The Role of Anti-PD-1 as a Treatment for Cancer

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Abstract

Immunotherapy represents a therapeutic strategy to treat various cancers, that involves harnessing one's immune system to fight cancer. One common type of immunotherapy is anti–PD–1 treatment, which is commonly used in metastatic melanoma patients and patients who suffer from different cancers. In metastatic melanoma, patients typically respond well to anti-PD-1. Unfortunately, patients with other types of cancers such as glioblastoma do not respond as well. Anti-PD-1 may still have a role in tumors such as glioblastoma, but not as a single-agent therapy. Identifying more efficacious combination therapies will be critical to successfully treating these patients.

Introduction

According to the American Cancer Society, nearly 2 million people in the United States were diagnosed with cancer in 2022 and of these, nearly ⅓ of those patients passed away due to the disease (*Cancer Facts & Figures 2022*, n.d.). These statistics support the need for more durable, efficacious cancer treatments. Current cancer treatments encompass a wide range of treatment options including chemotherapy, hormone therapy, hyperthermia, photodynamic therapy, targeted therapy, surgery, stem cell transplant, radiation therapy, and immunotherapy. Depending on the type of cancer, different treatments have shown varying levels of efficacy.

One of the newest and most promising treatments for cancer is immunotherapy, which was first approved by the FDA in 1986 for hairy cell leukemia (Eno, 2017). However, immunotherapy has become mainstream only in the last 15 years. The goal of immunotherapy is to harness the immune system to attack cancer cells. Some cancers respond to certain therapies more effectively than others. For example, two aggressive forms of cancer, metastatic melanoma (skin cancer) and glioblastoma (brain cancer), respond very differently to immunotherapies, both in terms of efficacy and side effects. Immunotherapy is very effective in metastatic melanoma, but not in glioblastoma.

Normally, cancer cells use a variety of mechanisms to avoid the immune system. Immunotherapy works by boosting or changing how the cells in the immune system respond to tumor cells. Within immunotherapy, there are many types of treatments that are often used individually or in combination. Some examples of these treatments include cellular therapies, anti-tumor vaccines, and immune checkpoint blockade.

Immune checkpoint blockade (ICB) is one of the most commonly used immunotherapy treatments. Checkpoints are cell-surface receptor proteins that control the effector function of immune cells such as T-cell lymphocytes. In the absence of checkpoint blockade, the ligand binds with the receptor which shuts down the T-cell's ability to fight off the tumor. Checkpoint blockade blocks the connection between a receptor on the tumor cell and a T-cell receptor. By administering ICB, T-cells are able to then resume their typical effector function and kill tumor cells. The two most commonly researched and used ICBs are anti-PD-1 and anti-CTLA-4. This paper will review ICB, specifically anti-PD-1. This review will discuss the mechanism of action of anti-PD-1, as well as its clinical effectiveness in treating a range of cancers.

Mechanism of anti-PD-1

The function of PD-1 receptors on T-cells is to regulate T-cell function. When bound to another protein called PDL-1, the T-cell is stopped from killing nearby cells. In the context of a tumor, PD-1 binds to PD-L1 on a tumor cell. When the T-cell and tumor cell signal through these two receptors, the T-cell undergoes dephosphorylation, where its normal functions are modified. This reduces proliferation, activation, and cytokine production, and leads to altered metabolism and cytotoxic T lymphocytes (CTLs) killer functions, and eventually apoptosis (Egger et al., 2016). Overall, signaling through the PD-1 receptor shuts down the T cell's ability to fight off the tumor. The role of anti-PD-1 is to intercept the connection between PD-1 on the T cell and PD-L1 on the tumor cell receptors. Blocking PD-1 stops the interaction with PD-L1 from affecting the T-cell, preventing the "shut down" of that T-cell. The T-cell is then able to function normally and kill the tumor cells surrounding it. The end goal is that by inhibiting these receptors, the T-cells can properly target the tumor cells, resulting in tumor cell death and ultimately longer cancer-free survival for patients.

For some cancers, such as metastatic melanoma, checkpoint blockade is an extremely effective treatment. Checkpoint inhibitors, specifically against CTLA-4 and PD-1, have shown to be much more efficacious compared to older treatments like chemotherapy (Raedler, 2019). To increase the proportion of cancer patients who can benefit from checkpoint inhibition, researchers are looking at combining multiple checkpoint inhibitors with other therapies for maximum benefit. However, for some cancers, such as glioblastoma, the lack of T-cells that traffic into the tumor presents an additional challenge to anti-PD-1 therapy. Furthermore, additive side effects and toxicities of combined therapies must also be considered

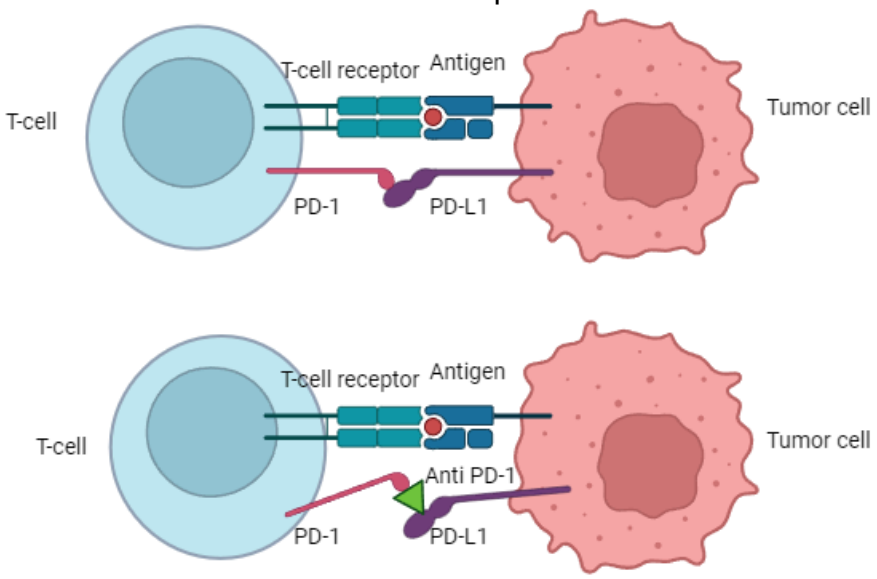

Figure 1. Mechanism of Anti-PD-1 Anti-PD-1 inhibits the binding of PD-1 to PD-L1. Created with BioRender

Anti-PD-1 and Melanoma

Melanoma is the deadliest form of skin cancer. In particular, patients with metastatic melanoma, cancer that spreads beyond the origin (also called stage IV cancer) (National Cancer Institute, 2020), have a 5-year survival rate of only 16%. Alarmingly, based on an analysis from 1970 to 2009, patients with metastatic melanoma between the ages of 18 and 39 have recently increased significantly in women - 8 fold; in men - 4 fold. In these patients with tumors that have spread, surgery and radiation therapy are often ineffective. The first cancer to receive approval for the use of ICB was metastatic melanoma (Alexander, 2016). Three types of checkpoint blockade have been approved, CTLA-4, PD-L1, and PD-1 (Raedler, 2019). Of these anti-PD-1 drugs, there are two approved for use in patients with metastatic melanoma, nivolumab and pembrolizumab (Raedler, 2019).

In the KEYNOTE-001 clinical trial, pembrolizumab (PD-L1 inhibitor) was shown to be remarkably effective in metastatic melanoma patients, including treatment-naive patients. The estimated 5-year overall survival rate increased from 16% to 34% in all melanoma patients. This was further increased to 41% in treatment-naive patients (Hamid et al., 2019). According to the analysis of the data from KEYNOTE-001, “The 5-year estimated PFS rate was 21% and 29%, respectively. Median progression free survival (PFS) was 8.3 months (95% CI, 5.8–11.1) in all patients and 16.9 months (95% CI, 9.3–35.5) in treatment-naive patients” (Hamid et al., 2019). This shows that the progression-free survival (PFS) for patients is relatively high, especially in treatment-naive patients due to the lack of exposure and therefore lack of immunity towards pembrolizumab. This analysis of the 5-year study “confirms the durable antitumor activity” in metastatic melanoma and how well one can tolerate the treatment (Hamid et al., 2019). The success rate of pembrolizumab alone is 30-40%.

Though pembrolizumab was shown to be a very durable treatment for metastatic melanoma, 86% of patients also experienced treatment-related adverse events (AEs), which included any side effects experienced by the patients. There are multiple grades of AEs, the higher the grade, the more severe the AE is. In the KEYNOTE-001 study, 17% of patients experienced grade 3 or 4 treatment-related AEs (TRAE), and no grade 5 was reported (Hamid et al., 2019). 36 of the 411 patients discontinued the treatment due to TRAEs. Compared to existing previous therapies and treatments, the KEYNOTE demonstrated how immunotherapies could revolutionize cancer treatment strategies

Anti-PD-1 and Glioblastoma

Glioblastoma (GBM) is an aggressive form of brain cancer with a median 5-year OS of 4.7% (Jaoude et al., 2019). Often, the course of treatment followed by patients with GBM, if not spread too much, would be surgical resection, followed by chemotherapy and radiation. Given the 5-year OS with all these treatments, the efficacy of current standard-of-care therapies for patients with GBM still remains poor.

In the brain, inflammation is limited because there is a finite amount of space available in the human skull. As a result, immune cells are suppressed when entering the brain. Immune infiltration is when immune cells enter the tumor. Immune infiltration typically helps fight cancer; however, in the setting of GBM, the tumor changes the infiltrating macrophages into tumor-associated macrophages, which create an immunosuppressive tumor microenvironment, therefore preventing the immune system from attacking the tumor. PD-1 signaling is just one of the many challenges in the tumor microenvironment, suggesting that combined therapies may

be required to overcome the immunosuppressive tumor microenvironment. In addition, patients with GBM also suffer from a compromised immune system because GBM affects the immune system outside of the brain (Lorrey et al., 2023).

Due to the many genetic variations in the tumor of GBM patients (Rocha Pinheiro et al., 2023), it is difficult to treat with anti-PD-1 or any type of immune checkpoint inhibitor. In CheckMate 143, nivolumab, an anti-PD-1 inhibitor, is compared to bevacizumab, an approved therapy for GBM patients (a type of chemotherapy). Unfortunately, the median overall survival was similar in both trials, 9.8 months for nivolumab and 10.0 months for bevacizumab. Both treatments resulted in a 12-month overall survival of 42%. These results showed that nivolumab in GBM patients did not provide any more clinical benefit than existing approved therapies.

Discussion

Immunotherapy has significantly fewer risks and costs when compared to surgery, radiotherapy, and chemotherapy, allowing cancer treatments to become more accessible to all (Pinheiro et al., 2023). However, there still are risks associated with immunotherapy, particularly in the AEs that may occur. Most people overlook how much AEs can affect one's recovery from cancer. Due to the high toxicity levels of therapies, specifically anti-PD-1, which is necessary for the therapy to be effective, patients often face AEs, sometimes so severe that it may lead to patients discounting treatment or increased mortality. Due to these harsh consequences of the therapies, more research must be focused on decreasing the severity and occurrence of these AEs.

Anti-PD-1 will likely be a vital ingredient to the cocktail of cancer drugs available to oncologists, but can not be the only therapy to be relied on. Researchers expect combination therapy to be the most effective treatment for patients with GBM (Pinheiro et al., 2023). For example, trials have shown that combining pembrolizumab and bevacizumab can prolong survival time and benefit tumor control (Yang et al., 2020). Though the results can be discouraging, immunotherapy is viewed as a fundamental factor in increasing patient life expectancy and quality of life.

Like most therapies, anti-PD-1 is not a one-size-fits-all solution to every and all cancer patients. Though it provides a durable (18% increased survival rate (Hamid et al., 2019)) response to metastatic melanoma, patients can still experience severe AEs. These AEs can diminish a patient’s quality of life significantly, something arguably just as important as extended survival. This is even more true for glioblastoma and other cancers. Researchers will need to continue to persevere and be thoughtful about different drug combinations and rationally design interventions with the specific challenges for each cancer in mind. This will take collaboration from many different fields, but once successful, could save millions of lives.

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