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Original Research Article

Update of therapies in metastatic urothelial carcinoma

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ABSTRACT

The prognosis of metastatic urothelial carcinoma (mUC) is poor, with a median overall survival of about 14 months. Platinum-based chemotherapy has been standard for first-line treatment of mUC for a long time, but there is still no predictive biomarker to help guide treatment and select patients most likely to derive benefit from these regimen. Recent advances in immunotherapy has changed the landscape of mUC, with significant improvement in overall survival among responsible patients. Moreover, the advent of next-generation sequencing has resulted in both an improved understanding of the fundamental genetic changes that characterize mUC and identification of several potential biomarkers and therapies. Within this review, we summarized these emerging novel immunotherapy and targeted therapy, which may improve or have improved the outcomes of mUC.

Keywords: metastatic urothelial carcinoma; immunotherapy; targeted therapy

The treatment of metastatic urothelial carcinoma (muc) is mainly chemotherapy, and there has been no breakthrough in the treatment for decades [1,2]. However, in recent years, with the development of programmed cell death protein 1(programmed cell death protein 1, The checkpoint inhibitor (CPI) immunotherapy represented by PD–1)/ programmed death protein ligand 1 (PD-L1) broke the deadlock, and many other important targets were found, which made the therapy of muc show a rapid development trend. In this paper, the main immunotherapy and targeted therapy related clinical research of muc are reviewed.

1. Immunotherapy

Since April 2016, FDA has approved five kinds of PD–1/PD-L1 monoclonal antibodies, namely Atezolizumab, Nivolumab, Durvalumab, Avelumab and Pembrolizumab, for second-line treatment of advanced bladder cancer. In addition, pembrolizumab was approved for first-line treatment of patients who could not tolerate cisplatin chemotherapy, which

opened a new chapter in the treatment of advanced bladder urothelial cancer.

1.1 Second-line immunotherapy

Pembrolizumab

Pembrolizumab is an anti-PD–1 monoclonal antibody, and KEYNOTE–045 study [3] is the first phase III clinical study in which Pembrolizumab is compared with chemotherapy (paclitaxel, docetaxel, or vinflunine) for muc patients with advanced platinum chemotherapy. It is also a drug with class I evidence-based medical evidence that PD–1 monoclonal antibody is used for advanced bladder urothelial cancer. The results showed that Pembrolizumab benefited significantly. Compared with the chemotherapy group, the median overall survival (mos) of patients in Pembrolizumab treatment group was 10.3 months: 7.4 months, and the median progression-free survival (median survival-ival, MPFS) was 3.3 months: 2.1 months, and the objective response rate (ORR) was 21.1%:11.4%. The median response time in the treatment group of Pembrolizumab was 4.4 months in the chemotherapy group, and the ratio of patients with sustained response time longer than 12 months in the two groups was 68%:35% respectively. Based on this clinical study, FDA has approved Pembrolizumab in May 2017 for second-line treatment of advanced bladder urothelial cancer after the failure of platinum therapy.

Atezolizumab

Atezolizumab, the first monoclonal antibody against PD-L1, was accelerated approved by the FDA for second-line treatment of advanced bladder cancer in April 2016. The key registry was obtained from the imvigor210 study [4], which enrolled muc patients after failure of platinum-based chemotherapy. The results showed that the ORR of all patients was 15%, the complete response (CR) rate was 5%, and the mos was 7.9 months. At a median follow-up of 11.7 months, 84% of patients who responded to treatment remained in sustained response, a benefit unprecedented in the era of chemotherapy. In IC2/3 patients (PD-L1 expression > 5%), ORR was 27%, CR rate was 11%, and mos was 11.4 months.

The phase III imvigor211 study of Atezolizumab versus conventional chemotherapy (paclitaxel, docetaxel, and vinflunine) was subsequently conducted after failure of platinum-based treatment with muc [5]. The results showed that there was no significant difference in mos between the two treatment groups in IC2/3 patients (11.1 months vs. 10.6 months, HR = 0.87, P = 0.41).

Nivolumab

Nivolumab was a PD–1 mab, and the CHEKMATE032 study [6] was a phase □/□ clinical study of Nivolumab treatment progression after previous platinum-based chemotherapy. Seventy-eight patients received Nivolumab monotherapy, ORR was 24.4%, mpfs was 2.8 months. The median response duration was 9.4 months and mos was 9.72 months. The ORR of PD-L1 positive (≥ 1%) and negative (< 1%) patients was 24% and 26%, and mos was 16.2 months and 9.9 months, respectively. The incidence of grade 3/4 drug-related adverse events was 22%, the most common were increased lipase level (5%), increased amylase level (4%), fatigue, maculopapular rash, dyspnea, lymphocytopenia, neutropenia, etc. Subsequently, the Checkmate 275 study [7] enrolled 270 muc patients who had failed platinum-based therapy. The median follow-up time was 7.0 months, and the overall confirmed ORR was 19.6%. ORR of patients with PD-L1 expression above 5%, above 1% and less than 1% were 28.4%, 23.8% and 16.1%, respectively. MOS was 8.7 months, and the mos of patients with PD-L1 expression above 1% and less than 1% were 11.3 months and 5.95 months, respectively.

Durvalumab

Durvalumab is a PD-L1 mab. The second-line data of Durvalumab in the treatment of advanced bladder urothelial carcinoma were obtained from a phase □/□ clinical study [8], which enrolled 191 patients with local progression or muc who had progressed after previous platinum-based chemotherapy, and the results showed that the ORR assessed by the center was 17.8%. The ORR of patients with high PD-L1 expression was 27.6%, while the

ORR of patients with low or negative PD-L1 expression was 5.1%. MPFS and mos were 1.5 months and 18.2 months, respectively, and the 1-year survival rate was 55%.

Avelumab

Avelumab, a PD-L1 mab, was initially reported in a multicenter phase □B clinical trial for advanced bladder urothelial carcinoma after platinum-based therapy failed. A total of 44 patients received Avelumab, with a confirmed ORR of 18.2%, mpfs of 11.6 weeks, mos of 13.7 months, and 1-year survival of 54.3%. For patients with positive expression of PD-L1 (tumor cell staining ≥ 5%), mpfs was 48.1 weeks and mos did not arrive, which were better than those with negative expression of PD-L1 [9].

Other drugs

Although some patients with muc who are treated with CPI achieve durable responses, the majority of patients will acquire resistance and eventually progress, which requires the discovery of other novel immunotherapies. Indoleamine–2, 3-dioxygenase (IDO) pathway acts on tryptophan metabolism. The depletion of this essential amino acid can promote the function reduction of effector T cells, proliferation of regulatory T cells, and eventually lead to tumor escape. IDO upregulation can be found in a variety of solid tumors treated with CPI, and IDO alone or in combination with CPI can further activate the immune system [10].

Bms–986205, a selective and potent IDO inhibitor, had an ORR of 34% and a disease control rate (DCR) of 48% in 29 muc patients treated with Nivolumab in a phase I/II study of multiline failed solid tumors. Among the 26 patients who had not previously received CPI, the ORR was 38%. Fifteen patients had PD-L1 expression ≥ 1%, and the ORR was 47%. The expression of PD-L1 was less than 1% in 11 cases, and the ORR was 27%[11]. In another phase □/□ study, Epacadostat (IDO inhibitor) combined with Pembrolizumab was used to treat cisplatin resistant muc patients, with an ORR of 35%[12].

1.2 First-line immunotherapy

The KEYNOTE–052 study [13] was a single-arm, phase II clinical study that used Pembrolizumab as first-line treatment for muc. The screening criteria for this study were cisplatin intolerance. [Eastern Cooperative Oncology Group, ECOG score was 2, 30 ml/min ≤ creatinine clearance < 60 ml/min, grade 2 neuropathy/hearing impairment, New York Heart Association Cardiac function class 3], and had not received systemic chemotherapy before. A total of 370 patients were treated, with an ORR of 29%, a CR rate of 7%, and a clinical benefit rate of 47%. The median time to remission was 2 months, with a median follow-up of 8 months. 74% of patients had sustained remission, and the median duration of sustained remission was not reached. Based on this study, the FDA approved Pembrolizumab for first-line treatment in patients with muc who could not tolerate cisplatin.

The efficacy and safety data of Atezolizumab as first-line therapy for patients who could not tolerate platinum-based chemotherapy showed a median follow-up time of 14.4 months, an ORR of 23%, a CR rate of 9%, and a response rate of 28% in patients with PD-L1 positive tumor invasive immune cells (IC2/3). Slightly higher than those with negative PD-L1 expression (21%), the response rates for upper tract and bladder urothelial carcinoma were 42% and 17%, respectively. Secondary end point: the longest duration of efficacy was 18 months, and 75% (21/28) of the 28 patients with effective treatment had no progress up to the time of analysis, and mos had reached 15.9 months [14].

Although these studies showed a lower ORR than previous standard cisplatin-containing chemotherapy regimens (30% to 50%), the duration of efficacy was longer in patients who responded to immunotherapy. If these patients do not participate in the clinical study, most of them may adopt the chemotherapy regimen of replacing cisplatin with carboplatin or paclitaxel combined with gemcitabine. The mpfs was 4.2 to 6.5 months, and the mos was 10 to 14 months. However, the incidence of serious adverse reactions caused by chemotherapy reached 20% to 40%, leading to treatment interruption and poor

quality of life of patients. However, patients receiving immunotherapy such as PD–1/PD-L1 mab not only tolerate significantly better than these regimens of chemotherapy, but also have better efficacy data, which brings good news to these patients.

Based on these data, current National Comprehensive Cancer Network (NCCN) guidelines recommend Pembrolizumab and Atezolizumab for first-line treatment of advanced urothelial Cancer that cannot tolerate platinum-based chemotherapy.

1.3 Expression of PD-L1 protein

PD-L1 is a PD–1 binding ligand expressed in tumor cells and microenvironment, which is involved in immune suppression and immune escape, and is associated with poor prognosis. At present, from the perspective of clinical studies, PD-L1 mab data more support PD-L1 detection: Patients with positive PD-L1 expression benefited more from immunotherapy, and muc patients with high PD-L1 expression had higher ORR use of PD-L1 mab (54% vs. 4% for Avelumab and 28% vs. 5% for Durvalumab). However, some muc patients with low PD-L1 expression were also effective. Several clinical studies on PD–1 mab have shown that patients with PD-L1 expression do not have obvious advantages. In the imvigor 211 trial, Atezolizumab did not have a higher response rate than chemotherapy in patients with high PD-L1 expression. More importantly, PD-L1 expression changes dynamically, which is related to whether to be treated and the duration of treatment. PD-L1 expression in the microenvironment inside and around tumors is heterogeneous. In addition, the current detection methods of PD-L1 expression, the definition and cutoff values of positive values and the judgment of results have not been unified. Therefore, PD-L1 expression is not a biomarker for predicting the efficacy of bladder cancer immunotherapy in clinical practice.

1.4 Selection of immunotherapy drugs

Since Pembrolizumab is the only approved first-line treatment for advanced bladder cancer that does not tolerate platinum-based chemotherapy, there is no doubt about the choice of such patients. For second-line treatment of bladder cancer, the other four drugs can be selected. Besides evidence-based medicine, the positive KEYNOTE–045 study by Pembrolizumab was the only randomized, controlled, phase III study that supported a recommendation as class I evidence for second-line treatment of advanced bladder cancer. With awareness of serious adverse effects and early intervention, more patients may benefit from combined CPI regiments, but this needs to be confirmed by further clinical trials. In addition, more attention needs to be paid to the predictors of the efficacy of immunotherapy, that is, the dominant population of immunotherapy. Pd-l1 expression cannot be used as a basis to support the selection of immunotherapy at present, and new immune markers or selection models need to be further explored.

2. Targeted therapy

In recent years, with the deepening of genome research, many promising targets of urothelial carcinoma have been found, and anti-vascular tyrosine kinase inhibitor (Tyrosine kinase inhibitor) has also been tried. TKI or human epidermal growth factor receptor–2 (HER–2) target therapy, at present, there are fibroblast growth factor receptor (Figure) fibroblast growth factor receptor (Figure) with better clinical application prospects. In addition, antigen-drug conjugates (adcs) showed good tolerance and response rate, which provides a new direction for muc system therapy.

2.1 Figure inhibitors

Figure 3 plays an important role in tissue development, regeneration and angiogenesis. Abnormal Figure 3 signaling pathway can be observed in 80% of non-muscle-invasive urothelial carcinoma (UC) and 50% of invasive UC, manifested as mutation, overexpression or both [15]. Figure 3 mutations are as high as 15%–20% in muc, and are mostly found in immunologically "cold" tumors, namely luminal type 1 UC. Only about 5% of ORR are treated with CPI. Figure inhibitors may be a promising treatment

for these patients [16].

The BLC2001 study [17] was a single-arm phase II study of Erdafitinib (an inhibitor of Figure 1–4) for the treatment of muc in patients with Figure variants, who had previously received at least first-line chemotherapy, or who could not tolerate platinum-based chemotherapy. The 2018 annual meeting of the American Society of Clinical Oncology (ASCO) presented preliminary data on Erdafitinib fitinib 8 mg, once daily continuous administration regimen, with a total of 99 patients enrolled. The median age was 68 years, 80% of patients had visceral metastases, 43% had previously received more than first-line systemic therapy, and 75% had Figure 3 mutations. The results showed that the independently assessed ORR was 42%, with a CR rate of 3% and a partial response (PR) rate of 39%. The median onset time was 1.4 months for DCR, 5.5 months for mpfs, and 13.8 months for mos. Of note, the ORR was as high as 59% in 21 patients previously treated with CPI. In terms of safety, the main adverse events were grade 1 to 2, including hyperphosphatemia (73%), mucositis (55%), dry mouth (43%), diarrhea (37%), taste disorders (35%), etc. No treatmentrelated grade 4 to 5 adverse events were observed, and 10% of patients discontinued the drug due to adverse reactions.

In a phase I trial evaluating the efficacy of the Figure inhibitor regorafenib, 219 patients were screened and 99 had Figure 1–3 mrna expression, with 87% Figure 3 mrna and 5% Figure 1 mrna. 8% had double Figure mrna expression (Figure 1/2, 1/3, or 2/3). Figure 3 activation mutations accounted for 7% and all had high Figure 3 mrna expression. Fifty-one patients were evaluated for efficacy, with an ORR of 24% (all PR) and a DCR of 73%. Twelve patients with hot spot mutations in genes encoding PIK3CA or RAS did not achieve PR, and seven of 14 patients with progressive disease (PD) carried these mutations. The ORR of PIK3CA/RAS wild-type patients was 30.6%. The ORR and DCR of 10 patients previously treated with CPI were 30% and 80%, respectively [18]. We conclude that it is feasible to select beneficiaries of regorafenib based on Figure mrna expression level, which has a good safety profile and promising antitumor activity, but need to exclude patients with PIK3CA/RAS mutations.

Other Figure inhibitors include BGJ398[19]. In phase □ trial, the ORR of muc patients with Figure 3 mutation/fusion who failed cisplatin therapy also reached 36%, and most of the adverse reactions were grade 1–2.

Compared with current immunotherapy and chemotherapy, the efficacy of Figure inhibitors has been significantly improved. Of course, this needs to be further confirmed by phase III controlled clinical trials. However, the current efficacy data are sufficient to support the treatment of these patients with targeted anti-Figure therapy. The FDA has granted breakthrough therapy accreditation and is expected to approve it soon, which will usher in a new era of targeted therapy for advanced bladder cancer.

2.2 Antibody-coupled drugs

ADC is a novel drug that combines monoclonal antibodies targeting tumor cells with active substances that can produce cytotoxicity. The ideal ADC targets tumor specific antigens and can specifically act on tumor cells to avoid or reduce drug exposure to normal cells.

In the phase □ clinical trial of EV–101 [20], Enfortumab Vedotin (EV) was well tolerated and showed good effect. Evs consist of monoclonal antibodies to Nectin–4, a common molecule on the surface of muc, and MMAE, a microtubule destructor. A total of 112 patients with tumors previously treated with CPI-containing chemotherapy were enrolled, including 84 patients (75%) with bladder cancer and 32 patients (29%) with liver metastases. 81% of patients had received cisplatin chemotherapy and 75% of patients had received CPI. ORR was 33%, CR in 3 cases, PR in 33 cases, and unconfirmed PR in 8 cases. The ORR in each subgroup was 32% (previous CPI treatment, 84 patients), 37% (no previous CPI treatment, 27 patients), and 26% (liver metastasis/previous CPI treatment, 23 patients). The most

common adverse events were fatigue (50%), and the most common adverse events greater than grade were anemia (7%), hyponatremia (6%), urinary tract infection (6%) and hyperlipidemia (5%). Based on these results, the EV–201 trial (NCT03219333, muc after failure of EV treatment for CPI) is ongoing.

Sacituzumabgovitecan[21] is another ADC conjugated with a monoclonal antibody TROP–2 and SN–38, the active metabolite of irinotecan. In a phase / trial after cisplatin regimen or CPI progression [20], the mpfs of all patients was 7.1 months, the mos was 16.1 months, and the ORR was as high as 36%, including 2 patients with CR. 80% of the patients had received previous multiline therapy, the mpfs was 6.9 months, the mos was 15.5 months, and the ORR was up to 30%. 34% of the patients had been treated with CPI, 5.4 months mpfs, no mos, and 29% ORR. It was well tolerated except for grade neutropenia, which accounted for 16%.

A phase II multi-center clinical study of HER–2 antibody coupled drug RC48-ADC in the treatment of advanced bladder cancer has been launched in China by Peking University Cancer Hospital, and the preliminary efficacy data are surprising. Therefore, drug therapy in the future in the field of advanced bladder urothelial cancer will obtain rapid development.

2.3 Antiangiogenic inhibitors

Upregulation of vascular growth factor (VEGF) receptor is associated with aggressive UC subtypes. Blocking the connection between VEGF protein and blood vessels helps to inhibit tumor growth by slowing angiogenesis and blood supply to donor tumors. Among the three known VEGF receptors, VEGF receptor 2 is closely related to VEGF-induced tumor vasculogenesis, and blocking this pathway may obtain survival benefits [22].

The RANG trial [23] was a multicenter, randomized, double-blind phase III study to evaluate the safety and efficacy of docetaxel in combination with Ramucirumab or placebo in patients with muc who had failed cisplatin treatment. The primary end point was met: patients in the docetaxel plus Ramucirumab group had a significant PFS benefit (4.1 months vs. 2.8 months, HR = 0.75, P = 0.0118) and an ORR of 24.5% (PR rate 20.4%, CR rate 4.2%). ORR was 14% (PR 1.4%, CR 4.2%) in the docetaxel monotherapy group. The proportion of patients in the trial who had previously received CPI was small, only 7% and 10%, respectively, and long-term OS data are also pending. The 2018 ASCO Annual Meeting reported the Asian population data of this study (110 cases). The PFS of patients in the combined treatment group was 3.0 months, which was comparable to the total intention-to-treat population, and the ORR was 26.4%, higher than that in the docetaxel monotherapy group (15.8%) [24]. This is the only randomized controlled phase III trial with positive results from chemotherapy combined with antiangiogenic inhibitors, but the data have been limited, so it may be an attempt for patients who do not respond to immunotherapy.

2.4 Targeted therapy for HER–2

The overexpression of human epidermal growth factor receptor (EGFR) family is associated with cell proliferation and apoptosis. EGFR1 and EGFR2 (HER–2) play important roles in bladder cancer cell proliferation and are potential therapeutic targets.

Trastuzumab is a monoclonal antibody against HER–2, which is used in combination with gemcitabine, paclitaxel and cisplatin to treat HER–2 positive muc patients [25], with an ORR of up to 70% and a mos of 14.1 months. However, another phase II trial found no significant improvement in survival in patients treated with gemcitabine and cisplatin combined with trastuzumab [26]. Lapatinib (double blocking of EGFR and HER–2) as a single agent in the second-line treatment of muc showed a lower benefit in the high EGFR expression group than in the low EGFR expression group (mos = 30 weeks: 17.9 weeks) [27], but lapatinib maintenance treatment after first-line chemotherapy showed no benefit [28].

In a phase II trial, 23 muc patients who had failed cisplatin therapy and were treated with afatinib, an EGFR and HER–2 inhibitor, were tested for

HER–2/HER–3 mutations by quantitative polymerase chain reaction or fluorescence in situ hybridization. The mpfs of patients with mutation and negative group was 6.6 months: 1.4 months [29]. These experiments suggest that screening HER mutation patients by gene amplification may be a better way to predict the therapeutic effect of muc than immunohistochemistry. A phase II trial of EGFR mutation muc that failed to be treated with alfatinib is underway.

3. Combination therapy of immunization and targeting

A phase I trial evaluated the safety and efficacy of cabotinib combined with Nivolumab(cabonivo) or cabotinib combined with nivolumab+inotuzumab (cabonivoipi) in muc. The results showed that the ORR of patients in cabonivo group was 50% and mpfs was 24.1 months. While in cabonivoipi group, ORR was 33% and mpfs was 10.1 months. Therefore, cabonivo regimen and cabonivoipi regimen have good tolerance and anti-tumor effect.

4. Summary

For many years, the systematic treatment of muc has been at a standstill. With the emergence of CPI and new targeted drugs, its blueprint for treatment has changed dramatically. Cisplatin-based chemotherapy is still the standard treatment for muc, but it is urgent to find effective biomarkers to screen patients who are sensitive to cisplatin, CPI and new targeted drugs. Although many biomarkers with clinical prospects have been found at present, they still need to be confirmed by clinical trials before clinical application. With the deepening of the understanding of UC biology at molecular level, more and more biomarkers and targeted therapies, such as Figure inhibitors, angiogenesis inhibitors, HER–2 inhibitors, mtor inhibitors, etc., will appear. ADC and combined therapy will also be the direction of further research. The drug treatment of muc is full of prospects, and the curative effect and prognosis of patients will be improved as a whole.

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