The usage of Pembrolizumab in Metastatic Urothelial Carcinoma

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Abstract. Bladder cancer is common cancer threatening countless people's lives. Urothelial carcinoma contributes to 90% of bladder cancer cases and has a low average five-year relative survival rate of 6% if metastasized. Finding appropriate therapy for those with metastatic urothelial carcinoma (MUC) is therefore crucial. Most patients cannot get first-line cisplatin-based chemotherapy, and a small number cannot receive any platinum-based treatment. The immune checkpoint inhibitor pembrolizumab blocking the PD-1 with the PD-L1 protein expressed on urothelial carcinoma cells. This blockade reduces immunosuppressive effects and restores effective neoplastic cell eradication. Compared to conventional chemotherapy strategies, pembrolizumab had significant improvement in the safety profile, reduction of adverse effect rate, and elongation of survival under certain conditions. It offers an alternative treatment option for those who are ineligible for chemotherapy. Pembrolizumab has been given the approval to be used in first-line settings for patients who are ineligible for platinum and second-line settings for patients who have already had chemotherapy. This paper summarizes the mechanism and application of pembrolizumab for treating MUC. The drug's efficacies under different conditions, advantages, current issues, and future investigation directions are discussed.

Keywords: Pembrolizumab, Metastatic Urothelial Carcinoma, PD-1 Inhibitor, Immunotherapy, Immune Checkpoint Inhibitor.

1. Introduction

There will be approximately 81,180 newly diagnosed bladder cancer (BC), causing around 17,100 deaths in 2022 [1]. Among all the cases, urothelial carcinoma accounts for about 90% of bladder cancer. A number of risk factors are linked to bladder cancer occurrences. First is gender; men are way more susceptible to BC compared to women though women tend to have a more advanced stage of disease [2]. Genotype is another critical factor; null genotypes of GSTM-1 and N-acetyltransferase express increased susceptibility [3]. Tobacco smoking is the most common modifiable contributor to BC occurrence, accounting for around 50% of the incidences, and its influence is accumulative. Cessation of smoking can greatly reduce the overall lifetime BC risk [4]. For patients who are already diagnosed with bladder cancer, their average five-year relative survival rate is 77%. However, this rate is much lower for patients who have metastasized tumors. The rate is 38% for patients with tumors spread to surrounding lymph nodes and regions, and only 6% of patients with metastasized tumors in distant organs [5]. Even for cases non-invasive at diagnosis, almost 70% of the patients will develop new occurrences or recurrence, and around 10-20% will have a more advanced state even metastasis within five years [6]. Therefore, it is crucial that these patients with urothelial cancer receive appropriate therapy.

For more than 20 years, the first treatment for MUC has been platinum-based chemotherapy [7]. Combining methotrexate, vinblastine sulphate, and doxorubicin hydrochloride with cisplatin offers an alternative to cisplatin-based therapy [8]. However, the patients need to satisfy a series of criteria for receiving cisplatin, and between 30 and 50 percent of patients are unsuited for treatment. For these patients that can't receive cisplatin, the next option is carboplatin-based chemotherapy which they are most likely to be eligible for, though it is not interchangeable with cisplatin-based therapy [9]. However, there is still a rare population that is unfit for all platinum-based chemotherapy [8]. Additionally, the survival may be hampered by the resistance. Active responses to chemotherapy are

not usually seen in patients with advanced BC, and adverse events prevent consistent chemotherapy usage [10]. Therefore, there is still a constant need for more and better treatments.

Recently, immunotherapy has emerged as a revolutionary way of treating cancer. In the case of urothelial cancer, the pathway of PD-1has shown to be an effective target [11]. Immune homeostasis and tolerance are supported by the PD-1 immune checkpoint. PD-1 belong to the B7/CD28 costimulatory receptor family [12]. Multiple different types of cells express the ligand PD-L1 including APCs, non-hematopoietic, and tumor cells [13]. Many immunosuppressive processes are triggered by the pathway, one of which prevents the activation, survival, and proliferation of cytotoxic CD8+ T lymphocytes. Cancer cells utilize these impacts to escape immune surveillance [14]. Urothelial cancer expresses PD-L1 and dampens the T-cell responses to prevent effective eradication. Thus, PD-1-specific human monoclonal antibodies can be used to prevent PD-1 ligation, reduce the unwanted suppressive effects, and restore effective T-cell functions for better elimination of the neoplastic cells [15].

Immune checkpoint inhibitor (ICI) pembrolizumab specifically targets the molecule PD-1. It has gained approval for use for patients who cannot receive platinum-based chemotherapy and as a second-line therapy for those who have already had platinum-based chemotherapy [7]. Its second-line usage is correlated with a significant three-month elongation of overall survival rate and a reduction in adverse effect rate compared to chemotherapy in metastatic urothelial cancer patients [16]. This review's objective is to assess pembrolizumab's use in treating MUC. discuss its efficacy, advantages, and limitations.

2. Background information and mechanisms of Pembrolizumab

IgG4 anti-PD1 monoclonal antibody pembrolizumab is totally humanized. It can bind to PD-1 without activating complement or engaging the Fc receptor, thereby avoiding cytotoxic effects. This binding can inhibit the combination of PD-1 with receptor and obstruct downstream immunosuppression [17].

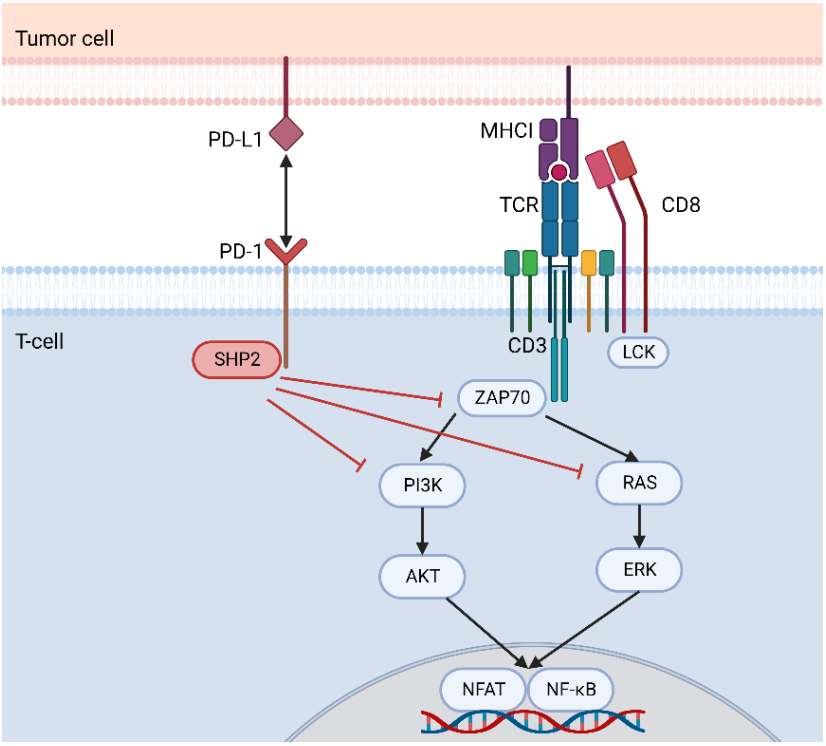

Figure 1. PD-1 pathway's core mechanism

PD-1 can inhibit effective immune activities through threshold regulation. Lymphocyte activation requires specific antigen recognition and additional coreceptor regulation.

CD28's interactions with B7.1 (CD80) and B7.2 (CD86), its ligands, provides a positive signal for effective activation [18]. The CD28 coreceptor family member PD-1 is implicated in the inhibition of lymphocyte activation. PD-1 ligation leads to downstream events of antigen-receptor complex's crosslinking with PD-1, which induces the recruitment of SHP2 phosphatase, counteracting the phosphorylation caused by major effector kinases such as ZAP70 in T cells and Syk in B cells [19, 20]. Specifically, in T cells, the inactivation of ZAP70's functions interferes with the downstream PI3K-AKT, and RAS signaling, which immediately suppresses the T lymphocyte growth and activation. Through inhibiting TNF-α and IFN-γ production, also a reduction of crucial transcription factors Eomes, T-bet, and GATA-3, T cell effector activities are reduced [21]. PD-1 can be seen on a variety of immune cells including myeloid cells, natural killer cells, B lymphocytes, natural killing T lymphocytes, and developing or activated T lymphocytes [22-24]. It starts functioning after the T cell activation and its expression is induced around the first or second division. The PD-1 tail lacks the binding motif for adaptor complex AP2, thereby not subjected to clathrin-dependent endocytosis and can be expressed continuously on the activated T-cell surface [18]. PD-1's activation-induced expression suggests its suppressive functions in immune responses' later phases such as effector activities, sustaining activation, and secondary responses [22]. The specific anatomical expression for the PD-1 ligands determines the location of the pathway's effects. Tumor cells including the urothelial cancer cells express a high level of PD-L1, which allows for the escape from elimination [15].

Cancerous cells that express PD-L1 have resistance to T lymphocyte-mediated cytotoxic responses, which suggests that the interaction between PD-L1 on targeted cancer cells and PD-1 expressed on CD8 positive T cells is a factor in the immune surveillance escape [25]. High PD-1 ligand expression has been linked to poor prognosis, further indicating the significance of PD-1 engagement in preventing T cell antitumor immunity [26]. The killing of tumor cells can currently be improved by blocking the PD-L1 PD-1 ligation. Therefore, the humanized mAb pembrolizumab's inhibition of PD-1 in cancers that upregulate PD-L1 such as urothelial cancer, could potentially shift the immunology tolerance towards antitumor activities [27].

3. Clinical observations

3.1. Past evidence supporting pembrolizumab's usage in treating urothelial carcinoma

The possibility of applying pembrolizumab for treating metastatic urothelial cancer was supported by past clinical trials. Another immune checkpoint inhibitor, atezolizumab, can bind to PD-L1 and prevent ligation which also targets the PD-1 pathway. This drug has been tested and approved for treating urothelial cancer before pembrolizumab. It was investigated as a first-line treatment for MUC ineligible for cisplatin chemotherapy. Durable responses and controllable safety profile were observed. Compared to historical chemotherapy clinical trials, the complete response rates were higher [28]. The results support the therapeutic application of atezolizumab for urothelial cancer patients, showing inhibiting the PD-1 pathway's medical advantages. In KEYNOTE-012, a clinical trial that is multi-cohort, non-randomized, open-label phase one b, pembrolizumab were evaluated in patients with MUC. All patients got at least one pembrolizumab dose for analysis. The result showed good toleration, controllable safety profile, durable response, and promising anti-tumor activities. A response of 26% was observed in the assessed patients; when compared to the previous second-line chemotherapy treatment, the median overall survival increased (13 months vs. 6 to 9 months) [29]. This study warranted further investigation, such as phase two and phase three studies of pembrolizumab as a means of treating MUC.

3.2. Application in individuals ineligible for any platinum-based chemotherapy as well as those unfit for chemotherapy based on cisplatin

The KEYNOTE-052 evaluated pembrolizumab in patients with advanced urothelial carcinoma who were unfit to receive cisplatin [30]. Patients with advanced UC who are ineligible for cisplatin and haven't experienced systemic chemotherapy were recruited for the study. A large percentage of

this population was elderly with poor performance and comorbidities. Every three weeks, 200 mg of pembrolizumab was administered intravenously. The clinical trial evaluated all patients' objective responses (complete or partial responses) and PD-L1 expression. Among the 370 patients that received the drug, 24% of the patients had centrally assessed objective responses, and 23% of the patients' best response was a stable disease state. A higher response percentage of 38% was observed in 110 patients population who possess higher than 10% PD-L1 expression, suggesting the correlation of pembrolizumab response to PD-L1 expression levels. This response was unrelated to multiple factors like age and location of primary/metastasis tumor, indicating the potential for applying pembrolizumab in a wide range of patients ineligible for cisplatin.

The tolerability for pembrolizumab appeared to be acceptable. Few adverse events of grade three or higher were documented from multiple patients. Only 10% of people develop severe side effects from treatment, and only 5% stop due to these adverse events. A small percent of patients (17%) experienced immune-mediated adverse events. Compared to cytotoxic chemotherapy, there was a remarkable difference in safety and efficacy. Pembrolizumab had significantly improved tolerability and showed an advantage in treating patients with impaired renal function [8].

The European Medicines Agency (EMA) and the FDA have both approved the usage of pembrolizumab as the first-line therapy for cisplatin-unfit patients with positive expression of PD-L1 as a result of the findings. Though the study didn't state the percentage of patients who were not eligible for all chemotherapies based on platinum, regardless of the PD-L1 status, the FDA continued to approve pembrolizumab for being a first-line therapy unfit for all platinum-based chemotherapies [7].

3.3. Combine with first-line chemotherapy in population able to receive therapies based on platinum

Usage of pembrolizumab as therapy in the people that is platinum-suitable was further investigated in another clinical trial KEYNOTE-361 [31].

In this open-label (both investigator and patients were unmasked), randomized phase three trial, 1010 patients greater than eighteen years old with untreated unresectable, metastatic, or urothelial cancer that has spread locally were recruited and randomly distributed into three groups: chemotherapy alone (n=352), pembrolizumab alone (n=307), or the usage of chemotherapy combined with pembrolizumab (n=351, 200 mg of intravenously administered pembrolizumab every three weeks plus intravenously administered gemcitabine chemotherapy together with cisplatin or carboplatin). The choice of platinum therapy was determined by the investigator, and the PD-L1 positive cells percentage relative to the total number of tumor cells, or PD-L1 combined positive score (CPS), was stratified. The survival in the chemotherapy plus pembrolizumab group, were 8.3 months and 17.0 months, respectively. For chemotherapy only, the survival for chemotherapy alone were 7.1 months and 14.3 months. Compared to chemotherapy alone, pembrolizumab plus chemotherapy have not improvement in overall survival or progression-free survival. Additionally, both in terms of the overall population and patients with CPS equal to or greater than 10, the pembrolizumab-only group's overall survival resembled that of the chemotherapy group. Nevertheless, pembrolizumab did have different characteristics compared to chemotherapy. It is correlated with lower percentages of any grade all-cause adverse events and associated with longer response duration. Chemotherapy, on the contrary, is correlated with higher initial responses number.

Though exploratory analyses suggested certain patients could benefit from first-line pembrolizumab treatment, the selection criteria for the appropriate patients still require investigation. The adding of pembrolizumab into the first-line platinum chemotherapy did not enhance efficacy to a significant level, and the PD-L1 CPS cutoff of 10 also did not improve the survival of urothelial carcinoma patients taking pembrolizumab monotherapy, indicating that no benefit can be gained through PD-L1 CPS selection. Therefore, for the eligible population, platinum-based chemotherapy continues to be the standard first line treatment.

3.4. Being second-line treatment for platinum pretreated individuals

Pembrolizumab was also evaluated in patients with MUC after platinum-based therapy. The pretreated recurrent patients usually have few treatment options and a poor prognosis. An study KEYNOTE-045 recruited 542 platinum pretreated individuals who had progressed MUC. The patients were randomized to receive either chemotherapy, who got paclitaxel, docetaxel, or vinflunine based on the investigator's decision, or the pembrolizumab treatment group in which every three weeks, 200 mg of pembrolizumab was given. Patients with at least 10 PD-L1 CPS were assessed for overall survival and progression-free survival [16].

The survival of the entire population in the pembrolizumab treatment group was 10.3 months, whereas the survival for chemotherapy patients was 7.4 months. The survival for individuals with PD-L1 CPS equal to or greater than 10 was 5.2 months in the chemotherapy group and 8.0 months in the pembrolizumab group. The pembrolizumab treatment led to significantly longer overall survival than the chemotherapy by about three months. This overall survival benefit seems unrelated to the expression level of PD-L1 and is observed at a similar level compared to all chemotherapy option groups. No significant progression-free survival differences were observed.

Compared to chemotherapy, pembrolizumab showed a durable response and significantly increased objective response rate. The majority who were given pembrolizumab had quick noticeable responses during the first imaging assessment. Additionally, lower rates of treatment-related side effects were observed in pembrolizumab group, 60.9%vs90.2% for any grade adverse events, and 15.0% vs. 49.4% for grade 3, 4, and 5 adverse events. This better safety profile compared to chemotherapy is essential considering the poor prognosis and complex condition of platinum pretreated individual with recurrent urothelial cancer. In comparison to chemotherapy of paclitaxel, docetaxel, or vinflunine, pembrolizumab was found to have a significantly three months longer overall survival as second-line therapy for patients with refractory advanced urothelial cancer who had previously received platinum treatment. Adverse events were also lower. Both the FDA and EMA have approved it to be a second-line treatment [7].

3.5. As maintenance treatment in patients achieved stable illness after first-line platinum chemotherapy

After or during completing first-line platinum-based treatment, MUC patients may continue to have disease progression, which suggests the requirement for more treatment options. In a double-blind randomized phase II trial GU14-182, pembrolizumab had been tested as a switch maintenance therapy after chemotherapy [32]. 108 MUC patients with a stable state after platinum-based therapy were recruited and randomly given pembrolizumab maintenance (n=55), which is 200 mg intravenously administered pembrolizumab every three weeks, or the placebo (n=53). Patients who received a placebo and developed disease progression could be crossed by pembrolizumab treatment. The overall survival and progression-free survival were evaluated along with PD-L1 CPS.

The pembrolizumab group had an objective response rate of 23% and 59% treatment-emergent grade three to four adverse events. The placebo group's objective response rate was 10% and had a grade three-four adverse event rate of 38%. Despite there being no variation in median overall survival, the progression-free survival for the pembrolizumab group was significantly longer than placebo (5.4 months vs. 3.0 months). The degree of PD-L1 expression did not appear to affect either overall survival or progression-free survival. Based on the observation that switching to pembrolizumab as maintenance therapy after platinum-based chemotherapy extended progression-free survival significantly, immune checkpoint blockade by pembrolizumab as a sequential integration may improve the clinical outcome of MUC patients.

4. Current usage summary and comparison to traditional chemotherapy treatments

To summarize the current usage of pembrolizumab in treating MUC. The administration method for pembrolizumab was highly consistent among the listed clinical trials, which was intravenously administration of 200 mg of pembrolizumab every three weeks.

Pembrolizumab's usage is approved under two scenarios. The first is to apply the drug as first-line therapy for urothelial carcinoma in patients who are ineligible for chemotherapy based on cisplatin or all platinum chemotherapy [30]. In this case, the pembrolizumab response correlates with the PD-L1 expression level. The application to be first-line treatment in PD-L1 positive cisplatin-ineligible patients was approved by both EMA and FDA, and the application as first-line treatment for patients ineligible for any platinum-based chemotherapy regardless of PD-L1 expression was approved by FDA [7]. The other scenario is as a second-line therapy for platinum pre-treated individuals who usually have poor physical conditions and few treatment options available. Pembrolizumab showed a significantly longer overall survival and higher response rate than chemotherapy of paclitaxel, docetaxel, or vinflunine [16]. Its application has been approved by both EMA and FDA [7].

There are also trials for applying pembrolizumab that showed less desirable effects or required more supporting evidence. The combination of platinum-based first-line therapy with pembrolizumab or application of pembrolizumab only in the platinum-eligible patients had not significantly increased either overall or progression-free survival compared to chemotherapy only [31]. Pembrolizumab's efficacy as a maintenance treatment for patients who had a stable disease state after first-line platinum chemotherapy was also tested and demonstrated prolonged progression-free survival when compared to the placebo group. The overall survival, however, did not show a significant change. [32].

Compared to conventional chemotherapy, one advantage of pembrolizumab is that it's related to lower treatment-related adverse event rates. This improvement in safety profile is especially important for patients with a poor prognosis and performance, which is common in patients unfit for platinum-based therapy, patients with impaired renal functions, and patients who had recurrent carcinoma after chemotherapy [8, 16, 30].

The result of the response comparison between pembrolizumab and chemotherapy depends on the application conditions. When applied as second-line therapy for pre-treated patients, pembrolizumab has a quicker response speed, longer response duration, and higher response rate than chemotherapy paclitaxel, docetaxel, or vinflunine [16]. However, when compared to chemotherapies that are based on platinum, pembrolizumab only has a longer response duration but a lower initial response number as first-line therapy [31].

5. Side effects and Predictive biomarkers

Only a certain subset of patients can have persistent durable immunotherapy responses, while the majority still get primary disease progression. Therefore, it is important to determine which patients tend to respond and benefit from pembrolizumab treatment. The desired result is to have biomarkers that can separate responsive and non-responsive patients despite the disease state (cisplatin eligibility, before or after platinum treatment) [33].

PD-L1 is one potential biomarker being studied in clinical studies, and the current findings have been inconclusive. A large percentage of PD-L1 negative patients are also responsive to the ICI [7]. Applying pembrolizumab to be the first-line treatment in individuals ineligible for cisplatin-based chemotherapy is the only condition for treating mUC that requires PD-L1 testing. This regulation is constructed based on KEYNOTE-052, which showed pembrolizumab response was connected with the expression of PD-L1, and those with PD-L1 CPS higher than 10 responded more favorably than individuals with CPS less than 10 [30]. However, in the trial KEYNOTE-045 testing pembrolizumab's usage as second-line treatment for chemotherapy pre-treated individuals, there was no observed relation between PD-L1 and the overall response rate [16]. This conflict might be due to differences in the chosen assays and the evaluated compartments.

Another potential signature for projecting pembrolizumab response is the expression of IFN-γ signal-related genes. Eighteen gene candidates were selected to predict pembrolizumab response in various cancers [34]. This gene signature achieved a much more accurate prediction for the pembrolizumab responder (86%) than the PD-L1 CPS (41%) in trial KEYNOTE-52 [30]. However, more evidence and trials are required to get a more robust evaluation of predictive power.

Pembrolizumab being an immune checkpoint PD-1 inhibitor, can improve immune response and cause immune-mediated adverse events (imAEs), which can influence various organs. The most commonly affected ones include the gastrointestinal tract, lung, skin, liver, thyroid, pituitary, and adrenal glands. Systems like nervous, renal, ocular, hematological, cardiovascular, and musculoskeletal systems can also be influenced. Symptoms include impaired thyroid functions, rash, hepatitis, fatigue, muscle and joint pain [7]. For pembrolizumab to have the best effect, it is essential to investigate the relationship between efficacy and imAEs and control the side effects properly and timely. Patients that are responsive to PD-1/PD-L1 inhibitor tend to develop imAEs compared to unresponsive patients, and this observation was not affected by the use of corticosteroids [35]. More studies and investigations are needed to validate the current analysis result so that in the future, better efficacy prediction of pembrolizumab can be done on patients with imAEs.

6. Possible application with other therapies for improving outcomes

There is the possibility of applying pembrolizumab combined with other types of drugs, for example, the antibody-drug conjugate (ADC). One possible conjugate is Enfortumab vedotin which is linked to a microtubule-disrupting molecule MMAE and specific for Nectin-4, a cell adhesion molecule that is abundantly expressed by the urothelial cancer cells. Its usage has been approved by FDA in the metastatic urothelial cancer patients who are pre-treated by chemotherapy or PD-1 & PD-L1 inhibitors [7]. Activity and safety of pembrolizumab plus enfortumab vedotin combination therapy were tested on patients ineligible for cisplatin. There was a controllable degree of adverse events, prospective durability, and activities [36]. The application of this combinatory option is currently being tested as a first-line treatment in patients fit for platinum [37].

7. Conclusion

Pembrolizumab has gained the approval to be used as second-line therapy for patients who have already had chemotherapy as well as first-line treatment for those who are unfit for cisplatin or platinum chemotherapy. It has a significantly improved safety profile in patients ineligible for standard chemotherapy and those with relatively poor prognoses. Despite the promising prospects mentioned above, pembrolizumab is still a relatively new treatment option that requires further investigations and monitoring. There is a need for predictive biomarkers that can separate the responders from the large percentage of pembrolizumab non-responders. Investigations targeting PD-L1 had shown rather inconclusive results probably because of the different evaluation assays and compartments. One seeming more promising signature is the eighteen gene candidates related to IFN-γ signaling, but there haven't been lots of supporting investigations. Another issue is the monitoring of the imAEs during the treatment process. Since these imAEs could be associated with enhanced immune activities and effective anti-tumor responses, properly managing these imAEs at the right time could be crucial for obtaining ideal treatment results. Pembrolizumab plus the ADC Enfortumab vedotin is one possibility that may offer an additional treatment option for metastatic urothelial cancer. There are still many possible applications of pembrolizumab combined with other drugs which might be worth pursuing. In conclusion, pembrolizumab is promising immunotherapy that can be applied in treating MUC. Compared to conventional chemotherapy, it substantially improved the safety profile. Further investigation and study on the drug might help better apply and monitor pembrolizumab.

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