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What about Treatment of Metastatic Bladder Cancer

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Abstract

Background: Bladder cancer is the most common malignancy of urinary tract with high rate of morbidity and mortality. Platinum-based chemotherapy remains the first line treatment of advanced disease. Despite several studies, the place of targeted therapies is not yet defined, whereas immunotherapy is currently the standard of care in second-line treatment.

Materials and methods: A comprehensive search of MEDLINE/Pubmed and Embase was conducted to identify conference abstracts, basic science, original and review articles in English.

Conclusion: This review of the literature will discuss the molecular mechanisms involved in tumor progression, the current management of metastatic bladder cancer and future potential treatment modalities.

Keywords: Bladder; Chemotherapy; Cisplatine; Target therapies; Immunotherapy

Abbreviations: UC: Urothelial Carcinoma; NMIBC: Non-Muscle-Invasive Bladder Cancer; BCG: Bacillus Calmette-Guérin; IBC: Invasive Bladder Cancer; CMV: Cisplatin Methotrexate Vinblastine; MVAC: Methotrexate Vinblastine Adriamycin and Cisplatin; TCGA: The Cancer Genome Atlas; NCI: National Cancer Institute; EGF: Epidermal Growth Factor; TKI: Tyrosine Kinase Inhibitors; IHC: Immunohistochemistry; VEGF: Vascular Endothelial Growth Factors; SOC: Standard of Care

Introduction

Bladder cancer is the most common malignancy of the urinary tract and accounts for approximately 3.2% of all cancer worldwide where it remains the seventh most commonly diagnosed malignancy in the male population [1]. If men are the first to be targeted by the disease, this type of cancer is more common in females due to high level of consumption of smoking. The prognosis of the disease depends on accuracy of the detection in line with the professional care that is adapted to the characteristics more or less invasive of the tumor [2]. The majority of bladder cancers are composed of urothelial carcinoma (90%) with the remaining less common subtypes including squamous cell carcinoma, adenocarcinoma, and small cell carcinoma. Seventy percent of the cases are diagnosed as non-muscle-invasive bladder cancer (NMIBC) with a favorable prognosis following transurethral resection and intravesical chemotherapy or immunotherapy with Bacillus Calmette-Guérin (BCG) [3]. Nevertheless, approximately 40% of these patients will progress to muscle-invasive disease at five years depending on tumor pathological features [4]. Cisplatin-based combination chemotherapy is the current cornerstone treatment for metastatic and non-resectable invasive bladder cancer (IBC) [5]. For patients progressing despite platinum-based first-line chemotherapy, Vinflunine has received regulatory approval in Europe [6]. And recently, immunotherapy represents the new standard in second-line treatment [7]. Thus, there is an urgent unmet need to develop treatment approaches that yield more substantial gains in patient outcomes.

Materials and Methods

A comprehensive search of MEDLINE/Pubmed and Embase was conducted to identify conference abstracts, basic science, and original and review articles in English.

Results

Chemotherapy

Bladder cancer is a disease that is sensible to chemotherapy but is not curable. Below the table 1 concludes the principle drugs in monotherapy.

Drug	Response rate (%)
Cisplatine	30
Carboplatine	8
Methotrexate	29
Doxorubicine	17
Vinblastine	18
5 FU	17
Ifosfamide	28
Gemcitabine	28
Paclitaxel	22
Docetaxel	13
Vinflunine	18

Pemetrexed	8

Table 1: Principle drugs in monotherapy.

First-line treatment of metastatic disease

Combination cisplatin-containing chemotherapy is standard first-line treatment: Cisplatin has been used since the 1970s, One study comparing cisplatin, methotrexate, and vinblastine (CMV) versus methotrexate, confirming the advantage of platinum-containing regimens in the first-line setting [8].

Other studies established the superiority of MVAC (Methotrexate, vinblastine, adriamycin, and cisplatin) over other cisplatin-containing regimens. However, the toxicity of MVAC was significant, with increased rates of myelosuppression, neutropenic fever, and mucositis [9], limiting the use of this regimen in elderly population with frequent comorbidities.

In an attempt to improve the results of MVAC, EORTC evaluated the MVAC intensified admitistre every 14 days Instead of every 28 days with Increased doses of cisplatin and doxorubicin while using the of growth in primary prophylaxis. Progression-free survival was 9.1 months in the arm intensified against 8.2 months in the other arm (p=0.03) and survival at 2 years of 36.7% versus 25.2%, but the median overall survival difference remained Negligible (15.1 months versus 14.9 months) [10].

Gemcitabine and Cisplatin: An appropriate alternative to methotrexate, vinblastine, adriamycin and cisplatin

This regimen was advanced to a phase III trial comparing it with MVAC in 405 patients with stage IV UC [11]. Both arms had similar RRs (46%-49%) and OS (13.8-14.8 months), with improved toxicity profile in the GC arm. the similar disease outcomes and favorable toxicity profile of GC have established this regimen as an appropriate first-line treatment for patients with metastatic UC.

Combinations taxanes-salts of platinum

One trial of phase II estimating the association of docetaxel and cisplatine with a rate of 62% and a median of survival of 13.6 months [12] and that of the paclitaxel with the cisplatine revealing a response rate objectifies of 70% and median of survival of 12.7 months [13]. The comparison of the doublet cisplatine docetaxel *vs.* MVAC in a trial phase III has shown a clear superiority of the MVAC [14].

Combination without platine

Several trials phase II using different schedules of gemcitabine and showing rates of 37% and of 54% and the global survivals of 13.2 and 14.4 months with use of the paclitaxel (weekly or every two weeks) [15,16].

Triple therapy

In order to improve the response rate the combination of ifosphamide 1.5 g/m^2 J 1, 2 and 3, Paclitaxel 200 mg/m^2 and cisplatin 70 mg/m^2 J1 of a 28-day cycle obtained a response rate of 79% with a Rather high toxicity profile can be used only in very good patients and with a normal renal function. Another protocol has been evaluated associating this triplet of Gemcitabine and doxorubicin, sequentially, obtained 73% response rate with 12.1 months of progression-free survival and 16.4 months of overall survival. However, despite the use of growth factors the rate of hematological toxicity was quite high [17].

The triplet, cisplatin 70 mg/m^2 J1, gemcitabine 1000 mg/m^2 and paclitaxel 80 mg/m^2 J1 and J 8 evaluates a phase II trial gave a response rate of 77.6% [18], but the Phase III study with randomization versus the classic gemcitabine-cisplatin combination did not demonstrate Statistically significant benefit to the triplet, which was more toxic (progression-free survival 8.8 months *vs.* 7.7 months and overall survival 15.7 months *vs.* 12.8 months but with p=0.10) [19].

Other platinum agents in patients unfit to receive cisplatin

Cisplatin toxicity limits its use, particularly in patients with a glomerular filtration rate of less than 60 mL/min and those with baseline neuropathy. To this end, regimens incorporating other platinum drugs have been investigated [20].

Carboplatin combination regimens have been investigated more extensively. However, multiple studies, established the superiority of cisplatin over carboplatin-containing regimens.

b) Second–line treatment of metastatic disease

When we talk about a second line of chemotherapy, we know that we are in front of two situations, a relapse after a neo or adjuvant treatment or a progression after a first metastatic line, the potential for response to second-line chemotherapy can vary from single to double [21]. It is in the situation of the progression of the metastatic disease after a first line that vinflunine shows its benefit (6.9 months versus 4.3 months of overall survival median) in a randomized trial compared to supportive care [22].

B-Targets therapies

The progress made in understanding the molecular mechanisms involved in tumorigenesis and tumor progression, have led to the development of new therapeutic drugs called targeted therapies evaluated in patients with depending on their molecular profile.

Targeting molecular alterations in recurrent urothelial cancer

The Cancer Genome Atlas (TCGA), a collaboration between the National Cancer Institute (NCI) and National Human Genome Research Institute, is a large scale effort to integrate molecular profiling of a number of human cancers. Started in 2006, the TCGA has thus far characterized 33 cancer types and subtypes, including ten rare cancers. In 2014, the TCGA investigators published the initial results of a comprehensive genomic profiling effort in urothelial cancer involving 131 muscle-invasive bladder tumors. Data on DNA copy number, somatic mutation, mRNA and miRNA expression, protein and phosphorylated protein expression, DNA methylation, transcript splice variation, gene fusion, viral integration, pathway perturbation, clinical correlates and histopathology were included in the analysis. Importantly, this study identified potential therapeutic targets in most of the samples analyzed (69%), mainly in the MAPK pathway (including HER2 and FGFR3) mainly in the PI3K/AKT/mTOR pathway (42%) and in the MAPK pathway (including HER2 and FGFR3) (45%) [23].

Targeting the HER family of receptors

The HER family of receptors include four transmembrane receptor tyrosine kinases (HER1-HER4) that mediate the growth, differentiation and survival of cells [24,25]. Somatic mutations and copy number variation in EGFR (ErbB1), HER2 (ErbB2) and HER3 (ErbB3) are frequent in urothelial cancer and are underexplored as therapeutic targets in the clinic.

Activation of the EGF receptors is carried out by homo- or heterodimerization, after binding of the conducting ligand to an auto phosphorylation of intracellular tyrosine kinase residues and leading to a cascade of Intracellular signaling involving several pathways, in particular the RAF MAP kinase pathway and the PI3K pathway AKT MTOR thus leading to the activation of angiogenesis; Cellular proliferation and progression tumor and thus the progression of the disease (Figure 1).

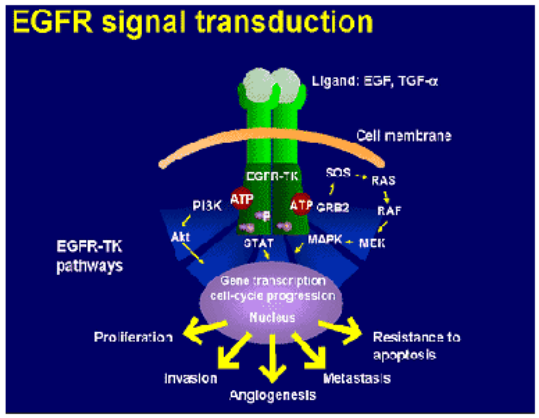

Figure 1: Pathway of EGFR signal transduction.

EGFR

EGFR overexpression, evaluated in immunohistochemistry, involves 31-48% of UC [26]. All layers cells are affected by this overexpression, which increases the contact between the tumor cells and EGF. This overexpression, correlated with stage and tumor grade, is a powerful prognostic factor of UC with decreased recurrence-free survival in five out of seven studies and decreased specific survival in 7 on 11 studies. Two strategies emerge: monoclonal antibodies that recognize antigenic sites on the extracellular part of the receptor and compete with the specific ligands for binding to Receptor and tyrosine kinase inhibitors (TKI) which are small molecules blocking intracellular tyrosine kinase activity at the level of the ATP binding domain.

Monoclonal antibodies (mab)

Cetuximab is a monoclonal antibody directed against HER1 that has been approved for the treatment of head and neck and colorectal cancers [27,28]. Phase II study was conducted, exploring cetuximab with or without paclitaxel in patients with refractory metastatic disease. The study design used early progression to assess for futility and an arm was considered not worthy of further testing if the median PFS was less than 8 weeks. The single-agent cetuximab arm was closed with a median PFS of 7.6 weeks, while the combination arm showed a PFS of 16.4 weeks.

A randomized Phase II trial evaluated the efficacy of gemcitabine plus cisplatin with or without cetuximab in patients with advanced urothelial cancer. The combination regimen was associated with more adverse events and no improvements in outcomes [29].

Tyrosine kinase inhibitors

Gefitinib (a tyrosine kinase inhibitor binding to HER1) has also been tested as a single agent, and in combination with cisplatin and gemcitabine, in single arm studies without evidence of improving outcomes [30,31]. A Phase II trial comparing docetaxel to docetaxel plus gefitinib as maintenance therapy for patients previously treated with chemotherapy has recently closed and the results are pending (NCT00479089).

HER2

The HER-2 oncoprotein plays a role in cell differentiation, mobility and cell adhesion. This Receptor is said orphan, because unlike EGFR, it has no specific ligand identified. However, it was overexpressed in 30% of breast cancers and this expression is correlated with a pejorative prognosis of the disease [32].

A meta-analysis has recently been published showing that HER2 expression is associated with poor prognosis [33]. We have been relatively few clinical studies exploring therapeutics targeting this pathway. A Phase II study tested the safety and efficacy of trastuzumab combined with cisplatin, gemcitabine, carboplatin and paclitaxel in patients with HER2 overexpression by immunohistochemistry (IHC), gene amplification and/or elevated serum HER2. The ORR was 70% and the overall survival (OS) 14.1 months [34].

Lapatinib, an oral HER2 and EGFR inhibitor, demonstrated modest efficacy with ORR of 1.7%, TTP of 8.6 weeks, and OS of 17.9 weeks in a phase II trial of 59 patients [35].

Afatinib dimaleate (an oral irreversible HER family blocker, HER1, 2 and 4) evaluated in patients with refractory urothelial cancer. Preliminary results were presented at the 2015 American Society of Clinical Oncology Genitourinary Cancers Symposium [36]. Out of 15 patients, all three responders had mutations in *HER* genes (*HER2* and/or *HER3* alterations), and none of the ten non responders had alterations in these genes. Time to progression was 8.1 months in patients with mutations versus 1.8 months in patients without ($p=0.02$).

Targeting the urothelial cancer neovasculature

Metastatic UC are vascular and produce high levels of proangiogenic factors, including vascular endothelial growth factors (VEGF). Increased VEGF expression correlates with poor survival in Metastatic UC [37].

Bevacizumab is a recombinant humanized monoclonal antibody that binds all isoforms of human VEGF; the first study was designed [38] to detect a 50% increase in median PFS from an expected 7.5 months with traditional cisplatin–gemcitabin to an improved PFS of 11.25 adding bevacizumab [39]. The overall response rate was 72% (PR in 53% patients and CR in 19%), and the OS was encouragingly high (19.1 months) but the study defined-goal was not met (8.2 months).

The second study with carboplatin was also powered to detect a 50% improvement in median PFS over a historical control; 49% patients Achieved response, the median OS was longer than expected (13.9 months) but the 95% one-sided lower confidence bound of 4.77 months for median PFS did not meet the pre-designated PFS of more than 4.8 months considered sufficient for further study [40].

All these results led to the design of a US NCI Cooperative Group (Alliance) randomized double-blind Phase III trial (Alliance) comparing gemcitabine, cisplatin and bevacizumab to gemcitabine, cisplatin and placebo in patients with advanced urothelial cancer (NCT 00942331) [41]. This trial has completed accrual and the results are eagerly awaited.

Sunitinib is an oral VEGF receptor tyrosine-kinase inhibitor, approved in advanced kidney cancer, has been evaluated in previously treated patients with MUC. Two dosing schedules of sunitinib were evaluated in 77 patients, resulting in modest efficacy and no significant difference between the schedules used [42].

Ramucirumab is a monoclonal antibody targeting VEGFR2, and icrumumab, a monoclonal antibody targeting VEGFR1, were both evaluated in combination with docetaxel chemotherapy in the second line setting. Ramucirumab and docetaxel resulted in ORR of 20% and PFS of 5.1 months versus ORR of 5% and PFS of 2.4 months for docetaxel alone [43]. Ramucirumab and docetaxel will be evaluated further in a phase III trial.

Pazopanib, sorafenib another inhibitors of multiple VEGFR tyrosine kinases, was evaluated in a phase II study in patients with MUC who were heavily pretreated. Activity was not interessante [44,45].

Cabozantinib, an oral potent inhibitor of multiple tyrosine kinase receptors, is currently being evaluated in a phase II study of pretreated patients with MUC. Early results demonstrate an ORR of 11%, with a further 37% of patients achieving stable disease, with manageable toxicities [46].

Vandetanib, an oral VEGFR and EGFR inhibitor, evaluated in combination with docetaxel in platinum-pretreated patients with MUC, resulted in PFS of 2.6 months versus 1.6 months with docetaxel alone. ORR and OS were not significantly improved with the addition of vandetanib (Table 2) [47].

Phase	Agent	Population	NCT number	Status
III	Gemcitabine/cispaltine ± bevacizumab	First line chemo naive	NCT00942331	Active, not recruiting
III	Ramucirumab+docetaxel	Second line and beyond	NCT02426125	recruiting
II	Pazopanib+paclitaxel	Second line and beyond	NCT01108055	recruiting
II	Gemcitabine+pazopanib	First line platinum ineligible	NCT01622660	Ongoing but not recruiting
II	Cabozantinib	Second line and beyond	NCT01688999	recruiting

Table 2: Clinical trials targeting tumor angiogenesis in MUC.

Targeting FGFR3 alterations

The fibroblast growth factor receptors (FGFR) are important regulators of urothelial carcinoma pathogenesis.

FGFR1 expression is increased in urothelial carcinoma, activating the mitogen-activated protein kinase (MAPK) pathway and promoting cell proliferation and survival [48]. In fact, in some studies FGFR3 mutations have been associated with improved prognosis [49].

Dovitinib is a multitargeted kinase inhibitor with activity against FGFRs, VEGFRs, in addition to other kinases. A Phase II trial was designed to explore the activity of dovitinib in patients with platinum-resistant metastatic urothelial cancer enrolling two parallel arms, one enrolling patients with FGFR3 mutations and the other enrolling patients with wild-type FGFR3. There were no responses in the FGFR3 mutant arm of the study and only one objective response in the FGFR3 wild-type arm [50] with MUC whose tumors harbor specific FGFR mutations (NCT02365597, NCT01004224).

Targeting the PI3K/AKT/mTOR pathway

The mTOR pathway, important in cell signaling and proliferation, is often dysregulated in Malignancies.

Everolimus (RAD001) is an orally administered inhibitor of mTOR, it showed only modest clinical activity in a Phase II trial in patients with platinum-resistant metastatic urothelial cancer [51]. However, one patient from this trial had a complete response and whole genome sequencing was subsequently undertaken, revealing that mutations in the *TSC1* gene correlated with everolimus efficacy [52]. This finding, along with the results of TCGA in bladder cancer, has led to a paradigm shift in research efforts, which now focus on finding targetable molecular alterations, hoping to result in effective, individualized therapy. Several ongoing trials are exploring PI3K/AKT/mTOR in patients with metastatic urothelial cancer (Table 3). In general, these trials are not selecting patients for enrollment based on genotype and highlight the challenges in identifying optimal predictive biomarkers for targeting this pathway.

Phase	Agent	Population	NCT number	Status mTOR
I/II	Temsirolimus+cisplatine/gemcitabine	First line chemo-naive	NCT01090466	completed
I	Everolimus+ cisplatine/gemcitabine	First line chemo-naive	NCT01182168	Active,not recruiting

II	Everolimus+paclitaxel	First line platinium ineligible	NCT01215136	completed
II	Buparlisib	Second line and beyond	NCT01551030	Ongoing, not recruiting

Table 3: Clinical trials targeting the PI3K/AKT/mTOR pathway.

C-Immunotherapy

Current evidence suggests that malignant cells have tumor-specific antigens that are recognized and targeted by the immune system [53]. Treg cells inhibit tumor-specific T cells as they produce IL-10, TGF and express cytotoxic T-lymphocyte-associated antigen (CTLA-4) and programmed cell death ligand 1(PD-L1) [54].

The first FDA-approved immune checkpoint inhibitor was ipilimumab, a monoclonal antibody targeting CTLA-4 which demonstrated a survival benefit in patients with metastatic melanoma. A Phase II trial of chemotherapy and CTLA-4 blockade for patients with metastatic urothelial cancer has completed enrollment and preliminary results demonstrated immunomodulatory effects measured in the peripheral blood of patients after the addition of ipilimumab compared with chemotherapy alone (NCT01524991) [55]. Studies combining CTLA4 blockade, with PD1 and/or PDL1 blockade, in patients with metastatic urothelial cancer are ongoing (Figure 2) [56].

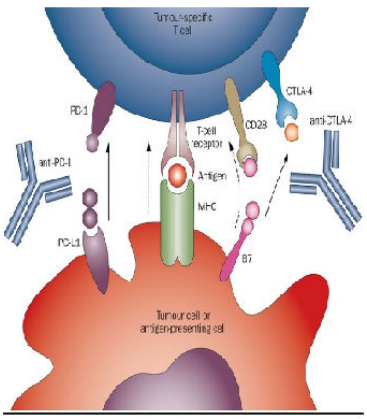

Figure 2: Mechanism of action of immunotherapy.

Anti-PD1/PDL-1 therapies

Atezolizumab (MPDL3280A) is a monoclonal antibody that blocks the interaction of PD-L1 with PD-1 and B7-H1. In an expansion cohort in the Phase I study, patients with chemotherapy refractory metastatic urothelial cancer were enrolled. Tumors were tested for the presence of PD-L1 expression on tumor-infiltrating immune cells which was correlated with outcomes. The ORR for patients with PD-L1 IHC 2/3 was 52%, highly encouraging for this heavily pretreated group of patients [57].

Atezolizumab was well tolerated and only 4% of treatment related adverse events. Based on the results from this trial, atezolizumab was granted accelerated approval by the United States FDA as the first PD-L1 inhibitor for the treatment of patients with mUC who were previously treated with platinum-based chemotherapy [58].

A phase II trial (IMvigor 210), multicenter, single-arm two cohort study assessed the efficacy and safety of atezolizumab 1200 mg every 3 weeks in patients with inoperable locally advanced or metastatic UC. Cohort 1 included cisplatin unfit patients who had not received previous treatment in the metastatic setting or had progressed at least 12 months since completing prior perioperative chemotherapy. Cohort 2 enrolled patients with locally advanced or metastatic urothelial carcinoma whose disease had progressed during or following platinum-based chemotherapy [57].

The authors concluded that atezolizumab was well tolerated and has the potential as a new standard of care (SOC) as first line for cisplatin unfit patients [58]. The cohort 2 results of IMvigor 210 were published, 316 patients who had progressed during or following platinum-based chemotherapy received atezolizumab. The median OS was 7.9 months for the entire cohort of patients; 11.4 months in IHC2/3 group and 8.8 months in the IHC1/3 group. Adverse events of any grade occurred in 69% of patients, with 16% of patients experiencing grades ¾ consisting most often of fatigue in 5 (2%) patient.

Pembrolizumab, an anti-PD-1 monoclonal antibody, has been studied in a cohort of patients with recurrent or metastatic urothelial cancer in the context of an expansion cohort of a Phase I study. This study enrolled only patients with PD-L1 expression in either tumor cells (defined as expression in at least 1% of cells) or tumor infiltrating cells. Three out of 29 (10%) were complete responders and four (14%) achieved a PR; PFS was 8-9 weeks and median OS was 9.3 months [59,60]. Currently, a phase II trial is evaluating the efficacy and safety of pembrolizumab in first line for advanced/metastatic unfit UC patients (NCT02335424). Additionally, a phase III trial comparing pembrolizumab versus chemotherapy (taxanes or vinflunine) second line for patients who have progressed following platinum-based has recently completed accrual (NCT02256436).

Avelumab is a fully human IgG1 monoclonal antibody against PD-L1 [61]. The results of the Phase I study of avelumab, (MSB0010718C), an anti-PD-L1 agent in patients with refractory urothelial cancer (NCT01772004) were presented at 2015 European Society of Medical Oncology Symposium. Avelumab is distinguished from the other antibodies in that it retains the potential for antibody-dependent cell-mediated cytotoxicity which could theoretically augment antitumor activity. Among 44 patients, responses were observed in 15.9% of patients (n=7), with one CR and six PR. The proportion of patients alive and progression-free at 12 weeks was 47.2%.

Nivolumab is a fully human IgG4 monoclonal antibody directed against PD-1 that is currently approved for metastatic kidney cancer that has failed prior VEGF therapy [62,63]. In data presented at ASCO

2016, Sharma P, et al. reported the results from phase I/II Checkmate 032 study of nivolumab monotherapy in metastatic UC. Seventy-eight patients were treated without regard to PD-L1 expression levels in tumor samples, 65.4% had received ≥ 2 prior therapies.

PD-L1 expression was determined on TC by Dako PD-L1 IHC 28-8 pharmDx kit. Grade 3/4 adverse events were increased lipase (3.8%), increased amylase (3.8%), fatigue (2.6%), neutropenia (2.6%) and dyspnea (2.6%) ORR was 24.4% in 78 response-evaluable patients. Median PFS was 2.8 mo and median OS was not reached [64]. There is currently ongoing phase II for patients with metastatic UC who have progressed to first-line chemotherapy (NCT02387996) and the results are awaited (Table 4).

Phase	Agent	Population	NCT number	Status
I	Avelumab	Second line and beyond	NCT01772004	Recruiting
I	Pembrozilumab and docetaxel or gemcitabine	Second line and beyond	NCT02437370	Recruiting
I	Cabozantinib+nivolumab+ ipilimumab	Second line and beyond	NCT02496208	Recruiting
II	Atezolizumab	First line chemo naïve and platinum ineligible , second line and beyond	NCT02108652	Ongoing but not Recruiting
II	APC-196+pembrolizumab	Second line and beyond	NCT02351739	Recruiting
II	pembrolizumab	First line platinum ineligible	NCT02335424	Recruiting
II	pembrolizumab	Maintenance after chemotherapy	NCT02500121	Recruiting
I	Pembrolizumab+ramucirumab	Second line and beyond	NCT02443324	Recruiting
II	Nivolumab	Second line and beyond	NCT02387996	Recruiting
III	MPDL3280A *vs.* chemotherapy	Second line and beyond	NCT02302807	Recruiting
III	Pembrolizumab *vs.* chemotherapy	Second line and beyond	NCT02256436	Ongoing, but not Recruiting

Table 4: Clinical trials Immune checkpoint blockade in utothelial cancer.

Recent data describing the immunoinhibitory pathways that are upregulated in cancer enabled a better understanding of the mechanisms by the tumors evade immune attack. New agents of immunotherapy are at various stages of clinical development, these drugs may directly stimulate cytotoxic T cells, block tumor expressed immunoinhibitory factors, inhibit Treg cells, block the inhibition of natural killer cell activity or block the activity of soluble factors [64]. Thus, these kinds of newer immunotherapies are now been explored in clinical trials as single agents or in combinations with checkpoints inhibitors.

Conclusion

Metastatic UC is a lethal disease, and platinum-based chemotherapy remains the standard of care in first-line therapy. Several news drugs have been tested as second-line therapy without improved overall survival.

After decades without substantial advances in the clinic in patients with metastatic urothelial cancer, the future is looking brighter. Atezolizumab is approved for the treatment of patients with locally advanced or metastatic urothelial carcinoma whose disease has worsened during or following platinum-containing chemotherapy or within 12 months of receiving platinum containing chemotherapy.

Immune checkpoint blockade is poised to change the treatment paradigm and serve as a new foundation on which to build. There remains no standard treatment although progress is being made with an acceleration of clinical trials in recent years. With this acceleration come the importance of appropriate clinical trial design and the importance of selecting enriched populations that are most likely to benefit from each therapy.

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