

The Evaluation of Effects, Mechanisms, and Clinical Data of Avelumab

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Abstract. Immune checkpoint inhibitors (ICI), the new frontier in the fight against cancer, have attracted much attention in the past few years. Among all types of ICIs, Avelumab is one of the most experimented upon because it is advantageous compared to other more traditional types of treatments like radiotherapy and surgery. Avelumab is capable of eliminating cancer from some patients who do not respond to the traditional treatments, or when their cancers reappear after being treated. Avelumab can target cancer more specifically, with minimal damage to other body cells like the death of hair follicles that result from chemotherapy. Though it is an effective treatment, there are a few areas in which it can improve, including lowering its costs, decreasing the risk of irAE, and making it effective to more patients. This paper will mainly discuss the history, mechanism, limitations, and treatment of different cancers using Avelumab, and focus on analyzing data on the effectiveness and performance of Avelumab in clinical trials when it is used to treat different cancers.

Keywords: Immune Checkpoint Inhibitors, PD-1, Avelumab.

1. Introduction

Immune checkpoint inhibitors (ICIs) belongs to immunotherapy and can benefit various malignant cancers despite low response rates and side effects. As one of the targets of it, the programmed cell death protein 1 (PD-1) receptor has received much attention and revolutionized cancer therapy in the past decade. Avelumab, which is the drug that will be discussed in this paper, targets PD-L1 and is one of the few ICIs that has passed the clinical trials phase and received approval from the FDA.

Central or peripheral tolerance are the two methods of immunological tolerance. The former protects autoimmunity by clonal deletion (triggering the apoptosis of T-cell with high affinity with self-antigen) during the adverse selection in the thymus. Unfortunately, self-reactivity is not entirely eliminated by selections in the thymus, so peripheral tolerance is required to offer further protection when T cells start circulating in the body. Peripheral tolerance mainly includes the removal of regulatory T cells (a subtype of T cell that inhibits the functioning of others). T cell anergy is also a cause of it, and other mechanism include the modulation of extracellular tolerogenic signals and peripheral clones [1].

T-cell activation is constituted of various steps, including the binding of stimulatory antigens to MHC molecules that are located on APCs that have TCR and co-stimulatory signals. Prior to its activation, the APCs will relocate the captured antigens to its MHC molecules. After the antigens bind to T-cells that exhibit cognate T-cell receptors after the effect of co-stimulatory signals, it will recognize the antigen and start functioning [2].

CTLA-4 and PD-1 can regulate T cell and the maintenance of peripheral immune tolerance. Typically, this regulatory mechanism maintains immune responses within the desired range to prevent autoimmunity or to avoid overreacting when harmless substances enter the body.

PD-1 is an adaptive and innate immune system inhibitor expressed in T cells, NK cells, B lymphocytes and others [3]. PD-1 is a coinhibitory receptor that is activated with engaged with (mainly) with the ligand PD-L1. Activation will lead to the recruitment of the phosphate SHP-2 and CD28 near the T-cell receptors, which will further lead to the dephosphorylation of the critical steps in the TCR and CD28 pathways, thus inhibiting T-cell activity and life span. Certain cell, such as tumor-specific T cells, is coupled with higher expression of PD-1. There two different ligands of it is

PD-L1 and PD-L2 differing in patterns. The former is found in low levels in APCs and many nonhematopoietic cells. In comparison, the latter is expressed only in professional APCs and, even then, in low expression. However, both ligands can be expressed by tumor cells where PD-L1 is more common [4].

Since 2010, immunotherapeutic agents have dominated immunotherapy, monoclonal-blocking antibodies targeted at immune checkpoint molecules [5].

There are various mechanisms by which a single immune checkpoint inhibitor can inhibit a single type of immune checkpoint molecule. Many pioneer studies and approaches aim to activate checkpoint glycosylation and ubiquitination/degradation pathways. Despite these pioneer studies, traditional immune checkpoint inhibitor inhibits the interaction between the immune checkpoint molecule and its receptor (As in the case of Avelumab).

Although Avelumab is an FDA-approved Immune Checkpoint Inhibitor, it has the shortest development time on the list. So, compared to other approved ICIs, it lacks systematic reviews and comprehensive clinical data. Also, due to its newness and novelty, there is not enough perspective about its future direction and improvement.

2. History of Avelumab

Many scientists contributed their time and efforts to developing checkpoint inhibitors, and many steps led to their final invention. The first observation of the checkpoints was in 1910, where researchers Gisa Kaminer and Ernest Freund from Austria discovered that the blood serum of cancer patients can prevent the destruction of cancer cells. Fourteen years later, they discovered a substance that, when added to a healthy patient's serum, reduces the standard blood serum's ability to dissolve cancer cells in the intestines of cancer patients. However, their death obscured their findings to the public until February 1966, when a team led by Karl Hellstrom and Ingegerd Hellstrom attributed an undiscovered blocking factor to the phenomenon that mice with chemically induced tumors could stop lymphocytes from participating in reactions in healthy patients. In June 1971, the Hellstrom team published an article in *Advances in Immunology* journal stating that tumor cells could evade immune surveillance by binding to the targets on the white blood cells.

This claim paved the foundation for the subsequent discoveries of different antibodies, including Tasuku Honjo and his team's identification of PD-1 in November 1992. However, the functions of these proteins remained unknown until a team led by Gordon J. Freeman showed in October 2000 that cancer cells could escape the immune response by hijacking PD-1. Further research allowed the anti-PD-1 antibody to enter clinical trials on November 24, 2008, led by the company Medarex. In March 2017, Avelumab, which aimed to treat MCC in patients 12 years and older, was approved by the FDA.

Finally, there was official recognition for the contributions of James Allison et al. to the discovery of the checkpoint inhibitors when they received the Nobel Prize in Physiology and Medicine in October 2018.

Checkpoint inhibitors are still a relatively new area of technology and are developing rapidly. The FDA has approved seven drugs, and more are in the clinical trials. The global market for checkpoint inhibitors is also forecasted to reach \$29.3 billion in 2023, building up a new frontier against cancer [1].

3. Mechanism of Action of Avelumab

Avelumab, which is a pale yellow to colorless solution, is administered intravenously [1,6]. It is recommended that Avelumab be taken until the disease is relieved or there are severe adverse reactions [1]. In help of mononuclear cells or NK cells, Avelumab can degrade tumor cells with PD-L1 positive. The addition of Avelumab reduced the propagation of CD4⁺ T cells while rapidly activated CD8⁺ T cells, which produce IFN gamma leading to high expression of PD-L1 ligand in

tumors. The significant difference between Avelumab and other inhibitors is that it can induce the antibody-dependent cells to mediate cytotoxicity (ADCC) [7].

ADCC is an immune response in which Fc-receptor of antibody-producing B cells can kill cells that express the surface antigen corresponding to the antibody. Three common types of the B cells mediate FC γ RII (CD32), FC γ RIIIA (CD16), and IgG-dependent ADCC – FC γ RI (CD64). Specifically, the first one is the most common receptor involved in ADCC, and is predominantly expressed via NK cells. Activation of it is mediated by the interaction with membrane receptors of the target cells via various ligands expressed on NK cells. Commonly, non-transform cells express self-MHC class I molecules to protect them from the attack of NK cells by deactivating them. Cytokines such as IL - 15 and IL-2 are common cytokines that enhance and activate the expression of NK. Thus, ADCC is mediated against tumors [8].

Another unique aspect of Avelumab compared to other antibodies is its fast clearance from the body (4 days for it). This property is mainly due to its unique internalization mechanism upon PD-L1 ligand binding and FC γ R mediation. When Avelumab binds to PD-L1 ligand, the binding increases the internalization of Avelumab into granulocytes and monocytes, leading to faster clearance. Similarly, but to a less degree, FC γ R also interacts with Avelumab to accelerate its internalization. Studies have also shown a synergistic effect between PD-L1 binding and FC γ R mediation on the internalization of Avelumab [9].

4. Limitation of Avelumab

TRAEs, also named irAEs, appeared in about 70.5% of patients that took Avelumab. Fatigue and infusion-related reactions, which are all low-grade adverse events that can resolve in a short amount of time, were common. More immune-mediated severe TRAEs are identified in less than 13% of patients, including diarrhea, hyperthyroidism, hypothyroidism, pneumonitis, and other complications. No treatment related death (TRD) were found in the JAVELIN Merkel 200 study [8].

Although irAE is an adverse effect, its onset may represent a positive response to the treatment, which usually correspond to the improved clinical outcome (includes increased ORR, PFS, and OS). The specific pathophysiology of irAE is still unknown. However, Studies suggest that irAE might be caused by antigens, finally leading to the activation of T cells against both targets [10]. Despite the correlation with successful treatment, irAE is adverse and sometimes lethal to patients. It affects multiple organs, most commonly the G.I. tract, liver, skin, and endocrine glands. Other essential organ systems are also affected, but at a lower rate. Because of this, the enormous scope of organ impact requires collaborative and multidisciplinary management [11].

Avelumab has a bearable safety and tolerability performance. However, it has a relatively high proportion of patients who have severe adverse events (Not necessarily the JAVELIN Merkel 200 study). Like other ICIs, Avelumab has the risk of developing irAE but is generally manageable with proper treatment [8].

It is currently unclear why some patients have irAE while others do not. However, the current direction is to examine whether underlying germline genetic factors are correlated with the probability of acquiring irAE during the treatment. In addition, there is some investigation of the correlation between the microbiologic composition of patients with the appearance of irAE, as specific preclinical and clinical data suggest certain bacterial species are associated with the function of an immune checkpoint inhibitor [5]. In the study, 31.8% of patients have responded to Avelumab. In this study, 31.8% of patients responded to Avelumab. And, the researchers found that at 12 months, the objective response rate was 33.0%. Current attempts to utilize genomic and transcriptomic investigation to identify the genes positively correlated with the response or resistance of various ICIs to improve the overall response rate [11].

5. Types of Cancer Avelumab Target

Cancer that Avelumab targets can be categorized into monotherapy and combination therapy with other drugs. The clinical data is acquired from JAVELIN Solid tumor trial (NCT01772004) [10]. It tested the safety, efficacy, and clinical data of Avelumab targeting Urothelial carcinoma, NSCLC, melanoma, gastric cancer, ovarian cancer, breast cancer, glioblastoma, and more tumor types. This section primarily covers the clinical data involving MCC, urothelial carcinoma, and NSCLC with some minor supplements of the other tumor types [6].

6. Merkel Cell Carcinoma (MCC)

The risk factors of MCC included MCPyV exposure, U.V. irradiation-induced mutations, and aging. It generally has poor survival outcomes in metastatic disease, especially in advanced stages where chemotherapy is not durable and reliable. With chemotherapy, it has a 5-year Overall survival (O.S.) rate of 0% - 18% [10]. According to the result of JAVELIN Merkel 200 Part A, avelumab was granted as a therapy for treating MCC patients who progressed with one or more previous chemotherapy records on November 4, 2015 [6].

The Clinical data for Avelumab against MCC is primarily based on the study that includes 88 patients. Patients infected with MCPyV were excluded from the study. The results of the study showed an ORR value of 33.0%. At the same time, the complete response rate is only 9%, and the partial response rate is slightly higher, reaching 23% (1% accounted for non-complete response/non-progressive disease) (Collins and Gulley 2018). 74% of the response lasted more than one year with a 30% PFS, and O.S. was 30% [6, 13].

The results from the JAVELIN Merkel 200 far exceed the performance of chemotherapy trials towards MCC. Avelumab not only has high efficacy but is also well tolerated in clinical trials. There are only 5 grade 3 TRAEs in 5% of patients reported in the trial. It also shows improved quality of life after treating MCC patients with avelumab [6]. Although MCC is low, the proportion of patients who suffer relapse is approximately three times that of melanoma. Also, chemotherapy only produces limited and nondurable treatment with unsatisfying relapse treatment effects.

7. Urothelial Carcinoma (UC)

UC are bladder cancer, developing in transition epithelium in the urinary tract (bladder, renal pelvis, ureter). Since PD-L1 is expressed in Urothelial carcinomas tumors, Avelumab is a suitable drug for patients with Urothelial carcinomas. FDA approved Avelumab to treat advanced or metastatic UC during or after chemotherapy on May 9, 2017 [6].

The source of clinical data for this review is based on the result and analysis from the trial, which is a phase 3 trial, with 700 patients enrolled in a randomized manner. The patients with UC after receiving chemotherapy with gemcitabine plus cisplatin or carboplatin were selected as study participants. The exclusion criteria include receipt of adjuvant or neoadjuvant therapy within 12 months from the initiation of the trial or the application of another immune checkpoint inhibitor [11].

Overall, there are 668 patients included in the statistical analysis, including 334 patients, who were PD-L1-positive, and undergoing randomization. The O.S. and progression-free survival was longer in the avelumab group [11]. The above results show that the intervention effect of this drug on patients is significantly better than that of conventional interventions. If economic and other factors are not considered, clinicians may be able to consider this new plan when making a plan choice.

8. Non-small cell lung cancer (NSCLC)

About 85% of patients with lung cancer have the histological subtype named NSCLC. The most common cause is smoking. NSCLC tumors were found to have high PD-L1 expression. So anti-PD-L1/PD-1 treatments are suitable for this tumor subtype [14].

Avelumab was used for 184 patients with advanced platinum chemotherapy-treated NSCLC. In this study, the researchers' statistical analysis yielded a median patient age of 65.0 years, with no statistically significant differences among the groups. Most enrolled patients had advanced cancer (92%). And 86% had a history of smoking. At the same time, 66% of those who had prior or were receiving chemotherapy. The researchers further statistical analysis, the results show that 86% of the people highly expressed PD-L1 +. The final results found that in this population, the overall response rate was only 14.1%. In 184 patients, only 26 patients shrunk the target lesion by more than 30%. 11.6 weeks is median progression-free survival, and 24 and 48 weeks of it were 26% and 18%, respectively. The above data show that drug intervention is not all responsive to the effects of advanced cancer patients. However, for patients who are already on the brink of death, the development of new drugs is undoubtedly the last hope. Perhaps the ability to target targeting may be further improved in the future. It may be possible to improve the relief better [6,14].

However, it should not be overlooked that side effect occurred in most patients. Fatigue, nausea and other related clinical symptoms are more common. Serious TRAEs presentd in 23 of patients. One patient developed severe pneumonia, and 17 patients had to be discontinued due to serious side effects. Thirty-six patients had iRAEs, of which 4 had serious-grade irAEs [14]. The side effects of a drug are the biggest limitation limiting the use of a drug.

Compared to the MCC and Urothelial Carcinoma trial, the performance of Avelumab toward NSCLC is unsatisfying. The possible reason might be the low or non-PD-L1 expression in the patients selected for the trial [6].

9. Future Direction of Avelumab

Avelumab is available in 200mg vials, which cost 1039.43 per vial on average, which indicates US\$5.20 per mg. With the assumption that an average MCC patient weight 60kg requires 600 mg of Avelumab, including vial wastage, which costs US\$3118.30 [15]. Although there is a more expensive cancer drug, the price is still overwhelmingly high for many families. The price is expected to decrease gradually as the drug patent expires and FDA approves more similar mechanism drugs.

Since Avelumab is a fast-approved drug, much clinical data is insufficient compared to more completed ICIs. Especially on NSCLC, breast, and ovarian cancer, the enrolled patients in the clinical trial are limited and heavily pretreated with chemotherapy [7]. As shown in the trial, Avelumab has a poor performance against NSCLC, which require further investigation and prosecution to improve its safety and efficacy. A potential combination with one or more chemotherapy might be a plausible treatment plan that should be tested in future clinical trials [14]. Although Avelumab has a durable treatment, it only has a modest response rate. The potential solution might be to develop a more accurate standardized testing for PD-L1 expression to detect patients suitable for Avelumab [6].

10. Conclusions

Avelumab is providing a new frontier against cancer. It has saved many lives and will save more in the future. Avelumab targets the PD-L1 antibody and thus inhibits the cell's ability to escape from the immune system. The study shows that although Avelumab results were unsatisfying for NSCLs, it facilitated a 94% risk reduction of death for Merkel cell cancer and increased 12.9% the survival rate for urothelial carcinoma. As a relatively new technology, Avelumab is generally used as the last resort. After all, other treatments have been tried, not only because of their high cost but also because of their severe side effects and uncertain curing ability. Some people respond well to Avelumab, while others do not. Avelumab will provide people with a new way to fight cancer. Future research will, hopefully, be able to lower its costs, decrease the risk of irAEs, and make its curing abilities applicable to all patients.

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