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Editorial

Immunotherapy Perspectives for Pancreatic Ductal Adenocarcinoma (PDAC)

Sepideh Hajivalizadeh[1], Shahin Akhondzadeh[2]*

1. Osteoporosis Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran
2. Psychiatric Research Center, Roozbeh Psychiatric Hospital, Tehran University of Medical Sciences, Tehran, Iran

Pancreatic cancer commonly refers to Pancreatic Ductal Adenocarcinoma (PDAC) which accounts for more than 90% of pancreatic cancers (1). The substantial burden of disease is characterized by the approximate deaths of as many as cases annually. PDAC as the seventh leading cause of cancer-induced mortalities globally, has been a focal point of research in the field of oncology (2).

Despite the vast research and significant effort devoted to the treatment of PDAC, the 5-year survival rate for this cancer remained less than 5%. This scant survival rate is a consequence of late-onset diagnosis, accelerated tumor growth, and limited extant treatments. Hence, innovative strategies, such as immunotherapy, seek to enhance antitumor immune reactions, offering a more precise and targeted therapeutic alternative (1).

Immunotherapy is categorically segmented into four primary subtypes: vaccines, cellular therapies, cytokines, and antibodies, with Immune Checkpoint Inhibitors (ICIs) falling under the latter classification (3).

Cancer vaccines stimulate immune responses by leveraging tumor-associated antigens to activate cytotoxic T-lymphocytes. These antigens can be sourced from whole-cell tumor lysates, recombinant tumor peptides, or recombinant viruses (1). Regarding vaccines, messenger RNA (mRNA) vaccines have been more promising than conventional vaccines, which present various challenges, for a personalized therapeutic approach in pancreatic cancer. These vaccines utilize the genetic profile of an individual's tumors, particularly those with mutant Kras, and custom proteins can be encoded (3). KRAS as a proto-oncogene has been recognized as mutated among 90% of patients diagnosed with PDAC, making it a valid target. They enhance antitumor immunity against oncogenic KRAS by presenting oncogenic KRAS neoantigens to major histocompatibility complex molecules, leading to the generation of cancer-specific memory T cells with long-term efficacy. In terms of other vaccines that are under investigation regarding their efficacy in PDAC, telomerase vaccines, gastrin vaccines, survivin-targeting vaccines, heat-shock protein peptide complex-based vaccines, MUC-1 targeting vaccines, listeria-based vaccines, dendritic

*** Corresponding author**
Shahin Akhondzadeh, Pharm.D, PhD, FBPharmacolS
Psychiatric Research Center, Roozbeh Psychiatric Hospital, Tehran University of Medical Sciences, Tehran, Iran
Tel: +98 21 5541 2222
Fax: +98 21 5541 9113
Email: s.akhond@neda.net

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cell-based vaccines, Granulocyte-Macrophage Colony-Stimulating Factor (GMCSF)-allogeneic pancreatic tumor cells (GVAX) vaccines, and Hyper-Acute-Pancreas algenpantucel-L (HAPa), Mucin-1 (MUC-1) vaccines can be mentioned (4–6).

Adoptive cell therapy is a rapidly growing technology consisting of NK cells or T cells that are either allogeneic or autologous. and have been genetically modified to target specific proteins using chimeric antigen receptors and T-cell receptors. These engineered cells are designed to recognize a peptide/MHC complex to effectively eliminate cancer cells. Numerous Chimeric Antigen Receptor (CAR) T-cell therapies have been approved for the treatment of different hematological malignancies. In PDAC, mesothelin CAR-T therapy has shown promise in preclinical mouse models by extending survival. However, the translation of this strategy to clinical settings for solid tumors faces various obstacles. To address these challenges, the development of next-generation CAR-T cells is underway to enhance the effectiveness of this therapy (3,7).

Cytokine therapies, including the use of Interleukin-2 (IL-2) and Interferon alpha (IFN-α), have been utilized as an early form of immunotherapy in the management of malignant conditions, establishing them as foundational components of this treatment approach. Cytokines with immune stimulatory properties, including IL-2, IL-15, GM-CSF, and IFN-α, have been incorporated as adjunctive elements in comprehensive immunotherapy strategies for PDAC. While monotherapy with cytokines showed promise during the peri-operative period, no recent studies have been published on this subject in the last ten years (3,8).

ICIs are monoclonal antibodies that target specific extracellular proteins expressed by tumor cells or tumor-associated lymphocytes, leading to the suppression of the body's immune response against the cancer (1). To address some of the main ICIs, Anti-PD-1/Anti-PD-L1, Anti-CTLA-4, Anti-TIM-3, Anti-TIGIT, and Anti-LAG-3 can be mentioned. Anti-PD-1/Anti-PD-L1 blocks the PD-1 pathway in which PD-1 ligation induces self-tolerance by preventing the activation of T cells as well as their proliferation. In PDAC, despite other solid tumors, the efficacy of Anti-PD-1/Anti-PD-L1 as monotherapy was not as promising as its effectiveness in combination with chemotherapy. The inhibitory CTLA-4 receptor on T cells competes with the co-stimulatory receptor CD28 for binding to the CD80 and CD86 ligands on antigen-presenting cells (APCs). CTLA-4 has a higher affinity for these ligands. Lower levels of CTLA-4 and higher expression of CD80 in PDAC are associated with increased survival rates. Binding of CTLA-4 primarily inhibits the activation of naïve T cells in lymphoid organs, but may also hinder the direct anti-tumor activity of T cells in the effector phase, potentially by reducing the presence of suppressive regulatory T cells. Based on a previous study, the co-administration of GVAX with anti-CTLA-4 appears to stimulate a T cell-mediated immune reaction and could potentially enhance the survival rate of patients with advanced PDAC. Numerous clinical trials are currently underway to assess the efficacy of the combination of anti-CTLA-4 therapy with other immunotherapeutic agents and/or radiotherapy in the treatment of PDAC (8). Both PD-L1 and CTLA-4 are often overexpressed in a subgroup of PDAC and are associated with poorer survival outcomes, making them potential targets for therapeutic intervention (1).

In conclusion, despite the aforementioned substantial investigations regarding therapeutic approaches for PDAC, treatment of this highly impacting disease is hampered by so many obstacles. Further research is necessary to overcome the remission-disrupting factors such as immunity evasions, altered tumor microenvironment, immunosuppressive activities, *etc*.

Keywords: Pancreatic cancer, Vaccine, Cell therapy, Cytokine, Immune checkpoint inhibitor, CAR-T cell, Anti-PD-1, CTLA-4

Conflict of Interest

The authors had no competing interests.

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