

Single Drug Therapy of PD-1/PD-L1 Checkpoint Inhibitors for Advanced Urothelial Bladder Cancer

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Abstract. Since the first approval of Atezolizumab in May 2016, immunotherapy, PD-1/PD-L has completely changed the way bladder cancer is treated, as chemotherapy was the sole available choice as a treatment for bladder cancer, and the results still was not optimistic, with five licensed drugs treating bladder cancer. Despite the generally poor prognosis of advanced bladder cancer, some patients show persistent responses to immune checkpoint inhibitors. This review summarizes the efficacies and safety of the five drugs: Durvalumab, Atezolizumab, Avelumab and other drugs - from different studies respectively for treating advanced bladder cancer and mentions the side effects and future perspectives. For the treatment, all inhibitors that was licensed have akin efficacy and safety traits, but they differ in terms of dosage, frequency, and financial burden. Only Pembrolizumab, to date, has revealed advantage over conventional chemotherapy in a stochastic Phase III scenario. Pembrolizumab and Atezolizumab are also well tolerated and approved for patients who are unable to receive cisplatin treatment. Patients with bladder cancer now have some hope, thanks to immunotherapy. The current environment is continuously evolving, and new immunotherapy-combination trials are being conducted to further enhance results.

Keywords: PD-1/PD-L1, Checkpoint Inhibitors, Advanced Urothelial, Bladder Cancer, Immunotherapy.

1. Introduction

Bladder cancer (BC) is malignant cancers recognized by medical professionals around the world. Urothelial bladder cancer (UBC), also known as urothelial carcinoma, is the most common bladder cancer. A total of 4.7% of all cancers diagnosed in the USA are bladder cancers. The number of bladder cancer cases and fatalities in the US in 2017 was projected at 79,030 and 16,870, respectively. The bladder accounts for 90% of occurrences of urothelial carcinoma (UC). After transurethral resection, up to 50% of NMIBC patients experienced disease recurrence, and after numerous recurrences, up to 25% of the patients developed muscle-invasive diseases.

Immune checkpoint inhibitors (ICIs) are a common treatment choice for many solid cancers nowadays. Before the treatment of ICIs, systemically chemotherapy utilizing cisplatin-based ways was gold criterion of treatment, with a median survival time of roughly one year. The median survival for patients who had platinum-refractory malignancy was just a few months. Furthermore, comorbidities prevent about 50% of patients with mUC from receiving cisplatin, which limits the range of available therapies. The only options up until recently were carboplatin-based regimens, and clinical outcomes did not significantly improve [1]. High PD-L1 expression levels have been linked to aggressive bladder cancer tumours that progress and have a bad prognosis. Immunohistochemistry-detected PD-L1 expression seems to be linked to intravesical Bacillus Calmette-Guerin (BCG) therapeutic resistance. ICIs have shown a better benefit in cancers with a high tumour mutational burden (TMB) and significant CD8 immune cell infiltration, such as bladder cancer. The mechanism is linked to an improved antitumor immune response caused by more readily available neoantigens, which induce a more robust T cell-mediated antitumor immune response. After a long hiatus of more than 40 years, researchers have achieved enormous strides in the treatment of UC with the approval

of numerous inhibitors in metastatic UC. In order to further enhance results in different stages of UC. The effect of combination therapy of PD-1/PD-L1 inhibitors with multiple drugs is currently being explored. Due to findings from a phase II trial that showed increased response rates, Atezolizumab was granted in May 2016. Following this, all Pembrolizumab, Durvalumab, Nivolumab, and Avelumab have demonstrated therapeutic effectiveness in mUC, and as a result, these drugs have all been approved by the FDA following several clinical trials that revealed significant variations in response to ICI compared to chemotherapy. Though ICIs are effective as a treatment for metastatic urothelial bladder cancer, only a tiny percentage of those who receive treatment will experience a noticeable benefit. In contrast, many patients will experience possibly harmful toxicity and side effects without experiencing any improvement in the aspect of survival rate or the quality of life. At this time, no single biomarker has been connected to a response [1]. This review discusses the current relationship between immune checkpoint inhibitor therapy. A brief overview of the possible benefits of ICIs is provided as well. Lastly, a brief assessment of the function of anti-PD-L1 immunohistochemistry and other possible immune checkpoint inhibitor prediction biomarkers is provided.

2. PD-1/PD-L1 Checkpoint Inhibitors

2.1. History/Development

In 1992, PD-1 was identified in T cells that regulate immunological responses to human body cells encouraging self-tolerance by inhibiting T-cell inflammatory activity. Professors Honjo and Freeman, who discovered PD-1, discovered that PD-L1 is one of the PD-1 ligands that limit T-cell proliferation and produce cytokines by binding to PD-1. PD-L1 checkpoint inhibitors can prevent the binding of PD-L1 to its receptor PD-1. In 2006, the first medical medicine designed to block these molecules, Nivolumab (Opdivo), was introduced. These cell surface proteins can impede the immune system's ability to prevent the destruction of its associated cells. Immune checkpoint inhibitors' development has altered the standard for the treatment of advanced malignancies of several tumour types [2]. The majority of patients do not respond, despite others showing positive and occasionally long-lasting results. Tumours have acquired the PD-1/PD-L1 axis for immune evasion in order to promote tumour growth; this axis is a possible target for immune checkpoint drugs.

2.2. Mechanism of PD-1/PD-L1 Checkpoint Inhibitors

PD-1 is a protein present on T cells (a kind of immune cell) that regulate self-tolerance. PD-1 is an immunological checkpoint that prevents autoimmunity via two methods. First, T cells specific to lymph node antigens are thus trained to commit suicide. Second, it inhibits T regulatory cell (anti-inflammatory, suppressive T cells) death [3]. Figure 1 demonstrates that PD-1 binds not one but two ligands: PD-L1 and PD-L2. The former and PD-1 interact to block the immune system from targeting tumour cells by forming receptor-ligand complexes in the tumour microenvironment.



Figure 1. PD-1 Binding with PD-L1/L2 Ligands

When PD-1 and PD-L1 are connected, T lymphocytes are prevented from destroying other cells, particularly cancer cells [4]. The interaction between it, PD-1 is stopped by the medications known as PD-1/PD-L1. By inhibiting the immune system's ability to govern the death of its related cells,

these cell surface proteins contribute to preventing autoimmune diseases. This immunological checkpoint is also active in some types of cancer, during pregnancy, and after tissue donation [5]. PD-1 is expressed mainly on immune system T cells, while PD-L1 is predominantly expressed on neoplastic and antigen-presenting cells. Restoring the antitumor immune response triggered by T cells requires using inhibitors that prevent the interaction. The idea of using PD-1 and PD-L1 suppression as a treatment for cancer was not first proposed by researchers until 2001 [6]. Six therapeutic antibodies licensed to target PD-1/PD-L1 have shown exceptional clinical improvements in certain cancer types. These antibodies include Atezolizumab, Cemiplimab, Nivolumab, Avelumab, Pembrolizumab, and Durvalumab. Plans for the future include the creation of even more mAbs. Despite their rapid development, their use is limited by factors such as high production expense, low tissue penetration, and intracellular target inaccessibility. Therefore, inhibiting the interaction while minimizing the risk of deleterious effects may offer a novel approach to treating tumour. The interaction triggers the death of tumour-specific T lymphocytes and increases tumour cell resistance to cytotoxic T lymphocyte (CTL) assault, all while lowering T lymphocyte proliferation, survivability, and effector activities. It is possible for CD28 or IL-2 to reverse the deleterious impact that PD-1 has on T cells. In contrast to PD-1, which generally suppresses Akt activation, IL-2 increases Akt via STAT5, permitting regular Akt activity.

CTLA4 inhibits Akt phosphorylation rather than inhibiting PI3K activation via activating the phosphatase PP2A. Comparing the inhibitory effects of anti-CTLA4 and anti-PD-1 Ab on gene expression in T cells revealed that PD-1 was more effective in inhibiting the generation of mRNA and protein. Importantly, study indicated that only PD-1 interaction can hasten T cell death. Along this pathway, signals controlling the tolerance are delivered. The thymic cortex, thymocytes, and medulla all show evidence of their expression. PD-L1 participates in both positive and negative selection in the thymus. Expression of PD-L1 and PD-L2 on tolerogenic dendritic cells inhibits the formation and early activation of self-reactive T cells. T cell proliferation, effector activity, and reactivation are all inhibited by PD-1. Though the significant biological role of anti-PD-1 antibodies is to reawaken latent CD8⁺ T cells in patients with persistent viral infections or cancers, the antibody exerts additional, intriguing effects on other cell types potentially. It restores antibody titers in macaques infected with SIV by reducing the loss of activated memory B cells. By interacting with follicular T helper cells, germinal centre PD-L1 and PD-L1-expressing B cells regulate the formation of memory B cells. When PD-1 signalling was blocked, the formation of plasma cells with a long lifespan was significantly reduced. The level of PD-1 on Tregs was boosted. Sharpe et al. shown that PD-L1Ig, when paired with anti-CD3 Ab and TGF- β , can dramatically accelerate the de novo generation of iTregs from non-activated CD4⁺ T cells. During PD, sustained L1-Ig interaction with Foxp3⁺ iTregs led to sustained expression of Foxp3 and increased suppressive activity. The basic mechanics have been deciphered by the research teams of Haxhinasto et al. It is possible that there is a connection between the PD-1/PD-L1 axis and decreased levels of NK cell activity in animals that have malignancies. Recombinant or tumour-derived IL-18 can enhance immature NK cells in lymphoid organs where cancer has metastasized. These KIT⁺ NK cells rely on PD-1/PD-L1 to destroy DC in lymph nodes, and they overexpress B7-H1/PD-L1, LAG3, and CTLA4. This indicates that stopping the PD-L1/PD-1 pathway results in a significant reduction in the metastatic potential of nu/nu animals. These findings suggest, at least in mice, that immature NK cells from a third party can regulate the DC/NK cell interaction that promotes the activation of mature (effector) NK cells. This is the case even though the research was conducted on mice. There is a lack of clarity regarding whether or not this is relevant to the human body [7].

3. PD-L1 checkpoint inhibitors therapy for bladder cancer

3.1. Pembrolizumab in advanced UC

In a new study [8], patients who had previously received treatment for advanced, recurrent UC were compared to the efficacy of Pembrolizumab and investigator-selected chemotherapy. In this

study, patients received either standard-of-care chemotherapy with only one agent (272 patients) or Pembrolizumab (270 patients). The results showed that an OS with patients receiving pembrolizumab was 10.3 months and the control group 7.4 months. In the total selected population, pembrolizumab had an ORR of 21.1% vs. 11.4%. In individuals with advanced UC, the survival effect was shown regardless of PD-L1 expression. Additionally, patients using pembrolizumab had fewer major adverse events (grades 3-4) than those receiving chemotherapy. Pembrolizumab reduced the frequency of adverse events, however pruritus and other immune-mediated AEs such as pneumonitis (4% vs. 0.4%) were common [9].

3.2. Nivolumab in advanced UC for progression or recurrent on platinum

The Checkmate-032 [10], a recent study, examined Nivolumab therapy for recurrent metastatic UC. In this study, OS was 9.7 months for the total population, and ORR was 24%. The median PFS was 2.8 months and 5.5 months in the total population and PD-L1 expression was more than 1% in the subgroup, respectively. The severe adverse effects occurred in 21.8% of patients, with increased lipase (5.1%), fatigue, reduced neutrophils, and dyspnoea occurring in 2.6% of cases each. Efficacies of Nivolumab in the second-line treatment of advanced UC after platinum-based chemotherapy were shown in this trial as evidence of clinical practice. However, the variation of PD-L1 expression in tumour cells alone was not correlated with ORR.

3.3. Atezolizumab in advanced UC for progression or recurrent on platinum

The IMvigor study [11], an open-label, multicohort study. Cohort 2 of the phase 3 IMvigor 211 trial showed that Atezolizumab resulted in an ORR of 13.4% for all patients and a 22.8% ORR in patients with >5% PD-L1. However, the groups did not differ statistically significantly from one another receiving chemotherapy and Atezolizumab in the primary efficacy analysis of the IC2/3 subgroup for the OS. The median PFS was 2.1 months in the total population and 2.4 months in patients with PD-L1 expressing tumour-infiltrating immune cells. In this phase 3 trial, fatigue (31%) and nausea (14%) were the most common adverse events. The IMvigor 211 study indicated that Atezolizumab is well tolerated and has an enduring remission rate compared to chemotherapy.

3.4. Durvalumab in advanced UC

In Study 1108 [12-13], the majority of patients was treatment-naïve or had advanced cancer during or after platinum-based chemotherapy. An ORR was 17.8% in total patients and 27.6% in the subgroup of >25% tumour cells expressing PD-L1. At six months, half of the subjects still had a response. Median PFS was 1.5 and 2.1 months and median OS was 18.2 and 20 months in the total population or PD-L1 25% tumour cell subgroup, respectively. 6.8% of patients experienced side effects of levels 3-4 from the treatment. Fatigue was the most prevalent adverse event and was observed in 19.4% of patients. In this dose-expansion cohort, Durvalumab showed preliminary safety and effectiveness.

3.5. Avelumab in advanced UC for progression or recurrent on platinum

In the JAVELIN study [14], Avelumab was given to 249 patients in all that were recruited, which was summarized in table 1. The majority of patients (98%) have received prior platinum-based treatment. Survival efficacy was assessed in a subgroup of patients with >5% PD-L1 expression. Among these, ORR was 24%, median PFS was 2.8 months and median OS was 8.2 months. Fatigue (16%), and infusion-related reactions (29%) represented the majority of adverse treatment-related occurrences. The main immune-mediated adverse events were rash (10%) and hypothyroidism (4%), which were observed in 14% of patients. The JAVELIN study demonstrated that Avelumab responses were more prevalent in PD-L1-expressing tumours, but responses were still found in other populations.

Table 1. Summary of the results from clinical trials using PD-1/PD-L1 inhibitors for patients with advanced or recurrent bladder cancer.

Agent	Selected population	Patients (N)	Efficacy outcomes	AE rate	Trial
Pembrolizumab	Advanced UC, Recurrence or Progression after platinum	542	ORR, 21%, mPFS, 2.1mo, OS, 10.3mo	Grade 3-4 AEs 15%, Pruritus=20% Fatigue=14% Nausea=11% Diarrhea=9%	KEYNOTE-045
Nivolumab	Advanced UC, Recurrence or Progression after platinum	78	ORR 24.4% mPFS 2.8mo mOS 9.7mo	Grade 3-4 AEs 22%, Increased lipase=5.1% Increased amylase=3.8 % Fatigue=2.6% Decreased neutrophils=2. 6% Dyspnea=2.6 %	CHECKMATE-032
Atezolizumab	Advanced UC, Recurrence or Progression after platinum	931	ORR 23% mPFS 2.4mo mOS 11.1mo	Grade 3-4 AEs 22.8% Fatigue=31% Nausea=14%	IMvigor 211 cohort 3
Durvalumab	Advanced UC, Progression or recurrence during prior refused other therapies	191	ORR 17.8% mPFS 2.1mo mOS 20mo	Grade 3-4 Aes 6.8%	Study 1108
Avelumab	Advanced UC, Recurrence or Progression after platinum	249	ORR 17% mPFS 2.8mo mOS 8.2mo	Grade 3-4 Aes 8%	JAVELIN

4. The Challenge and the development of the inhibitor for BC

PD-1/PD-L1 inhibitor, as one of the hottest treatments in medical society in the last decade, has attracted oodles of attention. With the research on immunotherapy, it is known as an immune monoclonal antibody and has a great response to cancer. Despite this, since the overall response rate of its inhibitors to solid tumours is low when used as a single agent, this situation often leads to its side effects, which is a main factor in why PD-1/PD-L1 inhibitor immunotherapy cannot replace other therapies in a certain period of time. Furthermore, even though PD-L1 inhibitors could stimulate the immune system of the patient's body, which could strengthen the function of T cell immune checkpoint inhibitors, they can significantly improve the survival rate of patients. However, the abnormal human body can enhance normal immune response, resulting in an immune tolerance imbalance, which leads to a series of inflammatory side effects or irAEs [15].

Because of the allergic reactions caused by PD-L1 inhibitors, and the effect of it still needs to be improved, PD-L1 still serves the combination therapy most of the time. However, PD-1/PD-L1 also has a good therapeutic effect on head and neck tumors (neck tumors, ENT tumors, and oral and maxillofacial tumors). Early bladder cancer is usually treated with radiotherapies, such as chemotherapy and EGFR-targeted mab, but more than half of patients eventually develop recurrence or distant metastasis and are treated with palliative chemotherapy. The overall median survival was still less than 1 year. However, in the combination, the efficacy of BC clinical trials has been significantly improved.

Thus, the inhibitors are significant in immunotherapy. Nowadays, it has gradually come into the view of people, and cancer immunotherapy is slowly beginning to show great promise in the medical field. In December 2019, Tislelizumab, an anti-PD-1 drug, was approved for sale in mainland China. Tislelizumab is the first PD-1 mab approved for urothelial carcinoma in China. In 2014, Nivolumab was granted for melanoma and for the treatment of NSCLC in 2015. As mentioned in the previous content, nivolumab has a positive therapeutic effect on refractory squamous cell head and neck cancer under the effect of combination therapy. The combination of PD-1 inhibitors and other therapies to further improve response rates may be a future research direction for the pharmaceutical industry. Inhibitors currently, PD - 1 as a single drug used for solid tumours of the overall response rate is low (15%-20%), in addition to melanoma was 50% [16], while the drug prospects are extensive, but the antitumor medicine treatment the effect of the combination is still hard to predict, but with the deepening of the research, immunotherapy will be another powerful countermeasure against cancer.

5. Conclusions

The development of checkpoint immunotherapies has quickly established itself as a crucial weapon in the arsenal against bladder cancer after years of roadblocks in drug development for the disease. For treating advanced UBC, all PD-1/PD-L1 inhibitors have currently been licensed, including Pembrolizumab, Durvalumab, Nivolumab, Avelumab, and Atezolizumab. Pembrolizumab and Atezolizumab particularly demonstrated promising efficacy and a tolerable safety profile. However, immune-related adverse effects (irAEs), which may be severe and even lethal, can result from the use of PD-1 pathway inhibitors. As a result, clinicians need to be aware of the irAE characteristics related to the use of such medications. Moreover, compared to patients with other malignancies, patients with mUC are more likely to be elderly and comorbid, and there are rising worries regarding the cost and accessibility of novel treatments. Therefore, significant effort is needed to close the gap between treatment guidelines and actual practice. Immunotherapy has demonstrated substantial promise in sustaining and increasing the quality of life in bladder cancer patients, particularly in individuals with significant comorbidities who are not candidates for traditional therapies. In conclusion, immunotherapy will roll on to influence the paradigm for treating bladder cancer, and the prospects for treating the illness after a lengthy gap are clearly promising.

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