CAR T-Cell-Based Combination Therapy for Pancreatic Ductal Adenocarcinoma (PDAC)

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Abstract. It is projected that by 2030, following the lung cancer, pancreatic cancer will rank among the deadliest cancers. Because of the limited initial symptoms and early diagnosis, PDAC has one of the most dismal prognosis among all types of malignancies. Therefore, it is crucial to develop promising treatments for PDAC cases. Genetically engineering the T lymphocytes to express designed chimeric antigen receptors (CAR) is an emerging direction, but the major hindrance is the complex tumor microenvironment (TME) that restricts its performance. This review paper discusses the existing combinations between CAR T-cell and other therapies, the challenges, and future improvements in promoting the therapeutic outcomes of PDAC. Multiple chemotherapeutic drugs remodel the complicated TME to upregulate the potency of T cells. Some radiotherapies augment tumor-associated antigen expression to increase the anticancer activities. Additionally, the cytotoxicity of the engineered T cells is enhanced by checkpoint inhibitor blockade (CPB). Oncolytic viruses (OVs) represent another novel approach in CAR T-cell combination. OVs stimulate cytokines, which then trigger the chemokines in CAR-T-cell regulations. Being well-versed in the potential concurrent therapies in CAR T-cell-based manner facilitates researchers in conducting future studies in a more targeted way towards PDAC.

Keywords: Cancer, Chimeric antigen receptor, Chemotherapy, Radiotherapy, Immunotherapy.

1. Introduction

As a top primary contributor of tumor-caused mortality, pancreatic ductal adenocarcinoma (PDAC) comprises the predominant portion, constituting more than 80% of all pancreatic adenocarcinoma instances, and will turn into the runner-up of most fatal type of tumors within the next decade [1]. Various precancerous lesions can be categorized based on their size and functions in the pancreatic ductal system and are only resectable in early detection [2]. The most predominant precancerous pancreatic neoplasm is microscopic pancreatic intraepithelial neoplasia (PanIN), featuring a size of < 0.5 mm. Less than 10% of PDACs arise from macrocystic lesions, specifically known as the intraductal papillary mucinous neoplasms (IPMNs) with a greater size compared to PanIN [3]. In the neoplastic cells, somatic mutations of tumor suppressor genes and oncogenes, transcriptional reprogramming, chromosomal alterations, and epigenetic alterations are the molecular alterations that account for a part of the causes of PDAC [2]. Additionally, cellular alterations of the non-neoplastic tumor environment also contribute to the development of PDAC. For example, the immune alterations may affect PDAC progression and cause the lack of response when treated with immunotherapies [2]. Therefore, novel therapies that target the signals contributing to the immunosuppressive microenvironment are needed for clinical response improvement. Besides, cancer-associated fibroblasts (CAF) form desmoplastic stroma in PDAC, and can exhibit both tumor-promoting and tumor-suppressive properties by providing metabolic support to the tumor cells [4]. Recent studies demonstrate that CAFs can act as antigen-presenting cells while they were previously known to trigger T cell exclusion for immunosuppression, suggesting crosstalk of different types of cells that are not neoplastic inside tumor microenvironment (TME) [4, 5].

Although some improvements on therapies have been achieved in the past two decades, the overall survival (OS) of PDAC over a 5-year period remains the lowest among that of all types of cancers [6, 7]. The gloomy prognosis of PDAC is mainly attributed to the scarcity of early symptoms for detection, and thus PDAC is prone to spread to adjacent tissues with a size exceeding 2 cm at the diagnosis stage, where surgical resection, the only current curative method for PDAC, is no longer

feasible [2,6]. In screening, only 11% of PDAC diagnoses are localized while 52% of PDAC patients have developed metastasis with minimal chances of cure [2]. As a result, the current average overall survival (OS) of PDAC patients with and without treatments is 10-12 months and 5-6 months, respectively [2]. Therefore, systemic therapies towards PDAC remain a significant goal for improving the prognosis [8]. Current standard treatment for first-line therapy is chemotherapy (Gemcitabine with Nab-Paclitaxel) plus radiotherapy and is dependent on the stage of PDAC [2, 7]. Nonetheless, from 2012 to 2022, the chemo plus targeted therapies that are approved by FDA have only increased the 5-year OS from 2% to 11% [2]. Studies suggest that high T cell infiltration in PDAC causes improvements in survival effect, indicating that immunotherapies may bring potential benefits for PDAC patients [9, 10]. Checkpoint inhibitor is a novel immunotherapy for various types of malignancies, but the outcomes of its use in PDAC remain modest. Most immunotherapies are restrained by TME complexity and the limited tumor-related neo-antigens as a desirable target in the immunological responses [8].

Significant enhancements in personalized cancer immunotherapies are attained by engineering T cells to express chimeric antigen receptors (CARs). Firstly, T lymphocytes are isolated from patients' blood, bioengineered to express designed CARs for targeting specific tumor antigens, and then transfer back into the patient's blood stream. The addition of costimulatory domain enhances both T cell proliferation and survival in second generation CAR [7, 10]. CD19-targeted CAR is a FDA-approved therapy that results in desirable outcomes in refractory and relapsed patients with haematological malignancies [7]. In clinical trials of acute lymphocytic leukemia (ALL) in B cells, with CD19-CAR-armed T cells in its second generation, the complete remission (CR) is 80%-90% [10]. However, it is less efficient towards solid tumors, and is mainly restricted by the stromal hindrance, limitations in TME, and off-tumor toxicity [7, 10]. As CAR T-cell monotherapy alone is not an optimal approach in PDAC treatment, combination therapies with chemotherapy, radiotherapy, and immunotherapy itself are currently researched for increasing the treatment efficiency while reducing the hindrance effect [7, 10]. This paper discusses the existing status of different CAR T-cell-based combination therapies, the corresponding challenges, and future directions for PDAC treatments.

2. CAR T-cell-based Combination Therapy

2.1. Combination with Chemotherapy

2.1.1 Gemcitabine

Immunosuppressive cells infiltrate TME and dampen the antitumor responses in CAR T-cell therapy. Some types of these cells are regulatory T lymphocytes (Tregs), tumor-associated macrophages (TAMs), as well as myeloid-derived suppressor cells (MDSCs). Moreover, CAFs form another obstacle to limit CAR T cells penetration into the TME. In consequence, these cells have a negative effect on the final therapeutic performance for various solid tumors [11]. Currently, chemotherapies are used for TME remodeling and mitigating tumor size for cytotoxic T lymphocytes (CTLs) attack [11, 12]. Reducing the amount of immune suppressor cells and repolarizing the anti-inflammatory microenvironment are two ways of remodeling TME. For instance, both preclinical and clinical studies suggest that gemcitabine can reduce MDSCs while enhancing the cytotoxicity of CTLs and natural killer (NK) cells [11]. Enblad et al. showed that CR was achieved by 60% of the patients when gemcitabine was used as a neoadjuvant treatment [13]. Based on the existing research outcomes, gemcitabine is suggested to be operated as a combination therapy towards PDAC, in which the MDSCs and Tregs would be decreased and disabled in peripheral blood without altering the effect of immune cells [10-12]. This approach also causes TAMs polarization to shift them from M2 phase (a tumor-promoting state) to M1-like (a tumor-inhibiting state) phenotype, facilitating the immunostimulatory cytokine secretion for more antitumor activity [11].

2.1.2 Paclitaxel

Paclitaxel, another commonly used chemotherapeutic drug in PDAC treatment, can also manipulate the TME conditions. The Tregs and MDSCs are reduced when paclitaxel is used prior to T-cell infusion in lung malignancies and melanoma, respectively [11]. In pancreatic cancer, dense desmoplastic stroma forms a physical barrier that restricts the penetration of the engineered T cells, effective agents, and different immunocytes [10]. Paclitaxel modifies the TME by disrupting the stromal hindrance through depletion of CAFs and the corresponding extracellular matrix (ECM), allowing more immune cells to penetrate into the TME [11]. Nonetheless, the outcomes of paclitaxel and CAR-T-cell combination approach may vary under different dosage and specific treatment conditions.

2.1.3 Decitabine

In addition, the outcomes of the therapy are dependent on both the antigen presence and the antigen density [14]. Ideally, the target antigens present only on all cancerous cells without expressing on non-tumor cells to let the engineered T cells competently attack the tumors and avoid off-tumor toxicity [7]. As no such tumor-antigens express in PDAC, the antigen intensity becomes even more critical for the engineered T cells to effectively function. Tumor relapse is prone to occur if the antigen density is insufficient, and the administration of epigenetic modulators is considered a promising way to upregulate the target antigen density and overcome tumor immune escape in CAR T-cell therapy [14, 15]. Mucin 1 (MUC1) is overexpressed on approximately 90% of the human primary pancreatic cancer cells and undergoes predictable O-linked glycosylation, thereby becomes a type of target antigens in preclinical models of PDAC [10]. Anurathapan et al. developed a pancreatic cancer model targeted by CAR-MUC1 T cells with the introduction of decitabine, a hypomethylating agent (HMA) that belongs to a subset of the epigenetic modulators. The results demonstrated that decitabine upregulated the intensity of MUC1 expression for more than 7 times on the pancreatic cancer cells, and consequently improved the final treatment outcomes [15].

It should be noticed that the patients receive single or multiple doses in a short-term regimen and thus, the CAR T-cell pertaining determines the therapeutic efficacy. Any administration of chemotherapeutic drugs after CAR T-infusion may affect the long-term efficiency of the cells and their persistence [11]. Chemotherapy might cause temporary depletion of T cells, and this impact varies between different agents and types of T cells. The overall performance this combination therapy highly leans on the specific treatment conditions and schedule, some factors include dosage, cancer types, and types of chemotherapeutic drugs. Hence, optimizing regimen design is essential for the T cells to sustain and lead to the favorable clinical outcomes in this combination approach [11].

2.2. Combination with Radiotherapy

Radiotherapy is capable of enhancing the major histocompatibility complex (MHC) class I expression. Similar to HMAs, this regulation ability results in augmented antigen density and sensitivity for CTLs to attack, both locally and at distant tumor sites [14]. Therefore, tumor metastasis can be suppressed remotely with the use of radiotherapy. When combined with other monotherapies, radiotherapy aids in mitigating the TME limitations. For example, it promotes the antitumor immunological activities and infiltration of CAR-T cells in concert [14, 16].

Marcus et al. demonstrated that photon-based radiotherapy exhibits synergistic antitumor effect while minimizing the downsides in fusion with CAR T-cell therapy [17]. Moreover, iodine 125 seed brachytherapy with Robo1-specific CAR-NK cells, an alternative combination approach, dampens the development of PDAC cells along with in mice models [16]. However, radiotherapy exhibits a dual nature, meaning that distinct immunomodulatory responses can occur due to variations in the radiation dosage and number of fractions [16]. Sometimes radiotherapy causes immunosuppressive TME and depletes the activity of CTLs. In consequence, the fractionation times and radiation dose need to be optimized for best performance [16]. Although deficiency of knowledge on the standard regimen appears in this combination therapy, other studies showed that 8 Gy ×3 is the optimal dose-

fraction on the combination treatment of radiotherapy with checkpoint blockade (CPB). A few other studies pointed out that because of the resulting immunological effects, a lower dosage less than 2-4 Gy may be more suitable in CAR T-cell therapy [16, 18].

PDAC bears low mutation load and a weak sensitivity to immunotherapies. In a preclinical study established by DeSelm et al., low-dose radiation therapy was applied to heterogeneous PDAC with sialyl Lewis-A (sLeA) as an antigen target for CAR-T cells [18]. sLeA was used as a target antigen in this model, from which 25% of the cells lacked sLeA expression. The result indicated that with 2 Gy low-dose radiotherapy, the sensitivity of both sLeA+ and sLeA- cells was upregulated, and the non-antigen tumor relapse rate was decreased [14, 16, 18]. Activated engineered CAR-T cells can generate an apoptosis-triggering ligand by tumor necrosis factor (TNF), eventually mediating the cancerous cell-death. Thus, low-dose radiotherapy alleviates antigen escape, causing the augmented response rates and treatment efficacy in PDAC [14, 18].

As mentioned in the previous section, the complicated TME acts as a primary hindrance to CAR T-cell functions, and for this reason combination therapies are needed to overcome this limitation. NKG2D, an activating immune receptor on NK cells, may function to regulate the tumor growth and modulate the immunosuppressive TME after activation of the innate and adaptive immunity [16]. Nonetheless, the ability of 2 Gy radiation in remodeling the TME for CAR-T-cell functions remains unclear and is still under research. Although some preclinical results reveal that radiotherapy improves the immune responses of CAR-T cells towards PDAC, there are no approved associated products for clinical usage towards solid tumors [16]. More research needs to be done on this type of combination therapy to further confirm and explore its impacts on PDAC and other types of solid tumors.

2.3. Combination with Immunotherapy

2.3.1 Checkpoint Blockade (CPB)

In the immune system, checkpoints not only prevent autoimmunity, but also function in keeping a homeostasis in T-cell regulations. The existence of certain checkpoints on immune suppressor and pancreatic cancer cells makes them an attractive target in immunotherapy [19]. In malignancies, programmed death-protein or ligand 1 (PD-(L)1) is upregulated, which then dampens the activity of CTLs in local tumor sites while promoting tumor growth and metastasis. PD-1/PD-L1 diminishes CTLs activity through ligand binding (B7-H1 & B7-DC), resulting in a primary mechanism of immune suppression in the TME. Recently, PD-1/PD-L1 monoclonal antibodies have emerged as a representative immunotherapy in achieving impressive success towards multiple types of malignancies [20]. PD-1/PD-L1 inhibitors improve antitumor immunological responses by obstructing the evasion mechanisms of cancer immunity. However, the monotherapy of anti-PD-(L)1 has limited clinical activity for PDAC treatments [8].

Several studies suggested that in vivo, combination therapy involving anti-PD-(L)1 therapy upregulates T-cell cytotoxicity [7]. CARs contain an extracellular domain for ligand recognition, which is conjugated to extra intracellular signaling domains (CD28, CD137, OX40) in the third-generation CARs [19]. In addition to ligand recognition, the PD-(L)1 recognition extracellular domain of CARs also hampers the immune suppression activities caused by PD-1/PD-L1 interactions [20]. Compared to wild-type PD-1 CTLs, CAR-PD-(L)1 T cells have greater immune responses in decreasing the tumor volume. Yang et al. introduced an engineered 3rd-generation chimeric receptor targeting PD-1-CD28-4-1BB (PD1ACR) and PD1CAR T cells in mouse models with pancreatic cancer [19]. The result suggested that both approaches achieved around 80% efficacy at identifying and eliminating PD-L1-overexpression CFPAC1 cells with increased T cell retention [19, 20]. Another advantage of this combination therapy over the monotherapy against PD-(L)1 is that long-term memory is triggered towards the target antigens, which leads to faster immune responses in relapses.

Target specificity largely determines the CAR T-cell attack ability towards PDAC. Hence, the outcome of this combination therapy is also dependent on the PD-(L)1 expression intensity and the

corresponding binding affinity on different models [19]. It should be emphasized that host immune activity targets different tumor-associated antigens. In PDAC, potential tumor antigens encompass MUC1, mesothelin, and carcinoembryonic antigen, meaning that the response and performance of CAR-T cells may vary with different target antigens. This inconsistency in efficacy is a main limitation in this regimen since there is no ideal single tumor-antigen in PDAC, and therefore necessitates further research on this issue [20].

Comparably, in PDAC, the inclusion of cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) also interferes with T cell response in malignancies. In the peripheral tissues, while PD-(L)1 is often presented on T cells during late stages in immune response, CTLA-4 on T cells is one of the earliest negative regulators that impact positive costimulatory effects [20]. This arises from the higher binding affinity of CTLA-4 compared to CD 28 to different ligands, such as CD80 and CD 86, which are expressed at the cellular membrane of antigen presenting cells (APCs). Low CTLA-4 with high CD80 expression benefits the OS of PDAC patients [21]. However, while achieving some therapeutic effects in other types of cancer, anti-CTLA-4 monotherapy does not show promising results in treating PDAC. Several studies proposed various anti-CTLA-4-based combination therapies with other chemotherapeutic or immunological agents, but the regulation of anti-CTLA-4 antibodies on CAR T cells remains unclear and requires more research [21, 22]. Cell-extrinsic immune reactions generated from the depletion of CTLA-4+ Tregs by anti-CTLA-4 therapy may potentially improve CAR T-cell performance [22].

2.3.2 Oncolytic Viruses (OVs)

Currently, the combination with oncolytic viruses (OVs) is an intriguing research topic to enhance the CAR T cell activities. OVs represents a novel tumor immunotherapy that utilizes genetically engineered viruses that do not interfere with normal non-cancerous cells [23]. Regarding its favorable outcomes in cancer therapy, oncolytic viruses have a tumor-specific replication mechanism and consequently generate tumor-specific immunity. The complex TME can be regulated by OVs introduced with antitumor agents. More specifically, the re-engineered OVs alter and control the secretion of cytokine and chemokines in TME, leading to augmented the recruitment, development, and endurance of CAR T cells [7, 23].

As a type of therapeutic agent, chemokines play a critical role in treating advanced and metastatic cancers. In recent years, different OVs have been engineered to secrete multiple cytokines, including TNFα, type I interferons (IFNs), and several interleukins (ILs) [23]. When these mediators (especially TNFα and type I IFNs) are present in a substantial population, their intrinsic susceptibility allows them to induce direct toxicity towards adjacent tumor cells. Thus far, there are limited studies on analyzing the synergistic therapeutic performance regarding the addition of cytokine-armed OVs with the modified T cells. Watanabe et al. proposed an example that represents the current state of this combination therapy. In the established PDAC-engrafted mouse model, CAR-T cells with mesothelin-redirected functions were integrated with TNFα-IL2-expressing oncolytic adenoviruses (OAd-TNFα-IL2) to augment the antitumor efficiency and persistence of the T cells, which were dependent on the amounts of tumor-infiltrating lymphocytes (TILs) [24]. While the number of TILs were significantly upgraded and the proliferation of TILs was enhanced by OAd-TNFα-IL2, metastasis in lungs was observed. Nonetheless, no mice died from the metastasis as TNFα and IL2 counteracted the metastasis development. Moreover, the meso-CAR-T cells were increased in accumulation at PDAC tumor sites in regimen [23, 24]. Furthermore, another combination approach was built by combining the CAR-T cells with murine-TNFα-IL2-expressing adenoviruses (Ad-mTNFα-mIL2) in PDAC exhibiting high degree of aggressiveness and immunosuppression. The results demonstrated that Ad-mTNFα-mIL2 could enhance the trafficking of both CAR-armed and host T cells to the tumor sites. Ad-mTNFα-mIL2 also stimulated the production of CD80 and CD86, causing polarization of TAMs and dendritic cells to M1 phase for maturation [24]. As a primary proinflammatory cytokine, TNFα secreted multiple chemokines (CXCL-10, MCP-1, and RANTES) that aided in immune cells recruitment in the tumor. Meanwhile, T cells from the host immunity and the with CARs were both strengthened to suppress the tumor progression [24]. Therefore, the

combination therapy with cytokine-expressing oncolytic adenovirus is a potential novel treatment to conquer the challenges of TME in PDAC.

However, only tumor lines were tested in this study. Hence, the therapeutic performance of this combination therapy towards PDAC xenograft still remains unknown. Besides, there is an absence of a full immune system in the used brand of laboratory mice. This may potentially affect the immunological outcomes of the OAd therapy as the cytokines and chemokines mainly function in modulating the immune responses [24]. Although this combination approach has achieved success in greater T cell infiltration, there is limited information about the optimal dosing and the routes of administration. Intra-tumoral injection allows most OVs to be delivered into the tumor sites, but it cannot effectively deliver most OVs to the tumor milieu when visceral tumor or metastasis occurs. On the other hand, systemic injection potentially elicits the secretion of neutralizing antibodies that decrease the immunological functions of OVs [23]. Different routes of injection can induce significant differences in therapeutic outcomes. In the optimal situation, the OVs are competently delivered to the tumor lesions for TME remodulation before the T-cell infusion and amplification of different immune-cell infiltration, which eventually upgrade the general antitumor responses.

3. Conclusion

PDAC is primary type of pancreatic cancer with the second highest fatality rate and lowest 5-year OS among all malignancies. The lack of early symptoms leads to low early detection rate, which then causes limited resectability in PDAC. While the current standard therapies have not significantly improved the OS of PDAC patients, novel technologies including engineered CAR-T cells may have more potential. In terms of therapies for solid tumors, the complicated TME and stromal hindrance are the major limitations. These challenges can potentially be overcome through combination with other monotherapies, comprising chemotherapy, radiotherapy, and immunotherapy.

Gemcitabine is a chemotherapeutic drug that downregulates the MDSCs and Tregs in the TME while maintaining the normal antitumor immunity. Paclitaxel also helps modify the TME by depleting CAFs and ECM, interrupting stromal hindrance and allowing more immunocytes to penetrate into the cancer regions. As an epigenetic modulator, decitabine can increase the intensity of MUC1 expression, which significantly enhances the performance of the combination therapy towards pancreatic cancer cells. Notably, chemotherapy may induce temporary CAR T-cell depletion, and various combination designs generate different outcomes towards different tumors. Radiotherapy, for instance photon-based radiotherapy, offers the opportunity to upregulate the CTLs in both local and distant tumor regions. Studies showed that low-dose radiotherapy increased antigen recognition sensitivity to optimize the therapeutic results of the engineered T cells. However, the best dosage and regimen schedule have not been clearly studied for the combination with radiotherapy. Since immunosuppressive TME and decrease of CTLs may be triggered by radiotherapy, more research is required for this combination therapy to properly and effectively function in PDAC and other types of solid tumors. Currently, CPB is the most widely used immunotherapy in PDAC patients, but its performance is not desirable due to some TME limitations. When anti-PD-(L)1 monotherapy is integrated in PDAC, the tumor lesion size is reduced to a greater extent, and the immune system develops long-term memory aiding in future responses. For future potentials in CPB and CAR T-cell combination therapy, more studies need to be done for analyzing the regulation activities of other CPB therapies (for example, anti-CTLA-4) on CAR-T cells in PDAC. OVs has appeared as another promising novel treatment in various solid tumors, and they can be genetically modified to secrete certain cytokines, which enhance the CAR T-cell potency and sustainability in the TME by chemokine regulation. The major challenges associated with this combination therapy is the proper dosing and routes of administration. Since it is a fairly new approach, ongoing research of OVs and CAR T-cell combination therapy can potentially offer greater possibilities and therapeutic performance for PDAC treatments.

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