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The advancement in the application of immune checkpoint inhibitors in pNET

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Abstract. Pancreatic neuroendocrine tumor (PNET) is a unique subgroup of pancreatic cancer, which requires distinct treatment methods from the normal ones. The most common treatment for PNET is surgery, chemotherapy, and targeted therapy. Immunotherapy, especially ICIs, are hot topic in the oncology field in the recent years. However, researches found that the ICI therapies exhibit relatively lower significancy of patient outcomes for PNETs. Effects of long-term combination therapy still remains unanswered. This review analyzes the mechanisms of action, clinical applications, and potential adverse events associated with ICIs in PNET treatment. It was found that personalized treatment strategies, particularly when combining ICIs with other therapeutic modalities, could improve patient responses while minimizing adverse effects. The findings of this research provide valuable insights for future studies, highlighting the necessity of similarly exploration into the molecular determinants of response to ICIs in PNETs. While this work lays the groundwork for enhancing remedy techniques, questions concerning long-term results and finest patient selection stay unresolved. Future research should attention on those regions to boost the field of PNET management and improve patient care.

Keywords: Immune checkpoint inhibitors, PNETs, combination therapy.

1. Introduction

PNETs, a set of endocrine tumors originating in the pancreas, are considered one of the most common types of NETs. However, classified as one of the pancreatic cancers, only less than 2% of the patients are diagnosed as PNETs. This is because most of the pancreatic cancers start in the exocrine cells instead of the endocrine cells [1]. NETs have shown a significant surge in most of the developed countries. According to the data given, it is estimated to be around 1.01–5.25 cases per 100 000 population, which is becoming more and more influential in a negative way [2].

Improvements in imaging technology and the knowledge of these tumors have made it easier to diagnose PNETs that are asymptomatic or symptomatic. To diagnose a pancreatic NET accurately, a patient should undergo the following tests and procedures: blood tests, urine tests, imaging tests (e.g. X-ray, MRI, CT, PET scan), producing internal pictures of the pancreas, doing a biopsy to remove a sample of tissue for analysis, and gathering cells from other regions to examine whether the cancer has spread elsewhere [3,4]. Current approved standard treatments for pancreatic NETs have limited choice, including surgery, specific functional PNET treatments, chemotherapy, peptide receptor radionuclide therapy, and tumor ablation .

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Immune checkpoint inhibitors (ICIs) as one of the most effective immunotherapies, is not approved as a standard treatment for the PNETs. Aiming to inhibit tumor growth and destruction directly, traditional cancer treatments, such as radiotherapy, chemotherapy, and targeted agents still have a long way to go before reaching the effectiveness of immunotherapies. The sustained effectiveness of these direct-acting medicines is frequently restricted by resistance mechanisms and toxicities. In contrast, immunotherapies work with the patient's immune system and make it well-equipped to fight cancer [5,6]. If it is possible for ICI approved for PNETs treatment, not only will the patients gain more choices, but also a decrease in mortality rate of PNETs.

This review will provide a comprehensive analysis of whether ICIs are effective for treating PNETs, and problems and improvements of ICIs towards PNETs. Starting with the mechanism of ICIs, including PD-1 and CTLA-4, a clear explanation of this immunotherapy is given for a better understanding of this paper. There will be further discussion on the application of ICIs including negative responses from patients and drug resistance. Improvements on the ICIs about combination and personalized treatments are also deliberated.

2. Mechanism of ICIs

Throughout the years, the development in immunotherapy has shown promising results, especially in ICIs, where several inhibitory immunoreceptors, such as PD-1, CTLA-4, LAG3, TIM3, TIGIT, and BTLA, have been identified and further investigated in relation to cancer [7]. These receptors frequently deliver inhibitory signals via mono-tyrosine signaling pathways, such as ITSM and ITIM. Since they are surface molecules, blocking antibodies that obstruct ligand-receptor contact is an easy way to reduce their activity [8]. However, only PD-1 and CTLA-4 are extensively studied and approved by the FDA. Thus, the most broadly used in treating cancer around the globe in terms of ICIs.

Originally, the immune system checkpoints are designed to avert the immune response from being too overactive or exaggerated and accidentally harm healthy cells. The specific activation of tumor antigen T cell receptor and MHC connection allows T cells to identify cancerous cells. In normal cases, an immune response will be triggered and the T cell will release cytokines to eliminate the tumor cell whenever the TCR bind to the antigen of cancer cell. When the complementary proteins and checkpoint bind together, T cells get a "shut down" sign. This may prevent the immune system from destroying the malignancy by deactivating the T cell [9]. In order to avoid being killed, cancer cells usually express a high level of immune checkpoint proteins. This leads to a higher chance of binding with the receptor on T cells, causing it to be turned off. Hence, fewer cancer cells are being destroyed.

The most important discovery in cancer treatment over the last 10 years has been the introduction of T cell-focused immunomodulators that block the immunological checkpoints CTLA-4 and PD-1/PD-L1. Ipilimumab, the first antibody to suppress CTLA-4, received FDA approval in 2011. Soon after this, new types of monoclonal antibodies that aim at PD-L1 and PD-1 followed. Anti-PD-L1 includes atezolizumab and durvalumab, and anti PD-1 includes pembrolizumab and nivolumab. The two abovementioned antibodies are now among the anticancer medications that are prescribed the most frequently. These days, T-cell-targeted immunomodulators are used either alone or in combination with chemotherapy as first or second lines of treatment for about 50 distinct forms of cancer. Approximately two-thirds of all clinical trials in cancer are now underway, with over 3000 trials assessing T cell modulators [10].

2.1. PD-1

T cells, B cells, and NK cells are immune cells that express the cell surface receptor PD-1. Because it modifies T-cell activity, induces antigen-specific T cell apoptosis, and inhibits regulatory T cell apoptosis, PD-1 is crucial for reducing immunological responses and promoting self-tolerance [11]. When PD-1 attaches to its ligand, PD-L1, T cell activation is inhibited and downstream signaling pathways are activated [12]. As a transmembrane molecule, PD-L1 is also considered to be a co-suppressive factor in immunity. By inhibiting PD-L1, the growth of certain cells that release cytokines to destroy cancer cells can be hindered. (Fig.1) However, it happens only when combined with blocking

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PD-1. Certain tumors can evade the immune system's identification thanks to PD-L1, and inhibiting PD-L1 enhances the immune system's capacity to identify and combat various cancer types. Cancer is able to evade host immunity through the immune checkpoint signaling pathway known as the PD-1/PD-L1 axis [11].

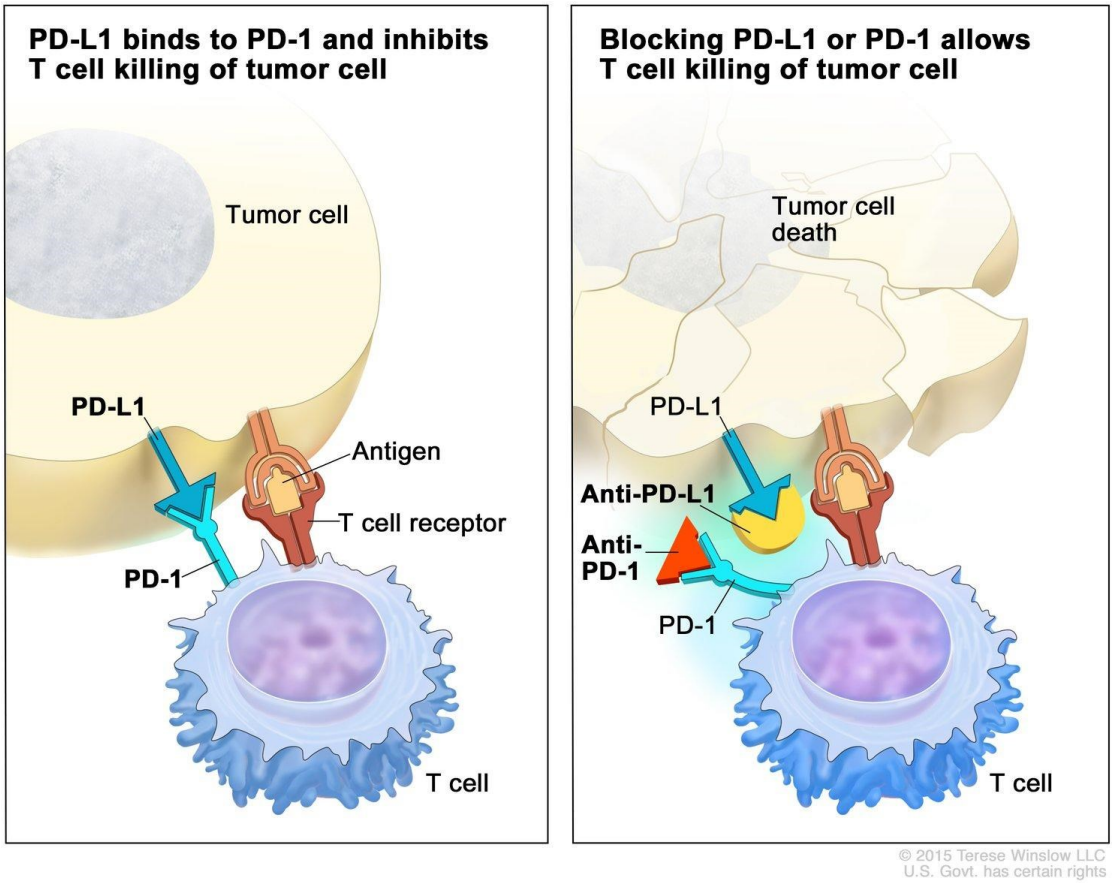

Figure 1. The left-hand side shows the release of cytokines of T cell is inhibited by the binding of PD-1 and PD-L1. The right-hand side shows through the binding with anti-PD-1 and anti-PD-L1, the T cell is able to destroy the tumor cell [13].

2.2. CTLA-4

CTLA-4 is the other unfavorable modulator of T cell immunity. It is thought to regulate T-cell proliferation early in an immunological response, primarily in lymph nodes [14]. Both CD4 and CD8 positive cells frequently express CTLA-4, which binds to T-cell-costimulatory factors on the surface of APC. CTLA-4 binding inhibits T-cell proliferation and the generation of IL-2 [15]. The inhibitory molecule CTLA-4, often referred to as CD152, is found on the surface of T cells that have been activated, and it keeps B7 from attaching to CD28. Its mechanism reduces T cell responses by stopping the first phase of naive T cell stimulation in the lymph nodes. The purpose of anti-CTLA-4 antibodies is to decrease T cell activity by preventing CTLA-4 binding [16].

3. Application of ICIs on PNETs

3.1. Drug

Treatment management for PNETs is extremely challenging as most of them only shows little efficacy. NETs are a subtype of neuroendocrine neoplasms (NENs) that are generally well-differentiated and low-proliferating [17]. NETs usually show low tumor mutation burden (TMB).

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However, in terms of treatments targeting PNETs, there is no specific FDA or other regulatory approval for the use of either pembrolizumab, nivolumab, ipilimumab, etc. Hence, the data of the use of these ICIs are limited and only based on small studies or case reports.

From the KEYNOTE-028 study, only 16 patients had PD-L1-positive tumor among 106patients. It is evaluated that the use of pembrolizumab in the 16 PNETs patients only shows 6.3% objective response rate (ORR), but early response and durable, which is significant given the advanced, heavily pretreated nature of the patients [18].

Data from PanNEN phase I/II clinical trials of different ICIs have been widely collected. T Phase Ib data on the PD-1 inhibitor tirapalimab showed an ORR of 22.2% among the PanNEN subgroup, which is composed of patients with positive PD-L1, TMB-H, or MSI-H status. Yet, no significant benefit between ICI monotherapy and NENs in newly conducted trials [19]. ICIs treatments show limited efficacy on PanNENs. Since ICI monotherapies appear to have little anticancer effect, dual ICI treatments have been employed in the clinic to boost clinical efficacy. From the DART phase II clinical trial, 44% of patients with high-grade NETs experienced tumor shrinkage (full or partial response) after receiving ipilimumab and nivolumab together. On the other hand, patients with low-grade NETs did not show any decrease in size of the tumor [20]. PNET patients may benefit from this pharmaceutical application regimen more than non-PNET patients due to the 20% ORR that comes with the combination of targeted anti-angiogenesis and ICI therapy [21]. It can be concluded that combined treatments show higher efficacy in PNETs. Overall saying, the application of ICI on PNETs is still undergoing investigation and the information provided by those small-scale researches is not enough to make a definite conclusion on the effectiveness of the application of ICI.

3.2. Adverse events

In KEYNOTE-028 study, 94% of the patient experienced adverse events (AEs). The most frequent side effects associated with pembrolizumab therapy were fatigue and diarrhea, but the PNET cohort did not experience any discontinuations due to treatment-related adverse events. One patient in the PNET cohort had malaise and grade 2 dyspnea. There were few treatment-related grade 3 adverse events, and neither cohort experienced any grade 4 adverse events or mortality [18]. In DART study, where patients are treated with ipilimumab and nivolumab together, the two most prevalent toxicities overall were nausea, and fatigue. Aspartate transaminase increase and hypothyroidism were the most common immune-related toxicities of any grade. Abnormal liver function and colitis, among other immune-related toxicities, were the most common grade 3 toxicities. However, both deadly toxicity and immune-related pneumonitis instances were absent [20]. Overall, fatigue is the most common adverse events of PNET treatments. Although there are various adverse events that may affect the patients negatively, all treatments have undergone safety control that all approved treatments only show some minor ones and will not threaten the lives of patients.

3.3. Drug resistance

As combination therapies often shows a higher efficacy towards PNETs, it can be hypothesized that monotherapies solely may not be able to overcome the drug resistance [22]. Therefore, combination therapies including two ICIs, ICIs with target anti-angiogenesis, or ICIs with chemotherapy are necessary in treating PNETs more efficiently. Proved in many studies, combinatorial therapies give maximum clinical impact. In order to develop more successful treatment strategies, there is the need to understand the immunological features and tumor microenvironment of PNETs, where the tumor microenvironment may play a role in promoting drug resistance mechanisms in this type of disease [22]. Since a pathogen or tumor is less likely to exhibit resistance to many medications at once, combination treatments have the major benefit of reducing the development of drug resistance.

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4. Optimization

4.1. Personalization

Optimizing treatment outcomes necessitates personalizing cancer immunotherapy by genetic analysis, biomarker identification, and T-cell dynamics monitoring. By identifying specific biomarkers, the response of patients to ICIs become predictable, which is a crucial part for personalizing treatment. For example, higher levels of CD8+ T-cell infiltration correlate directly with better responses to ICI therapy. While PD-L1 expression also shows some positive correlation with the responses, it is not always consistent [23]. In terms of genomic and transcriptomic profiling, high TMB and high MSI have shown a higher probability to respond to ICIs, leading to better outcomes. Mutational analysis is also vital in ICI therapy by identifying somatic mutations and understanding resistance mechanisms. By finding mutations that create an ultramutator phenotype in specific genes, such as POLE and POLD1, it may be feasible to identify individuals who could respond well to therapy. Moreover, if more scientific researches are done on mutations that lead to resistance (e.g., in PTEN, EGFR, STK11), the choice of combination therapies or alternative treatments to improve patient outcomes could have a clear path [23]. All of these aforementioned can help personalize treatment decisions. By evaluating them, clinicians can identify and prioritize patients who are more likely to benefit from immunotherapy, leading to a more effective treatment strategy.

4.2. Combination therapy

Combination therapy often shows higher efficacy. ICIs, especially, have the flexibility to combine with many other therapies. For instance, two different types of ICIs, chemotherapy, targeted therapy, anti-angiogenic agent, cancer vaccine, radiation therapy, etc. However, treatments for PNET using combination therapy are not widely studied yet, only dual ICIs, chemotherapy, and targeted therapy are studied in small scale. As dual ICIs are discussed previously, it is not going to be mentioned again here. For ICI combined with targeted anti-angiogenic agent, the combination of atezolizumab (an ICI) and bevacizumab (an anti-angiogenic agent) in patients with grade 1/2 PNETs and non-PNETs are studied. Resulting with a 20% ORR for both and 1-Year PFS rates of 75% for PNETs and 52% for non-PNETs, PNET patients may benefit more from this combination therapy [23]. In a Phase II study of ICI combined with chemotherapy, 12 out of 15 patients with advanced NETs were treated with nivolumab and temozolomide. Outcomes showed 25% achieved PR, 67% had SD, while one patient had PD [21]. This indicates potential effectiveness of this regimen in advanced NETs.

5. Conclusion

This review has discussed the application of ICIs on PNETs--from the mechanism of ICIs to the personalized treatment and combination therapy for PNETs. Up till this moment, there is no ICI therapies approved by the FDA specifically for PNET as the efficacy is too low. While ICIs have shown promising result in treating other types of NETs, particularly in small cell lung cancer and melanoma, their role in PNETs remains less indispensable. Yet, combination therapy shows relatively higher efficacy in treating PNETs since they are more able to overcome drug resistance. As mentioned in the introduction, PNET is a rare type of NET and pancreatic cancer, hence, not much studies are done. Since the effectiveness of ICIs treatments on PNETs are not significant, ICIs could never be one of the common treatments for PNETs until better outcomes are seen or new checkpoints discovered. However, it is crucial to recognize this review's limits. The long-term effects of combination therapies and the molecular predictors of response to ICI remain underexplored. Additionally, our analysis did not extensively cover the role of the tumor microenvironment, which could greatly influence treatment efficacy and patient prognosis. Looking ahead, research in the future should concentrate on finding biomarkers for patient classification and conducting long-term studies to evaluate the efficacy of combination medicines. enhance patient outcomes in the end and open the door for novel PNET treatment modalities.

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