Transactions on Materials, Biotechnology and Life Sciences
ISSN: 2960-1932, eISSN: 2960-2319 | Volume 5
MMTCS 2024

The Contemporary Immunotherapies of Pancreatic Cancer

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Abstract. Pancreatic cancer is a malignant tumor found in the digestive system with hidden onset, rapid progression, poor therapeutic effect and prognosis. In the last few years, immunotherapy has been included in the various solid tumors' treatment, and pancreatic cancer immunotherapy has gradually attracted attention. Over the past decades, clinical studies have demonstrated some currently typical immunotherapies of pancreatic cancer which has already accepted by the Food and Drug Administration (FDA) which are immune checkpoint inhibitors (ICIs), CAR T-cells and vaccine. Optimistically, results provided by the scientists had described effective outcomes of these immunotherapies in treating this cancer. By combining these new treatments with the traditional, safe therapies, such as surgery or chemotherapy, an increase in patients recover or survival rate has been shown through this combination. However, new therapies mean certain hurdles are existed in these methods due to the identity of "newbies." The emerging immunotherapeutic treatments for pancreatic patients will be explored, in order to provide more rational treatment recommendations for the patients of pancreatic cancer.

Keywords: CAR T-cells; GVAX vaccine; Pancreatic cancer; PD-1.

1. Introduction

Pancreatic cancer is known as a worldwide fatal malignant tumor and one of the major factors of causing cancer mortality in many places, especially developed countries. There are two main types of this cancer which are the adenocarcinoma and pancreatic endocrine tumors. In America, the pancreatic ductal adenocarcinoma (PDAC) is currently the third most common disease causing the mortality of cancer, overtaking breast cancer. Furthermore, before 2040, PDAC is expected to rank just one spot behind lung cancer as the leading cause of cancer mortality [1]. The cornerstones of pancreatic cancer are chemotherapy and surgery for the past decades which are safe and standard treatments for this cancer, while the treatment effect is not satisfactory [2].

Fortunately, according to novel scientific findings, immunotherapy which is still a new method for treating cancer has also been growing fast over the last few decades on pancreatic cancer. Numerous trials were made by scientists and has demonstrated many positive results. The prevailing immunotherapies that have been utilized on pancreatic cancer patients are immune checkpoint inhibitors (ICIs), chimeric antigen receptor (CAR) -T cells therapy and vaccine. Latest advancements on these immunotherapies includes programmed death 1 (PD-1), programmed death ligand 1 (PD-L1), and cytotoxic T lymphocyte antigen-4 (CTLA-4) and other immune checkpoint molecules in cancer patients that receives the ICIs therapy which stimulate their anti-tumor immune responses and improve clinical results, the discovery of CAR T-cells' second and third generation operate longer when treating pancreatic cancer and GVAX vaccine demonstrates satisfactory effects on the patients that possesses pancreatic cancer. While, at present, most of the cognition of immunotherapy is relatively simple, and it is not a good way to explore the benefits or shortcomings of different therapies. This review will focus on the applications and limitations of the following immunotherapies: Immune checkpoint inhibitors, CAR T-cells therapy and vaccine therapy.

2. Immune Checkpoint Inhibitors (ICIs)

ICIs were identified as one of the cancer immunotherapies in 2011 when its initial treatment, ipilimumab, was approved by the FDA. ICIs aimed on the immunological receptors on the T-

lymphocytes to foster anti-tumor responses. The inhibitors exhibited enduring outcomes accompanied with minor toxicity [3].

2.1. Application

PD-1 is proposed for treating pancreatic cancer patients that have tested positive in distinctive gene alterations including microsatellite instability (MSI) and mismatch repair deficiency [4]. PD-1 inhibitors indicate no clinical advantages on other pancreatic cancer patients. However, scientists conducted new trials to test the effectiveness of PD-1 inhibitor combining with radiation therapy, chemotherapy, viral vaccinations.

According to preclinical research, a stronger antitumoral outcome is demonstrated by the combined of PD-1 inhibitors with gemcitabine in a mouse specimen that contained pancreatic cancer. Furthermore, cancer vaccination GVAX along with PD-1 inhibitor treatment has also displayed high improvement in the overall survival rate and enhanced the CD8+ T cells that generate IFN-gamma penetration [5]. Another clinical trial has been conducted by Shulan (Hangzhou) Hospital which supplied PD-1 combined GnP therapy to 27 patients with advanced pancreatic cancer during February 20, 2019, and June 21, 2021. The result of this trial was released at the end of 2022 (28th of December) that ten (37.04%) participants obtained partial response (PR), ten (37.04%) of the patients acquired stable disease (SD) and a total of seven (25.92%) patients got progressive disease (PD). Interestingly, a person experienced an outstanding tumor decrease after taking PD-1 combining GnP therapy four multiple times. The patient also underwent a surgery following a discussion of multidisciplinary treatment (MDT) [6].

CTLA-4, another treatment for this cancer has exhibited that pancreatic adenocarcinoma tumor growth could be decreased by injecting CTLA4 monoclonal antibody (mAb) in a small dose form. Results shows a markedly extended survival (median 81 days) in animals after having three 30 μg of anti-CTLA4 mAb injections [7]. Other phase 1 study suggested that the median of this cancer's overall survival (OS) increased after combining the GVAX vaccine with CTLA-4 which it elevated from 3.6 month to 5.7 month and the OS rate of one year also grew from 7% to 27%. Greater change in T cell receptor repertoire is presented through these two therapies' combination which corelates to a much longer life duration [8].

2.2. Limitations and Solutions

There are less limitations of ICIs' ability in treating pancreatic cancer as unpleasantly, so far, the FDA has just authorized only one PD-1 inhibitor which is the pembrolizumab and it is only effective on the high microsatellite instability (MSI-H) patients. This reveals that there are currently no ICIs therapy for patients that does not possess MSI-H. Furthermore, the major reason of less immune checkpoint inhibitors approved by the FDA is because the PDAC has demonstrated exceptional immune checkpoint inhibitor resistance. Apart from that approximately 97% of patients with microsatellite stable status (MSS) exhibited no advantages after treated by ICIs. Similar result also showed in the trials of chemotherapy and ICIs combination [7]. The presence of biomarkers also indicates the resistant effect to ICIs from PDAC. From the research paper, tumor mutational burden-high (TMB-H) and MSI-H is indicated in 0.5 percent of the tumors indicated MSI-H and tumor mutational burden-high (TMB-H). In other trials, 24 PDAC patients demonstrated 0% of objective response rate (ORR) which revealed the distinct resistance function of PDAC to ICIs. Besides, recent preclinical research has shown that in the pancreatic cancer tumor microenvironment (TME), immunosuppressive cells were increased. In order to solve this immunosuppressive cell increasing problem and to foster the production of the response of anti-tumorigenic T cell within PDAC, Royal and many other scientists investigated the monotherapy of ipilimumab's safety and effectiveness in patients wth mPDAC or progressed locally in an ongoing phase II trial [9].

3. CAR T-cell Therapy

The treatment of CAR T-cell is under the adoptive cellular therapy category in treating cancers. The idea of this treatment is to extract a number of patient's T cells through their bloodstream and insert special genes to attach to the CAR which form numerous CAR T cells in the laboratory. Those "new" T cells then is infused back into the patients and will kill the cancer cells by binding onto them. The very first CAR T-cells therapy was acknowledged in 2017 from the FDA which revealed that it is still a new and developing immunotherapy [10]. From latest studies, there are five generations of CAR T-cells currently investigated by researchers. In a nutshell, the signaling of CD247 domain is added in the initial generation of CAR T-cells, CD28 and TNFRSF9, two co-stimulation domains were added to CD247 domain in CAR T-cells second and third generations. Another co-stimulation domain, the IL-12 expression system was included to CD247 after the fourth generation was invented and newest generation, the fifth, has combined the STAT3-binding intracellular domain of a cytokine receptor, for example the IL2RB chain segment with the domain of CD247 [11].

3.1. Application

In pancreatic cancer, CAR T-cells second and third generation are actively used in clinical testing. Evidence indicates that in comparison with the T cells transduced with the former, first generation CARs, the transduction of T cells applying either second or third generation CARs function longer [12]. Among these trials, some of the major target antigens are carcinoembryonic antigen (CEA), prostate stem cell antigen (PSCA), mesothelin (MSLN), HER2, MUC1, and CD133.

Mesothelin, an antigen expressed on the surface of the cell in 80-85% of pancreatic cancer cases amongst the others [13]. One prestigous American university had conducted a clinical testing on the MSLN-specific CAR T-cell has shown that after three weeks of CAR T-cell therapy in the vein of a pancreatic cancer patient, it had demonstrated the result of perfectly stabled the cancer. Additionally, another clinical study on the adjusted CAR T-cells that target mesothelin treatment yielded a potent anticancer influence on tumor xenografts and pancreatic cancer cell lines. From research, a phase 1 trial of pancreatic cancer with metastases which had established immunity to chemotherapy has prove the autologous mesothelin-specific CAR T-cells (CARTmeso cells) possess a substantial, secure anticancer ability.

Moreover, by combining this therapy with pancreatic cancer traditional treatments including surgery and radiation therapy may improve the treatment effectiveness on the tumor cells. In a phase 1 trial, the CAR T-cells were treating the HER2, a cancer stem cell marker, in advanced pancreatic tumors by combining with nab-paclitaxel and cyclophosphamide, two chemotherapy treatments. The outcome of this trial exhibits the feasibility, safety, and possible therapeutic advantages of HER2-targeting CAR-T therapy by having a median progression free survival (PFS) of 4.8 month, a partial response lasting 4.5 month of one patient and five out of eleven patients possessed stable illness [9]. Secreting particles in other immunotherapies with the CARs could create an "enhanced CAR T cells" which may contain better therapeutic effects on pancreatic cancer. The molecules involved in this secretion are cytokines, checkpoint inhibitor antibodies and costimulatory molecules [14].

3.2. Limitations and Solutions

As the therapy is a new technology that is discovered in recent years, there are some limits that this treatment still needed to improve in order to reinforce this treatment's efficacy in fighting tumors and lessen the side effects and of it. The biggest and challenging limitation of this therapy is the antigen escape. An example of an antigen escape is that when treating CAR T-cells treatment, there is a huge percentage about 70–90% of patients that has malignant cells demonstrated either completely or partially loss of the expression of target antigen [15].

The CAR T-cells treating in pancreatic cancer is limited by the tumor microenvironment's (TME) characteristics which includes heterogeneous antigen expression, immunosuppression and stromal desmoplasia. The stromal desmoplasia is like an obstacle which avoid transporting CAR-T cells

through the patient's body which reduce this therapy's effect. There are two solutions for this limitation, however one has not been investigated in pancreatic cancer therapy which is the intratumoral (local) delivery of CAR T-cells. The other approach is that the enzymes against chemokine receptors (like CXCR1 and CXCR2) or tumor stroma (like heparanase) which they stimulate infiltration and match tumor chemokines. Other challenge this therapy contains ist he microenvironment immunosuppression in this type of cancer. Preconditioning chemotherapy, discovered in early research, is a way to overcome this challenge by boosting the persistence of CAR-T cells and eliminates inhibitory immune cells. Combine ICIs (such as anti-PD-1/PDL-1) with CAR T-cells therapy is a second way. This prevents fatigue and senescence away from CAR-T cells. The third method of this immunosuppressive microenvironment limitation is the production of proinflammatory cytokines (for example IL-12 and IL-27) by CAR T-cells' generation [16].

4. Vaccine Therapy

Vaccine therapy is the most well-known immunotherapy in treating cancer. It boosts the body's innate immunity to against and clear tumor through helping the immune system inside our body to identify, respond and eliminate the antigens linked to tumors in cancerous cells. As to now, among the vaccines that is still investigating or is used in clinical trials, the human papillomavirus (HPV) vaccine is one of the successful vaccines created in treating cervical cancer by fighting against the human papillomavirus infections [17].

4.1. Application

Dendritic cell (DC)-based and tumor cell-based vaccines are the two forms of cell-based pancreatic cancer vaccines now available on the market. DC vaccines are normally packed with an antigen and then reinfused into the patients [14]. Cytotoxic CD8+ T cells is activated from the CD4+ and CD8+ T cells presented by the antigens. DC vaccines also secrets cytokines like TNF, IL-15, IFN-γ and IL-12 [11]. Twelve patients that infected pancreatic cancer was treated with DC vaccination loaded with the mucin 1 (MUC1) peptide in a clinical experiment of phase I/II. Based on the exhibited outcome, after the vaccination, four of them lived for more than 4 years without any symptoms of recurrence [14]. Besides, other trials made by scientists presented that combining chemotherapy or other immunogenic treatments with DC vaccinations have produced moderate fourteen to twenty percent PRs in a small group of patients. The GVAX vaccine is one of the tumor cell-based vaccines. In phase 1 study of the GVAX vaccination, it shows that the vaccine is safe and induces immune responses. In the study of phase 2 GVAX along with chemoradiation that is based on 5-FU has caused an one year OS rate and a 67.5% 1 year disease free survival (DFS) rate [11].

4.2. Limitations and Solutions

Although, there are numerous tirals proving the pancreatic cancer vaccines showed beneficial results in the patient survival rates, recent research discovered by scientists shown that the vaccines still have limitations for future improvements. According to a phase 1 study, all of the vaccinations that increased responses of T cells specific to tumors has shown zero effect in survival on a long time basis in pancreatic cancer. Proteins, peptides, whole tumor cells, or recombinant structures are comprised in these vaccinations that stimulate T lymphocytes that are specialized to tumors which target and attack cancer cells. This trial has prompted a serious concern on the efficacy of therapeutic vaccinations as a PDAC treatment. From several studies, CD8+ T cells has demonstrated the ability of infiltrating tumors, but meanwhile also trigger the Tregs recruitment which has defined as a possible causation of the unknown inadequate improvement of the patient survival rate. However, other scientists proved that Treg depletion can save defective T cells, allowing for therapeutic vaccination. Other scientists suggested that the GVAX vaccine improvement in the survival rate is still unknown in pancreatic cancer as less research is made in changing the GVAX vaccine to enhance the DFS and OS. Furthermore, another investigation displayed that combining the GVAX vaccine

with checkpoint blockade, for example PD-1 may be able to functionally repair CD8+ T cells as this combination is currently under studying [18].

5. Conclusion

This article underscores the three types of immunotherapies in pancreatic cancer by presenting specific results from a variety of research to describe the present success in applications of ICIs, CAR T-cells and vaccine as a therapy to patients of pancreatic cancer and several enhancements to increase the survival rates and effects. PD-1 inhibitors, mesothelin and GVAX vaccine are three outstanding examples demonstrated in this article. The combinations of the three treatments with traditional cancer therapies for instance, surgery, chemotherapy and radiation has also been discussed to have positive effects on patients. While there are challenges in these immunotherapies, new treatments are under testing and potential approaches for these limitations continue to develop. It is believed that with the continuous deepening of the study of tumor immune mechanism, various immunotherapy targets are constantly discovered, and immunotherapy for pancreatic cancer will certainly achieve gratifying results (more effective, safer and less side effect).

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