line setting in bladder cancer.[22] A total of 39 patients were randomly assigned to 4-week cycles of cetuximab at 250 mg/m² with or without paclitaxel at 80 mg/m² per week. The arm assessing single-agent cetuximab closed after 9 of the first 11 patients had progressed by 8 weeks. However, there appeared to be some synergy between anti-EGFR monoclonal antibodies and taxanes. Cetuximab may well augment paclitaxel antitumor activity; in the combination arm (which accrued 28 patients) there was a 25% response rate, with 12 patients having progression-free survival (PFS) beyond 16 weeks. However, in small studies such as this one, the data must be interpreted with caution, since the median PFS and overall survival (OS) times observed (16.4 and 42 weeks, respectively) were very modest and within the range reported for other agents in this disease setting. Other trials currently evaluating cetuximab include TUXEDO (Cancer Research UK trial number CRUK/09/021), a phase II trial in the United Kingdom of cetuximab administered concurrently with chemoradiation therapy (using either mitomycin-C and 5-fluorouracil or cisplatin) in MIBC.

**Panitumumab**

A phase I, multicenter, open-label study sequentially enrolled 86 patients with advanced refractory solid tumors, to receive the EGFR antibody panitumumab (given at 6 mg/kg every 2 weeks or 9 mg/kg every 3 weeks).[23] Objective responses were reported in four patients (5%) with colon, rectal, esophageal, and bladder cancers. The results suggested that panitumumab administered at 9 mg/kg every 3 weeks appeared to be safe, and studies using this dosing schedule are ongoing. Further evaluation of panitumumab in urothelial carcinoma was planned in a randomized, multicenter, phase II study by the German Association of Urological Oncology ([AUO] trial AB 34/09) comparing GC in combination with panitumumab vs GC as first-line therapy for patients with locally advanced/metastatic urothelial carcinoma. Unfortunately, this study was terminated due to insufficient recruitment.

**Agents Targeting HER2**

The second member of the EGFR family, HER2, plays an important role in the pathogenesis of urothelial carcinoma. Several studies have reported HER2 protein overexpression rates of 5% to 80% in bladder cancer. Lae et al analyzed 1,005 MIBC tissue samples for overexpression of HER2 and HER2 gene amplification.[24] HER2 protein overexpression was found in 11.4% of tissue
samples. HER2 gene amplification was found in 5.1% of MIBC. A study evaluating 80 cystectomy and lymph node dissection specimens found 28% of cystectomy cases (22 of 80) were HER2-positive and 53% (17 of 32) had positive lymph nodes.

**Trastuzumab**

In a phase II trial, the anti-HER2 humanized monoclonal antibody trastuzumab was used in combination with paclitaxel, gemcitabine, and carboplatin to treat patients with advanced HER2-positive bladder cancer. The regimen produced a 70% response rate, including CRs, in patients with metastatic disease.[25] Trastuzumab administered concurrently with paclitaxel chemoradiation treatment is being evaluated in patients with MIBC who have undergone transurethral resection of bladder tumor and are not candidates for radical cystectomy.

A study investigating trastuzumab combined with standard GC doublet chemotherapy for bladder cancer in the first-line setting closed enrollment early (ClinicalTrials.gov identifier: NCT02006667). Another study investigating single-agent trastuzumab in the second-line setting (ClinicalTrials.gov identifier: NCT02013765) closed early because of recruitment difficulties.

**Lapatinib**

The dual EGFR and HER2 TKI lapatinib is also being studied in combination with chemotherapy for MUC. Although single-agent treatment with lapatinib in unselected patients with platinum-refractory MUC yielded only a 1.7% ORR, it led to markedly worse OS in those with low copy numbers of EGFR and HER2, compared with patients who had high overexpression of EGFR and/or HER2.[26] This subgroup analysis reinforces the concept of selecting appropriate patients for targeted therapies. Importantly, 18% of patients in the postoperative treatment group (no chemoradiation prior to surgery) who were determined preoperatively to have T3 or T4 disease or lymph-node metastasis were found to actually have T1 or T2 or node-negative tumors on pathologic examination of the resected specimen. This important observation clearly highlights the limitations of preoperative staging at the time the study was performed, and perhaps the potential for overtreatment of some patients. The finding underscores the need for accurate staging so as to avoid unnecessary treatment of patients with early-stage tumors.

A recently completed phase II/III trial (n = 223) comparing maintenance lapatinib vs placebo after first-line chemotherapy in patients with locally advanced or metastatic bladder cancer found no difference in OS or PFS, even in HER2-positive patients.[27] A phase I trial that combined lapatinib with GC has recently been completed (ClinicalTrials.gov identifier: NCT00623064).

**Agents Targeting the FGFR**

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**New Hope for Patients With Advanced Urothelial Cancer**

There has been a paucity of new drugs developed for the treatment of metastatic urothelial cancer, with no drugs approved for this indication by the US Food and Drug Administration (FDA) in more than 30 years. This lack of progress likely has myriad causes, including a poor understanding of the pathogenesis and heterogeneity of the disease, a patient demographic characterized by older age and smoking-related comorbidities, and inadequate interest on the part of industry. However, after decades without substantial progress, a series of advances in both the laboratory and the clinic in the past few years have begun to change the outlook for patients with advanced urothelial cancer.
How Have Targeted Approaches Changed Diagnosis and Treatment?
Several factors underlie recent advances in the management of urothelial cancer; these include comprehensive efforts to define the molecular pathogenesis of urothelial cancer, and the introduction of novel therapies directed at targets that range from tumor angiogenesis, to activating somatic mutations in growth factor receptors, to adaptive immune resistance. Antibodies directed against the immune checkpoint inhibitors programmed death 1 (PD-1) and programmed death ligand 1 (PD-L1) have demonstrated durable responses in a subset of patients with platinum-resistant urothelial cancer. Now, with the recent FDA approval of the PD-L1 inhibitor atezolizumab, this drug class represents the first to gain regulatory approval in this disease setting. Small-molecule inhibitors of mutated FGFR3 (fibroblast growth factor receptor 3) have demonstrated single-agent responses in the clinic, finally validating mutant FGFR3 as a relevant therapeutic target in this disease. With the increasing availability of these tools in the clinic, it will be incumbent upon the bladder cancer research community to begin to focus not only on developing new drugs but also on developing new therapies. Questions regarding when to optimally employ these newer agents, in which patients, and in which sequences and combinations will only be determined through iterative cycles of bench-to-bedside research.

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Dovitinib

Mutations of the FGFR3 gene are prevalent in both non-MIBC and MIBC. The multikinase inhibitor dovitinib targets FGFR3 kinase. This agent was evaluated in patients with platinum-refractory metastatic disease as part of a phase II trial enrolling 44 patients and using a two-stage design.[28] Median PFS was 3 months. Because of a lack of treatment response in the first stage and because most patients did not receive more than 6 months of therapy, patients were not recruited for the second stage of the trial. It is not clear why dovitinib lacked activity. Possible reasons include lack of target inhibition due to low drug potency (much more potent FGFR3 inhibitors, including BGJ398 and JNJ-42756493, are now available and have shown activity in humans) or inadequate selection of patients (since activating translocations and FGFR3 expression were not quantified and may better identify responders). It is also possible that the profile of kinases inhibited by dovitinib is not optimal for effectiveness.

Antiangiogenesis Agents

Vascular endothelial growth factor (VEGF)
The VEGF family binds with high affinity to three tyrosine kinase receptors (VEGFR-1, VEGFR-2, and VEGFR-3), mediating normal and pathogenic angiogenesis in various cancers, mostly through interaction with VEGFR-2. VEGF is important in the pathophysiology of urothelial cancer. It is often overexpressed in bladder cancer. A high level of VEGF in both serum and urine is correlated with tumor progression, a higher recurrence rate,[29, 30] and poor survival. VEGFR-2 is expressed in 50% of urothelial carcinomas, and expression is significantly higher in MIBC than in non-MIBC.[30] Inoue et al evaluated the prognostic value of tumor VEGF expression in patients with MIBC treated with neoadjuvant MVAC chemotherapy and radical cystectomy.[31] They examined VEGF expression before and after neoadjuvant chemotherapy, along with basic fibroblast growth factor and interleukin-8 expression and microvessel density by immunohistochemistry in biopsy specimens from 55 patients with MIBC. VEGF expression and microvessel density in pretreated biopsy samples showed a correlation with disease recurrence (P = .032 and P = .015, respectively). VEGF appears to be a rational therapeutic target. Various VEGF-targeting agents are currently being evaluated in MIBC. Although targeting angiogenesis by way of VEGF is a promising strategy in urothelial carcinoma, the results with TKIs that target VEGFRs have not been encouraging.

Bevacizumab

Bevacizumab is a monoclonal antibody targeting VEGF-A. Bevacizumab combinations have been evaluated as first-line therapy in MUC. The Hoosier Oncology Group treated 43 chemotherapy-naive patients with MUC and reported a 72% ORR, with 19% of patients attaining a CR. The median OS was 19.1 months.[32] Of note, grade 3 or higher vascular events, such as deep venous thrombosis or pulmonary embolism, were observed in 21% of patients. This was postulated to be due to the initial
1,250-mg/m² dose of gemcitabine. In another phase II study of chemotherapy-naive cisplatin-ineeligible patients with metastatic disease, whose expected survival time was approximately 9 months, bevacizumab combined with GC and carboplatin led to a 63% response rate and an OS of 13.9 months.[33] Both of these studies showed better results than might be expected compared with historical controls. Given these encouraging results, a phase III trial of GC with and without bevacizumab as first-line treatment was launched as an intergroup study led by the Alliance cooperative group (ClinicalTrials.gov identifier: NCT00942331). In the metastatic setting, a phase II trial of bevacizumab with GC as neoadjuvant therapy followed by adjuvant paclitaxel has completed accrual (ClinicalTrials.gov identifier: NCT00268450). The results of these studies are pending.

Bevacizumab has also been investigated in the neoadjuvant setting. In two phase II trials, it was combined with either GC or dose-dense MVAC, resulting in pathologic response rates of 31%[34] and 53%,[35] respectively, with downstaging to less than stage T2. The combination of bevacizumab plus GC was associated with postoperative complications in some patients (5 of 12 [42%]), including enterovesical fistula, delayed wound healing, prolonged ileus, and pelvic abscess.[35]

**Aflibercept**

Aflibercept (also known as VEGF-Trap) is a recombinant fusion protein that binds and neutralizes multiple VEGF isoforms. A small phase II study evaluated this agent in 22 patients with measurable, metastatic, or locally advanced urothelial cancer previously treated with 1 platinum-containing regimen. One PR was reported. Median PFS was 2.79 months (95% CI, 1.74–3.88 months). Aflibercept was well tolerated, with toxicities similar to those seen with other VEGF pathway inhibitors. However, it was demonstrated to have limited single-agent activity in patients with platinum-pretreated urothelial carcinoma.[36]

**Ramucirumab**

The fully humanized immunoglobulin (Ig)G1 monoclonal antibody ramucirumab blocks the binding of VEGF to VEGFR-2. It is approved as a single agent or in combination with paclitaxel or docetaxel for gastric cancer. In vitro, ramucirumab chemosensitizes bladder cancer cell lines to docetaxel. A randomized phase II trial compared docetaxel at 75 mg/m² (n = 45) intravenously (IV) vs ramucirumab at a dose of 10 mg/kg IV in combination with the same dose and schedule of docetaxel (n = 46).[37] These urothelial cancer patients were required to demonstrate progression within 12 months of administration of treatment with platinum-based regimens for metastatic disease, or neoadjuvant/adjuvant therapy. The addition of ramucirumab to docetaxel met the prespecified efficacy endpoint for prolonging PFS in second-line treatment for patients with locally advanced disease or MUC. PFS was significantly longer in the combination arm compared with docetaxel alone (median PFS, 5.4 months [95% CI, 3.1–6.9 months] vs 2.8 months [95% CI, 1.9–3.6 months]; stratified HR, 0.389 [95% CI, 0.235–0.643]; P = .0002). OS, a secondary endpoint, was not significantly different between the two arms. The most common grade ≥ 3 adverse events were neutropenia, fatigue, febrile neutropenia, and anemia. Patients in a third study arm, treated with the VEGFR-1–directed antibody icrucumab plus docetaxel, demonstrated a worse overall median PFS (1.6 months).[37] To further confirm these observations, RANGE (ClinicalTrials.gov identifier: NCT02426125), a phase III study, is comparing docetaxel vs ramucirumab plus docetaxel.

**Sunitinib**

Sunitinib, an oral inhibitor of multiple tyrosine kinase receptors, including VEGFR, has shown synergistic antitumor effects with both cisplatin and gemcitabine in preclinical models of urothelial cancer.[38] Sunitinib monotherapy produced mixed effects in patients with advanced urothelial cancers, when administered either as a first-line therapy for patients who were not candidates for cisplatin-based chemotherapy (because of renal impairment) or as second-line therapy after chemotherapy.[39]

In trials in which sunitinib was combined with GC for either first-line metastatic or neoadjuvant treatment of patients with urothelial cancer, high rates of toxicity and intolerability were a major issue. Sunitinib, given as maintenance therapy in a randomized phase II trial to patients who had achieved stable disease or a PR or CR after 4 to 6 cycles of chemotherapy, did not improve 6-month PFS compared with placebo.[40] Because of these disappointing results, there are no ongoing trials of sunitinib for MUC.
MET/Hepatocyte Growth Factor 1 (HGF1) Inhibition

Cabozantinib

The TKI cabozantinib primarily targets VEGFR-2 and c-MET (also known as MET or HGF1), which might be potential targets in urothelial carcinoma.[41] Cabozantinib is being studied in an ongoing phase II trial as second-line treatment of MUC.[42] In a preliminary report of 25 patients with refractory urothelial cancer treated with 60 mg of oral cabozantinib daily, PRs were demonstrated in 14% of patients, and another 38% had stable disease. Grade 3 toxicities included fatigue and mucositis. Of note, myeloid-derived stem cells and regulatory T cells (Tregs) were evaluated in patients whose urothelial cancer was treated with cabozantinib; patients with low Tregs at baseline had an improved PR rate ($P = .014$), PFS ($P = .059$), and OS ($P = .071$). Tregs decreased with cabozantinib treatment ($P = .015$). Overall, programmed death 1 (PD-1) expression in Tregs increased after cabozantinib ($P = .011$).[43]

Cytotoxic Agents

Cabazitaxel

Cabazitaxel is a taxane that exhibits preclinical antitumor activity in both docetaxel-sensitive and -resistant tumors. A survival benefit has been demonstrated with cabazitaxel use in metastatic castration-resistant prostate cancer. Modest antitumor activity has been demonstrated with other taxanes, such as paclitaxel and docetaxel, with responses ranging between 6% and 20%. In cisplatin- and gemcitabine-refractory cell lines, cabazitaxel demonstrated less cross-reactivity than standard agents such as pemetrexed, methotrexate, oxaliplatin, and paclitaxel.[44] These preclinical data justify further evaluation of cabazitaxel in urothelial carcinoma. The National Cancer Institute evaluated cabazitaxel (ClinicalTrials.gov identifier: NCT01437488), initially dosed at 20 mg/m$^2$, then escalated to 25 mg/m$^2$ at the investigator’s discretion, and administered with growth factor support. No responses were observed in 14 patients, with 1 patient dying from refractory hypoxia. Therefore, further evaluation of cabazitaxel as a single agent in the treatment of urothelial carcinoma is unwarranted. Cabazitaxel had limited clinical activity in platinum-refractory MUC and was associated with toxicity (fatigue, diarrhea, anemia, nausea, neuropathy, increased creatinine levels, lightheadedness, and hypophosphatemia). Unfortunately, the study did not proceed to the second stage; it was closed early, due to lack of treatment efficacy. An ongoing phase II clinical trial (ClinicalTrials.gov identifier: NCT01616875) is evaluating the efficacy of neoadjuvant cisplatin combined with cabazitaxel.

Eribulin

Eribulin is a novel synthetic antimicrotubule agent that binds to the vinca domain of tubulin and inhibits the polymerization of tubulin. It is an analog of halichondrin B, originally isolated from the sea sponge. This agent demonstrates improved survival over physician’s-choice chemotherapy in breast cancer patients who have received prior treatment. In an extended phase II trial by The California/Pittsburgh Cancer Consortium, eribulin was administered at 1.8 mg/m$^2$ on days 1 and 8 of a 21-day cycle to 150 patients with advanced urothelial cancer who had received prior platinum-based therapy. In developing the study, a response rate of 20% or higher was deemed by the authors to be of clinical importance; an ORR of 34.7% was reported.[45] The median PFS and OS were 4.1 and 9.5 months, respectively. There was no significant increase in neuropathy or hematologic toxicity in patients who were tubulin-naive compared with patients who were tubulin-exposed. Several trials are in development for the use of eribulin in patients with advanced urothelial cancer and renal dysfunction (ClinicalTrials.gov identifier: NCT00365157).

Antibodies for Immune Therapy: Immune Checkpoint Inhibitors

Immune therapy focusing on novel agents that target proteins in the immune checkpoint regulation pathway (especially PD-1 and its ligand, programmed death ligand 1 [PD-L1]) has produced a survival benefit in a variety of solid tumors, including metastatic lung cancer and renal cancer. Immune therapy is also emerging as a promising new treatment in bladder cancer, with significant potential demonstrated in preclinical models and early clinical trials (see Table 2).

Ipilimumab
The monoclonal antibody ipilimumab targets cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4). CTLA-4 is a potent immune checkpoint molecule that downregulates T-cell activation after binding to antigen-presenting cells. Ipilimumab first demonstrated clinical activity and improved clinical outcomes in patients with metastatic melanoma. To evaluate its efficacy in urothelial cancer, the Hoosier Oncology Group treated 36 chemotherapy-naive MUC patients with ipilimumab in combination with GC.[46] Patients were initially treated with 2 cycles of GC followed by 4 cycles of GC/ipilimumab, followed by ipilimumab maintenance administered every 3 months. The observed mean survival time of 14.6 months was no different from that of historical controls, but it was achieved at the cost of additional immune-related toxicities such as diarrhea (in 8% of patients), colitis (6%), and rash (6%). Treatment with ipilimumab was associated with an increased number of CD4+ and CD8+ T cells.

**Atezolizumab**

Atezolizumab (also known as MPDL3280A) is a high-affinity human anti–PD-L1 monoclonal IgG1 antibody. It has demonstrated clinical activity in melanoma, breast cancer, NSCLC, and renal cancer. In a phase I trial of second-line atezolizumab in TCC, tumor immune cell (IC) expression of PD-L1, but not tumor cell expression, correlated with outcome. IC 0, 1, 2, and 3 expression was defined as 0%, < 1%, 1% to 5%, 5% to 10%, and > 10% of immune cells expressing PD-L1. ORRs were 43% for patients with tumor immune cells expressing high levels of PD-L1 (IC 2/3), compared with 11% in patients whose tumor immune cells had low expression of IC (0/1).[47] The median duration of response has not been reached, and is independent of PD-L1 status. The median PFS was 6 months in the IC 2/3 group compared with 1 month in the 0/1 group.[48] The median survival in the IC 2/3 group has not yet been reached after a median of 14 months follow-up. The median survival in the IC 0/1 group was 8 months, similar to results with cytotoxic chemotherapy but with less toxicity. There were no treatment-related deaths on the study; 5% of patients had grade 3 or 4 immune-mediated toxicities, including elevated transaminase levels, increased bilirubin, and hypophysitis.

Atezolizumab was granted breakthrough therapy designation status by the US Food and Drug Administration (FDA) in June 2014, and priority review for locally advanced bladder cancer or MUC in March 2016. On May 18, 2016, it was approved by the FDA for the treatment of patients with locally advanced or metastatic urothelial carcinoma.

Two trials have been designed to confirm the initial data: a large phase II study of platinum-experienced patients (IMvigor 210; ClinicalTrials.gov identifier: NCT02108652) and a phase III trial comparing atezolizumab vs chemotherapy in 767 platinum-refractory patients (IMvigor 211; ClinicalTrials.gov identifier: NCT02302807). IMvigor 210 treated 315 platinum-refractory urothelial cancer patients with atezolizumab at 1,200 mg IV every 3 weeks. The primary endpoint of IMvigor 210 was a response rate by Response Evaluation Criteria in Solid Tumors (RECIST) of > 10%, which was achieved in each of the prespecified immune cell groups. Twenty-seven percent of patients with IC 2/3, 18% of those with IC 1/2/3, and 15% of all patients had response rates > 10% by RECIST. The median PFS was 2.1 months, and PFS was similar in all immune cell groups. The median OS was 11.4 months in the IC 2/3 patients and 8.8 months in the IC 1/2/3 patients. For all patients, median survival time was 7.9 months. An exploratory analysis found that PD-L1 immune cell prevalence was highly enriched in the basal subtype of urothelial cancer, compared with the luminal subtype (60% vs 23%; \( P < .001 \)); the median mutation load was significantly higher in responders than in nonresponders. The IMvigor 211 trial has completed accrual.

**Pembrolizumab**

Pembrolizumab is an anti–PD-1 antibody that blocks interaction with both PD-L1 and PD-L2. In KEYNOTE-012, a phase Ib trial that selected for patients expressing PD-L1 in tumor cells, 33 patients with urothelial cancer (approximately 75% of whom had prior platinum-based therapy) received pembrolizumab every 2 weeks. The ORR was 27.6%, with 10.3% of patients demonstrating a PR. The mean duration of response has not yet been reached; the median PFS and OS were 2 months and 12.7 months, respectively. Immune-related side effects included colitis, myositis, rhabdomyolysis, rash, and uveitis (with 1 patient discontinuing treatment due to myositis and rhabdomyolysis). There were no treatment-related deaths. A re-analysis of the PD-L1 immunoreactivity demonstrated no objective responses when this marker was evaluated both in tumor cell samples and in tumor-associated inflammatory cells. Immune-related gene expression using NanoString Technologies’ nCounter Platform found that a 13-gene T-cell receptor signaling panel predicted clinical benefit as measured by tumor response; however, no correlation with survival was found.[49] The phase III KEYNOTE-045 trial, which has completed accrual, is comparing pembrolizumab vs
treatment with paclitaxel, docetaxel, or vinflunine in patients with disease progression after platinum-based therapy (ClinicalTrials.gov identifier: NCT02256436). The phase II KEYNOTE-052 trial, currently recruiting patients, will investigate the efficacy of pembrolizumab in patients with advanced urothelial cancer or MUC who have not received any previous systemic therapy (unless it has been > 12 months since they completed neoadjuvant and adjuvant platinum-based chemotherapy) and who are ineligible for cisplatin-based therapy (ClinicalTrials.gov identifier: NCT02335424).

Conclusions

Advances have been made in targeted therapeutic and immunotherapeutic approaches to the treatment of MUC. Randomized clinical trials will define the role of antiangiogenesis therapy in combination with chemotherapy in both the first- and second-line settings. Identification of the dramatic activity of immunotherapy in urothelial cancer patients treated with immune checkpoint blockade is a significant advance in this disease; these response rates may be improved via refinement of the markers used to predict response, and by novel combinations of immune checkpoint inhibitors. The optimal sequences of immune therapy and targeted agents are yet to be defined.

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Table 1. Selected Trials of Targeted Therapy Agents in Advanced Bladder Cancer

Table 2. Studies of Checkpoint Inhibitors in Urothelial Cancer

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