INTERNATIONAL JOURNAL OF HEALTH & MEDICAL RESEARCH

ISSN(print): 2833-213X, ISSN(online): 2833-2148

Volume 03 Issue 03 March 2024

DOI : 10.58806/ijhmr.2024.v3i03n10

Impact Factor: 5.329, Page No. 146-154

Emerging Trends in Immunotherapy Management for Pancreatic Cancer: A Literature Review

Jhonny Joel Calle Bravo[1], Nicole Stephanie Rodríguez Acurio[2], Jessica Valeria Medrano Aulestia[3], Tatiana Carolina Rosales Pavón[4], Delia Soledad Calle Cadme[5], Nathaly Paola Castro Moscoso[6]

[1]Physician, Universidad de Especialidades Espíritu Santo, Master´s Degree in Occupational Health & Safety, ORCID: 0009-0005-8143-5317

[2]Physician, Universidad Nacional de Chimborazo, ORCID: 0009-0000-1642-5087

[3]Physician, Universidad Tecnológica Equinoccial, Master´s Degree in Health Management Universidad Antonio de Nebrija, ORCID: 0009-0000-3940-262X _

[4]Physician, Pontificia Universidad Católica del Ecuador, ORCID: 0009-0008-1785-2070

[5]Physician, Universidad Católica de Cuenca, ORCID: 0000-0002-4579-4030

[6]Physician, Universidad Central del Ecuador, ORCID: 0000-0002-4535-8394

ABSTRACT: The prognosis for pancreatic cancer (PC) is poor making it a substantial treatment challenge. A potentially effective treatment option is immunotherapy. To better understand the changing field of immunotherapy in PC management, this analysis will focus on important tactics and their consequences. To find relevant research published between 2019 and 2024, a thorough literature search was carried out using Scopus, Google Scholar, and PubMed. Tumor cells may be targeted and immune responses can be modulated using passive immunotherapeutic techniques such as CAR T-cell therapy and programmed death checkpoint inhibitors. Preclinical and clinical studies show enhanced effectiveness of combination therapy, such as anti-PD-1/anti-PD-L1 plus CTLA-4 inhibitors. Although their efficacy varies, active immunotherapeutic strategies, in particular cancer vaccines, seek to promote immune recognition of tumor antigens. Subpar response rates and treatment-related toxicity are obstacles. Checkpoint inhibitors, CAR T-cell therapy, and cancer vaccines are a few possible therapeutic options in the exciting field of immunotherapy for PC treatment. Nevertheless, further study is required to enhance these strategies and enhance patient.

KEYWORDS: Immunotherapy, pancreatic cancer

I. INTRODUCTION

One of the relatively few cancer forms for which the prognosis has not changed much over the last several decades is pancreatic cancer (PC). Although the overall 5-year survival rate for cancer is above 60%, the all-stage PC survival rate is still around 10% (1). The three main characteristics of pcs contribute to their dire prognosis and make them extremely challenging to treat. The difficult anatomic location is the cause of approximately 30% of patients who present with locally advanced disease, with tumor advancement along major abdominal vessels and propagation along the rich neural routes in the area. This predetermination also limits the ability to extend surgical resection margins, leading to about 80% R1 resections (2). Secondly, PC is more likely to cause early metastases, which may appear even before the main tumor is noticeable to the doctor (3). This is one of the reasons why even smaller primary resectable tumors often return even after curative resection, with only approximately 20% of cases ending in a 5-year survival rate (1). Systemic oncologic therapy is becoming the new norm in the neoadjuvant situation because of these two primary hallmarks of PC. Its goal is to consolidate the advanced tumor and/or prevent occult distant dissemination so that the best candidates for surgical excision may be identified. However, because of the PC microenvironment design, even if novel combination regimens like FOLFIRINOX or gemcitabine-nab-paclitaxel may be effective and promising in extending life, when given alone, they almost never result in a cure.

The thick stroma that surrounds the tumor cells and determines their chemoresistance is the third regrettable feature of PC (4). Ineffective medication delivery and hypoxia, which promotes endothelial-mesenchymal transition and PC cell invasiveness, are caused by a weak vascular tumor network (5). The dense fibrotic stroma physically prevents the injected medications from diffusing and lengthens the distance between the arteries and the tumor cells, preventing the pharmaceuticals from reaching the cancer cells at therapeutic concentrations (6). Consequently, any therapy that is administered passively would presumably be ineffective.

Carcinogenesis and tumor growth are actively influenced by the tumor microenvironment. The immune system's components are a part of this environment, and based on the balance and composition of immune cells, they can either help the tumor avoid effective recognition and elimination or tip the response toward tumor antigen recognition and an appropriate adoptive anti-tumoral response. Immunotherapy, the oncology subspecialty with the greatest rate of growth, is based on the manipulation of the immune response toward ongoing activation and tumor identification. Certain depressing cancer kinds, such lung cancer or malignant melanoma, have already seen a breakthrough in treatment thanks to immunotherapy (7). Patients with melanoma and kidney cancer, in particular, have shown improved long-term survival after receiving therapy with check point inhibitors (8). There is strong optimism that immunotherapy will significantly improve PC patients' prognosis. Compared to cytotoxic medications, immunotherapy has the potential to not only "work" throughout the course of treatment but also to self-replicate, amplify, and endure throughout the detection and treatment of cancer. This study aims to provide a thorough overview of the role and present efforts of immunotherapy for PC from the viewpoint of the physician in terms of potential integration in treatment, to map out the problematic areas, and to indicate potential areas for effective application.

II. METHODS

We used an integrated strategy in this thorough evaluation to methodically collect and assess pertinent material from reliable academic sources, such as Scopus, Google Scholar, and PubMed. Because immunotherapy treatment for pancreatic cancer (PC) is a difficult subject, we achieved a comprehensive analysis by using known procedures from related review research. Using keywords like "pancreatic cancer," "immunotherapy," "checkpoint inhibitors," "CAR T-cell therapy," "cancer vaccines," and "tumor microenvironment," we searched the literature.

Inclusion and Exclusion Criteria

We took into consideration articles that discussed the use of immunotherapy in the treatment of pancreatic cancer and were written in English and published in the recent 10 years (2018–2024). Included were studies with human participants and those that offered important new perspectives on the workings, developments, and therapeutic uses of immunotherapeutic approaches for PC. Studies that were not directly related to the issue or that lacked methodological rigor were, on the other hand, removed. Every article that passed the first screening based on abstracts and titles was carefully evaluated to ascertain its applicability and relevance for the review.

Categorization and Analysis:

We used a systematic classification strategy to arrange and examine the data on new developments in immunotherapy treatment for pancreatic cancer. Clarifying the function of immunotherapy in PC treatment and highlighting ongoing initiatives and difficulties in this area were the main goals of the study. To investigate the effects of different immunotherapeutic approaches on PC prognosis and patient outcomes, such as checkpoint inhibitors, CAR T-cell treatment, and cancer vaccines, analytical categories were created. Examining these immunotherapeutic methods' underlying processes, clinical effectiveness, and possible synergies was emphasized. Our goal in organizing the research around these topics was to provide readers a thorough picture of how pancreatic cancer immunotherapy is developing.

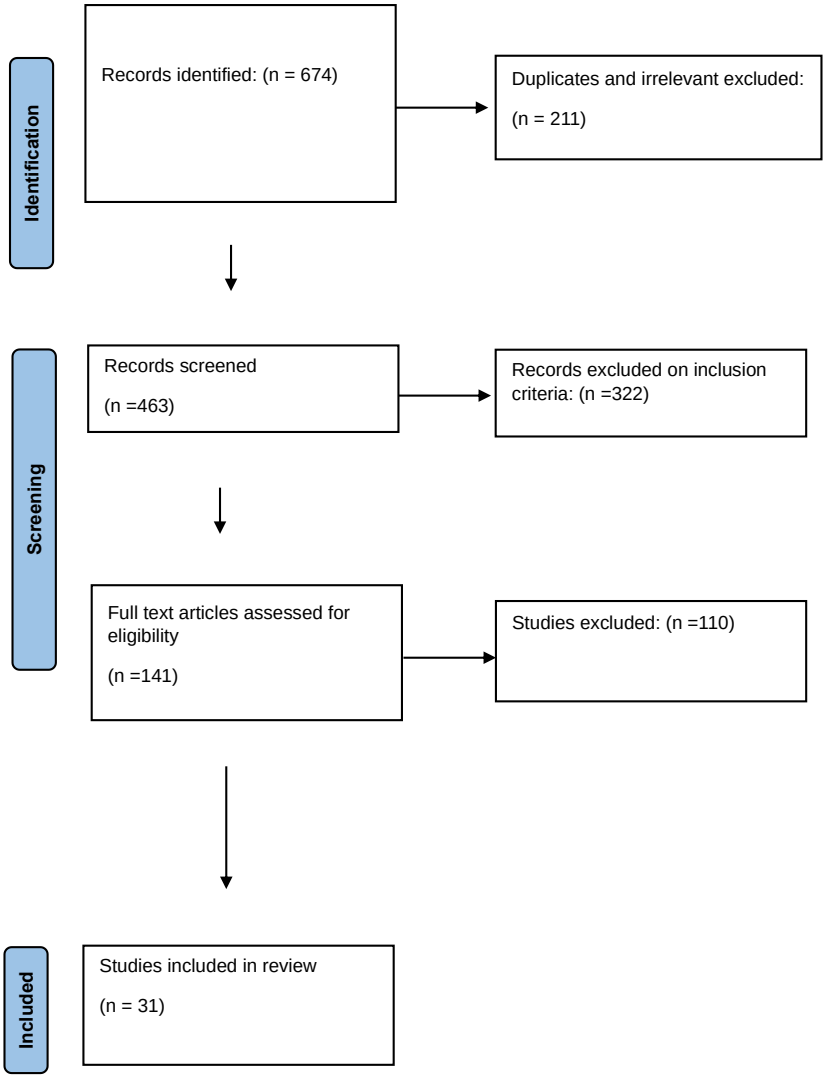

Figure 1. Flow Diagram for PRISMA

A. Passive Immunotherapeutic Strategies:

1) Programmed Death Checkpoint Inhibitors:

Program death protein ligands 1 and 2, or PD-L1 and PD-L2, are blocked by programmed death checkpoint inhibitors (9). These ligands are often linked to a bad prognosis. These ligands are overexpressed in tumor cells, which prevents CD8+ T-cell proliferation in the tumor microenvironment (TME) and evades the body's natural immune response. This evasion might lead to the tumor growing. Inhibitors of PD-1/PD-L1 stimulate and promote T-cell proliferation, which in turn targets the tumor directly (10).

a) Combination of Anti-PD-1 and CTLA-4 Inhibitors:

There are significant differences in the T cell immune regulatory mechanisms of CTLA-4 and PD-1. In patients with metastatic PDAC, a phase II clinical trial (NCT02558894) examined the impact of combining the anti-PD-L1 drug Durvalumab with Tremelimumab (a CTLA-4 inhibitor) with "Durvalumab monotherapy" after the failure of 5-FU or Gemcitabine-based treatment (11). With combination treatment, a response rate of 3.1% (95%CI 0.08–16.22) was seen. Durvalumab monotherapy did not result in any patient response. Sadly, there was no improvement in overall survival (OS) for individuals with previously treated metastatic PDAC when using durvalumab alone or in combination with Tremelimumab. Adverse effects, however, were comparable in groups receiving combination treatment compared to monotherapy. Anti-PD-1/anti-PD-L1 and CTLA-4 inhibitors together have shown increased efficacy in non-small cell lung cancer (NSCLC) and melanoma, among other tumor types (12).

Regretfully, PDAC cannot replicate the results shown in melanoma and NSCLC. PDAC has a low incidence of tumor mutations and a restricted invasion of immune cells, leading to an immunosuppressive microenvironment. Treatment becomes difficult since low levels of PD-L1 may also be expressed by certain PDAC tumors. Unfortunately, there is currently little data to support these combo therapy for PDAC. The effectiveness of combining Ipilimumab, another CTLA-4 inhibitor, with Nivolumab, an anti-PD-1 drug, in treating metastatic or advanced solid tumors, including PDAC, is being studied. Nevertheless, the findings are not yet accessible as of this writing. Adverse effects to PD-L1 and CTLA-4 inhibitors include encephalitis, nephritis, hypothyroidism,

hepatitis, colitis, and interstitial lung disease (13). The most serious adverse effects, affecting 1-4 percent of individuals, are digestive in nature. Moreover, a meta-analysis by Meserve et al. revealed that 193 patients had a 40% IBD recurrence after the treatment of PD-L1 or CTLA-4 immune checkpoint inhibitors (14). According to the data, patients treated with CTLA-4 inhibitors may have an increased risk of IBD recurrence when compared to those treated with PD-L1.

b) Combination of Chemotherapy and PD-1 Inhibitor Immunotherapy:

It has been shown that paclitaxel and gemcitabine, two examples of chemotherapy drugs, exhibit immunomodulatory qualities via a variety of pathways. To enhance the anti-tumor immune response, gemcitabine, for instance, upregulates the expression of major histocompatibility complex (MHC) class I and promotes T and NK cell penetration into the TME. Additionally, research has shown that gemcitabine may correct the faulty cross-presentation of tumor antigens by infiltrating dendritic cells (15). On the other hand, paclitaxel has been shown to enhance dendritic cell maturation and raise interleukin-12 (IL-12), which stimulates T and NK cells (16). Additionally, paclitaxel lowers the TME's Treg count. Because of this, these agents are quite intriguing. They might lessen immunosuppression, help immunotherapeutics, and expose the immune system to different tumor antigens. This is the justification for using PD-1 inhibitors in conjunction with such therapy for advanced or metastatic PDAC.

Gemcitabine and anti-PD-L1 have been shown to have a synergistic impact in animal models of PDAC (17). A number of clinical studies examining the combination of immune checkpoint inhibitor and chemotherapy have resulted from this. Phase Ib/II research examined the reduction in PDAC tumor progression rate in chemotherapy-naïve patients with metastatic PDAC (and other tumors) when pembrolizumab (PD-1 inhibitor) was paired with gemcitabine and Nab-Paclitaxel treatment (18). In patients with metastatic PDAC, progression free survival (PFS) and overall survival (OS) achieved a median OS and PFS of 15 and 9.1 months, respectively, due to a favorable correlation ($r = 0.777$). It also shown that people who have never had chemotherapy before may safely get such combo treatment. Despite this, patients had a significant prevalence of treatment-related side events despite being carefully chosen based on their performance status. To reduce toxicity, the research protocol was really changed to include pre-medication with dexamethasone on days when systemic chemotherapy was administered. Dexamethasone did, in fact, seem to be well tolerated and reduced the occurrence of a few adverse events. Thus, to improve treatment related adverse effects associated with such combination medications, dexamethasone should be included in future research or clinical implementation.

c) Combination of Radiotherapy and PD-1 Inhibitor Immunotherapy:

New pathways that enhance radiotherapy's effectiveness have been discovered via interactions between PD-1 inhibitors and radiation. Through the IL-6/MEK/ERK pathway, patients with non-small cell lung cancer (NSCLC) had greater radiation tolerance due to upregulated PD-L1 and downregulated NKG2D (19). A case study on an 83-year-old woman with locally advanced PDAC was published by McCarthy et al (20). The patient received pembrolizumab monotherapy after undergoing stereostatic body radiation treatment (SBRT). Following two pembrolizumab cycles, the tumor's volume and size decreased along with cystic degeneration. Furthermore, after therapy, the pancreas showed no signs of persistent dysplasia or cancer. Increased T-cell activity and numbers inside the tumor were linked to a greater tumor response, which also required the presence of CD8+ T cells and reduced myeloid cell infiltration. Furthermore, the prevention of liver metastases by radiation treatment was improved by the PD-L1 inhibition.

2) CTLA-4 Inhibitors:

PDAC cells are the target of cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitors. When CD4+ T-helper cells attach to antigen-presenting cells (APCs) via the CD80 and CD86 receptors, the CTLA-4 protein aids in their recruitment. Regrettably, PDAC tumors generally withstand CTLA-4 inhibitor monotherapy, with the exception of defects in mismatch repair. This is due to the TME's extreme specialization in immune system suppression, as was previously mentioned. In contrast to earlier research on metastatic melanoma, which revealed a considerable increase in CD8+ T-cell recruitment, a study conducted on PDAC animal models did not find a significant increase in CD8+ T-cell recruitment with the inflow of CD4+ cells (21). This, together with the particular immunosuppressive TME associated with PDAC, may help to explain why a number of clinical phase II studies including CTLA-4-opposing antibodies (such as Ipilimumab and Tremelimumab) in PDAC patients have not been able to significantly improve OS. For instance, Tremelimumab, a human IgG2 mAb CTLA-4 inhibitor, was assessed as a monotherapy treatment in patients with metastatic PDAC in a phase II open label research. This study discovered that a poor median OS of 4 months (95% CI 2.83–5.42) was experienced by 18 out of 20 patients who acquired progressive illness.

Additional clinical studies have provided some insight into the use of chemotherapy in conjunction with CTLA-4 inhibitor immunotherapy. In a phase Ib trial, Kamath et al. treated 31 patients with advanced or metastatic PDAC illness who had not responded to standard therapies with a combination of gemcitabine and ipilimumab (22). The three responders had a median response length of 11 months, with one patient's response duration reaching 19.8 months. The objective response rate was 14%. The median OS was 6.9 months (95% CI 2.63–9.57 months) and the median progression-free survival was 2.78 months (95% CI 1.61–4.83 months). Overall, the data showed that the PDAC tumors responded somewhat, leading to stable illness.

3) CAR T-Cell Therapy:

Adoptive cell transfer treatment includes CAR (Chimeric Antigen Receptor)-T cell therapy. Any extracellular molecular structure that can be recognized by an antibody may be targeted by CAR-T cells (23). In the end, it helps T cells identify tumor cells more easily and might enhance the immunosuppressive tumor microenvironment. Leukapheresis is utilized to collect T cells, which are subsequently grown, reinfused into the patient, and tailored to target a particular tumor antigen. To target the tumor, T-cells are often genetically modified to express CAR cell surface receptors (24). The majority of studies on reprogrammed CAR T-cells have looked on how they target mesothelin, a protein present in 80–85% of pancreatic cancer cases. Mesothelin has emerged as a key target for CAR T-cell treatment since it is overexpressed in a large number of pancreatic adenocarcinoma patients and has a high abundance on the tumor itself (25). The first study to look at the relationship between mesothelin and CAR T-cell therapy used eight intravenous and intratumorally injected CAR T meso cells in patients with advanced chemotherapy-resistant PDAC (26). They showed how mRNA-engineered T cells might be able to minimally cause side effects while mediating antitumor efficacy in patients with advanced PDAC by transiently expressing a particular CAR. Additionally, by analyzing the DNA and RNA from removed tumors, Rojas et al. created mRNA-engineered T cell vaccines (cevumeran) and paired them with atezolizumab and mFOLFORINOX (27). Half of the samples contained T-cells that reacted to more than one neoantigen, whereas the other half only responded to one. Eighteen months after surgery, there was no recurrence in any of the responders. The same team also looked at T-cells transiently expressing anti-mesothelin CAR in a phase I clinical study (24). An FDG PET/CT scan was used to quantify the tumor metabolic active volume in six patients who had metastatic PDAC that was resistant to chemotherapy. In three of the six patients, the metabolically active volume did not change; in one patient, however, it fell by 69.2%; in this case, only the liver lesions responded completely, with no impact on the underlying tumor. PFS values of 3.8 and 5.4 months were seen in two out of the six individuals. Although trials to far have not shown an improvement in PDAC survival with CAR-T cell treatment, stable disease was feasible. Targeting mesothelin together with PD-1 and CTLA-4 antibodies, CAR T-cells have been genetically produced in recent ongoing investigations.

B. Active Immunotherapeutic Strategies: Cancer Vaccines:

T and B lymphocytes' immune identification of TAAs is the basis for active immunotherapy's immune system activation. TAAs have been thoroughly investigated as cancer vaccines to treat PC in both clinical trials and in vivo mice models. There are three types of cancer vaccines: DC-based, antigenic-peptide pulsed, and entire cancer cell-based. These vaccines are designed to take advantage of and stimulate both active and innate immune systems in order to destroy tumor cells and prevent the illness from recurring in the future.

1) Antigen vaccines

The first idea behind immunotherapy is to increase the immune system's response to the tumor cells by repeatedly exposing it to foreign (cancer) antigens. Tumor-associated antigens that are absent from normal cells have the ability to trigger immune cell reactivity since cancer is produced from the body's own tissues and is thus more likely to cause immunotolerance. Most often, obliquitous mutations in PC—like those in KRAS, MUC1, and survivin—are the focus of attention (28)(29).

2) Peptide vaccines:

To increase their effectiveness, peptide vaccinations are often given in combination with an adjuvant. They offer the benefits of being inexpensive, simple to use, and easily merged with other therapies. Additionally, they typically have minimal adverse effects that are restricted to a localized response at the application site and are well tolerated. Almost all studies have shown detectable immunologic responses in response to their application. They are not very effective, however (1). Because of this, peptide vaccine interest has been waning and has almost completely faded in recent years. Not even in the adjuvant context after resection has there been any noteworthy outcome noted. Although there was no control group in this investigation, Palmer et al. observed survival after resection and immunization with seven KRAS peptides that were equivalent to that of the patients receiving adjuvant gemcitabine (28). Additionally, the updated current guidelines for adjuvant chemotherapy with combination therapy provide better outcomes. However, at least some of the patients have experienced an induction of an immunologic response to the vaccine agent as a proof of concept.

3) Whole tumor vaccines:

Whole-tumor vaccinations are an additional means of delivering antigen stimulation. The fact that the cells express many pertinent antigens gives them an edge over peptide vaccinations. Furthermore, it is not necessary to identify the particular antigens. The allogenic tumor cell lines in particular are easily accessible.

GVAX, which is made up of two allogeneic tumor cell lines, has been employed in the majority of studies to examine patients who have had their tumors removed and those that have spread and shown immunoreactivity. According to Le et al., patients with metastatic PC after prior treatment failure nearly doubled in survival when mesothelin-expressing Listeria monocytogenes was added to a combination of GVAX and the immunomodulating chemotherapeutic cyclophosphamide (P=0.02) (1). Specifically, extended survival has been associated with increased mesothelin-specific CD8+ T cell responses. However, the triple combination

did not demonstrate any benefit over the doctor's choice of single-agent chemotherapy in a subsequent phase IIb RCT (30). GVAX has also been shown to improve survival after PC resection, with a 93% one-year survival rate (1). Autologous PC stem cells were evaluated in a phase I study, although no survival data were reported. Even after resection, injection was tried on specific lymph node groups, and the median survival was 24.8 months, which is equivalent to conventional care (1). There aren't any phase III studies for these vaccinations as of now.

4) Vector vaccines:

A few research sought to improve the antigen presentation by using viruses or attenuated bacteria as the vector of delivery (31). By co-stimulating and supplying "danger signals," the vector may improve the engagement of innate immune signals. This might more successfully activate DCs and the subsequent cascade of T cell activation by the selected targets, such as CEA, KRAS MUC-1, etc. A few research have attempted to introduce oncolytic viruses at the local level. Phase II studies have not demonstrated any advantage, despite some indications in phase I trials towards better survival among responders.

Antibody-based trials have reached a high in publication throughout the last several years. The immune system produces ready-to-use products called antibodies that can be mass-produced. Like any other pharmaceutical medicine, the treatment processes may be standardized, leading to simpler safety regulations and mass manufacturing. Because clinical trials using antibodies are so simple to conduct, this accounts for their dominance in PC immunotherapy investigations during the last several years (1).

EGFR and VEGF-A are the most often targeted targets by antibodies in PC, which is probably because these antibody medicines have previously been approved for the treatment of other cancer types. Phase II and III antibody studies targeting EGFR and VEGF-A, even when used as first-line treatment, have not yet shown better survival whether given alone, in combination with other targeted medications, or in conjunction with chemotherapy in advanced prostate cancer (32)(33). Due to their higher toxicity, the rare combination studies involving more than one of these target drugs have limited utility even if they demonstrate some potential survival advantage (34)(35). Additionally, there has been no evidence of benefit when antibody therapy is combined with surgical resection (36) (37). Additionally, phase II and phase III studies have not shown increased survival when using various antibodies against IGF1R, MEK, BTK, and Notch2/3R such as ganitumab, selumetinib, ibrutinib, and tarextumab. Targeting elements of the tumor stroma, including matrix metalloproteinase-9, hasn't even shown a discernible advantage (38)(39). The most recent trials have concentrated on the combination of antibody and chemotherapy, as previous research has not shown any benefit from antibody treatment alone. Gemcitabine has seldom been used, sometimes in conjunction with nab-paclitaxel (40). While gemcitabine is the most tolerated available chemotherapy, FOLFIRINOX has significantly outperformed it in terms of increasing the survival of patients with advanced PC. However, the adverse profile of the antibody treatment may limit its ability to be used in conjunction with powerful chemotherapy, and it will be challenging to outpace its effectiveness.

III. DISCUSSION

A thorough examination of the many issues raised by pancreatic cancer (PC), which is distinguished by its aggressiveness, tendency to spread quickly, and resistance to traditional treatment approaches, is provided by this review paper (1). In spite of progress in cancer treatment, patients with PC have a poor prognosis; overall survival rates have not improved in recent decades (1). Because of PC's complicated biology and treatment resistance, novel therapeutic strategies are desperately needed. Offering innovative ways to get beyond the drawbacks of conventional medicines, immunotherapy has become a viable new avenue for PC treatment (1). Because they target cancer cells by using the body's immune system, passive immunotherapeutic strategies like programmed death checkpoint inhibitors have attracted a lot of attention. According to O'Reilly et al, clinical studies assessing the effectiveness of anti-PD-1/anti-PD-L1 in conjunction with CTLA-4 inhibitors or chemotherapy have shown encouraging outcomes in certain patient groups, but with differing degrees of success. Nonetheless, obstacles such unfavorable reactions to therapy and inadequate response rates highlight the need for more study to enhance treatment procedures and find prognostic biomarkers for patient classification (11).

Precise targeting of tumor-specific antigens may be achieved using CAR T-cell treatment, which is another novel approach to PC immunotherapy (23). According to Beatty et al. and Rojas et al, mesothelin is a protein that is overexpressed in a considerable number of PC patients. Preliminary research on CAR T-cell targeting has shown encouraging outcomes (27). Notwithstanding the positive results, obstacles including restricted effectiveness in enhancing overall survival and controlling treatment-related side effects continue to be major obstacles to the broad clinical implementation (24).

In order to activate the immune system to identify and eliminate cancer cells, active immunotherapeutic techniques, such as cancer vaccines, show promise. According to Muscarella et al. there has been evidence of immunologic responses to both peptide and whole tumor vaccines in preclinical and early clinical investigations; nevertheless, there is still uncertainty about their clinical effectiveness at improving patient outcomes (29). Additional approaches to improving the immune response to PC include vector vaccines and antibody-based treatments, albeit their efficacy varies.

IV. CONCLUSIONS

This analysis concludes by highlighting immunotherapy's promise as a cutting-edge approach to managing pancreatic cancer (PC), providing creative solutions to the problems this aggressive illness presents. Programmable death checkpoint inhibitors and CAR T-cell therapy are examples of passive immunotherapeutic strategies that have shown promise in destroying tumor cells and boosting the immune system. Cancer vaccines and other active immunotherapeutic techniques may help the immune system recognize tumor antigens. Significant obstacles still need to be overcome, however, such as poor response rates, toxicity associated with therapy, and a limited ability to increase overall survival. To fully achieve the therapeutic promise of immunotherapy in PC management, more research is required to improve treatment regimens, find predictive biomarkers, and minimize treatment-related toxicities.

Immunotherapy presents several encouraging therapeutic options for PC; nevertheless, there are some drawbacks and directions that need to be taken into account. First off, the varied nature of PC makes it difficult to predict therapy response and stratify patients, underscoring the need for individualized strategies and biomarker research. Furthermore, the emergence of resistance mechanisms and the possibility of immune-related side effects highlight how crucial it is to continue researching in order to improve treatment plans and patient safety. To overcome these obstacles and enhance results for PC patients, future strategies should concentrate on combination therapy, tailored delivery methods, and innovative immunomodulatory drugs. Large-scale clinical studies are also required to confirm the safety and effectiveness of immunotherapeutic strategies in a range of patient demographics, which will eventually open the door for the inclusion of immunotherapy in conventional PC treatment plans.

REFERENCES

1) Rangelova E, Kaipe H. Immunotherapy in pancreatic cancer - an emerging role: a narrative review. Chinese Clin Oncol [Internet]. 2022 Feb 1 [cited 2024 Mar 17];11(1):4–4. Available from: https://cco.amegroups.org/article/view/90353/html
2) Verbeke CS, Leitch D, Menon K V., McMahon MJ, Guillou PJ, Anthoney A. Redefining the R1 resection in pancreatic cancer. Br J Surg. 2006 Oct;93(10):1232–7.
3) Rhim AD, Mirek ET, Aiello NM, Maitra A, Bailey JM, McAllister F, et al. EMT and dissemination precede pancreatic tumor formation. Cell. 2012 Jan 20;148(1–2):349–61.
4) Johnson JI, Decker S, Zaharevitz D, Rubinstein L V., Venditti JM, Schepartz S, et al. Relationships between drug activity in NCI preclinical in vitro and in vivo models and early clinical trials. Br J Cancer. 2001 May 18;84(10):1424–31.
5) Feig C, Gopinathan A, Neesse A, Chan DS, Cook N, Tuveson DA. The pancreas cancer microenvironment. Clin Cancer Res. 2012 Aug 15;18(16):4266–76.
6) Olive KP, Jacobetz MA, Davidson CJ, Gopinathan A, McIntyre D, Honess D, et al. Inhibition of Hedgehog signaling enhances delivery of chemotherapy in a mouse model of pancreatic cancer. Science (80-). 2009 Jun 12;324(5933):1457–61.
7) Buchanan T, Amouzegar A, Luke JJ. Next-Generation Immunotherapy Approaches in Melanoma. Curr Oncol Rep. 2021 Oct 1;23(10).
8) Robert C, Schachter J, Long G V., Arance A, Grob JJ, Mortier L, et al. Pembrolizumab versus Ipilimumab in Advanced Melanoma. N Engl J Med. 2015 Jun 25;372(26):2521–32.
9) Brower V. Checkpoint blockade immunotherapy for cancer comes of age. J Natl Cancer Inst. 2015 Mar 1;107(3).
10) Ott PA, Bang YJ, Piha-Paul SA, Abdul Razak AR, Bennouna J, Soria JC, et al. T-cell–inflamed gene-expression profile, programmed death ligand 1 expression, and tumor mutational burden predict efficacy in patients treated with pembrolizumab across 20 cancers: KEYNOTE-028. J Clin Oncol. 2019 Feb 1;37(4):318–27.
11) O'Reilly EM, Oh DY, Dhani N, Renouf DJ, Lee MA, Sun W, et al. Durvalumab with or Without Tremelimumab for Patients with Metastatic Pancreatic Ductal Adenocarcinoma: A Phase 2 Randomized Clinical Trial. JAMA Oncol. 2019 Oct 1;5(10):1431–8.
12) Seidel JA, Otsuka A, Kabashima K. Anti-PD-1 and anti-CTLA-4 therapies in cancer: Mechanisms of action, efficacy, and limitations. Front Oncol. 2018 Mar 28;8(MAR).
13) Ji H huan, Tang X wen, Dong Z, Song L, Jia Y tao. Adverse Event Profiles of Anti-CTLA-4 and Anti-PD-1 Monoclonal Antibodies Alone or in Combination: Analysis of Spontaneous Reports Submitted to FAERS. Clin Drug Investig. 2019 Mar 4;39(3):319–30.
14) Meserve J, Facciorusso A, Holmer AK, Annese V, Sandborn WJ, Singh S. Systematic review with meta-analysis: safety and tolerability of immune checkpoint inhibitors in patients with pre-existing inflammatory bowel diseases. Aliment Pharmacol Ther [Internet]. 2021 Feb 1 [cited 2024 Mar 17];53(3):374–82. Available from: https://pubmed.ncbi.nlm.nih.gov/33314269/
15) Mcdonnell AM, Lesterhuis WJ, Khong A, Nowak AK, Lake RA, Currie AJ, et al. Tumor-infiltrating dendritic cells exhibit defective cross-presentation of tumor antigens, but is reversed by chemotherapy. Eur J Immunol. 2015 Jan 1;45(1):49–59.

16) Chen Y, Liu R, Li C, Song Y, Liu G, Huang Q, et al. Nab-paclitaxel promotes the cancer-immunity cycle as a potential immunomodulator. Am J Cancer Res [Internet]. 2021 [cited 2024 Mar 17];11(7):3445. Available from: /pmc/articles/PMC8332864/
17) Ho TTB, Nasti A, Seki A, Komura T, Inui H, Kozaka T, et al. Combination of gemcitabine and anti-PD-1 antibody enhances the anticancer effect of M1 macrophages and the Th1 response in a murine model of pancreatic cancer liver metastasis. J Immunother Cancer. 2020 Nov 13;8(2).
18) Weiss GJ, Blaydorn L, Beck J, Bornemann-Kolatzki K, Urnovitz H, Schütz E, et al. Correction to: Phase Ib/II study of gemcitabine, nab-paclitaxel, and pembrolizumab in metastatic pancreatic adenocarcinoma (Investigational New Drugs, (2018), 36, 1, (96-102), 10.1007/s10637-017-0525-1). Invest New Drugs. 2019 Aug 15;37(4):797.
19) Wu M, Huang Q, Xie Y, Wu X, Ma H, Zhang Y, et al. Improvement of the anticancer efficacy of PD-1/PD-L1 blockade via combination therapy and PD-L1 regulation. J Hematol Oncol. 2022 Dec 1;15(1).
20) McCarthy PM, Rendo MJ, Uy MD, Adams AM, O'Shea AE, Nelson DW, et al. Near complete pathologic response to PD-1 inhibitor and radiotherapy in a patient with locally advanced pancreatic ductal adenocarcinoma. Onco Targets Ther. 2021;14:3537–44.
21) Blando J, Sharma A, Higa MG, Zhao H, Vence L, Yadav SS, et al. Comparison of immune infiltrates in melanoma and pancreatic cancer highlights VISTA as a potential target in pancreatic cancer. Proc Natl Acad Sci U S A. 2019 Jan 29;116(5):1692–7.
22) Kamath SD, Kalyan A, Kircher S, Nimeiri H, Fought AJ, Benson A, et al. Ipilimumab and Gemcitabine for Advanced Pancreatic Cancer: A Phase Ib Study. Oncologist. 2020 May 1;25(5):e808–15.
23) Huber M, Brehm CU, Gress TM, Buchholz M, Alhamwe BA, von Strandmann EP, et al. The immune microenvironment in pancreatic cancer. Int J Mol Sci. 2020 Oct 1;21(19):1–33.
24) Beatty GL, O'Hara MH, Lacey SF, Torigian DA, Nazimuddin F, Chen F, et al. Activity of Mesothelin-Specific Chimeric Antigen Receptor T Cells Against Pancreatic Carcinoma Metastases in a Phase 1 Trial. Gastroenterology. 2018 Jul 1;155(1):29–32.
25) Pastan I, Hassan R. Discovery of mesothelin and exploiting it as a target for immunotherapy. Cancer Res. 2014 Jun 1;74(11):2907–12.
26) Beatty GL, Haas AR, Maus M V., Torigian DA, Soulen MC, Plesa G, et al. Mesothelin-specific chimeric antigen receptor mRNA-engineered T cells induce anti-tumor activity in solid malignancies. Cancer Immunol Res. 2014 Feb 1;2(2):112–20.
27) Rojas LA, Sethna Z, Soares KC, Olcese C, Pang N, Patterson E, et al. Personalized RNA neoantigen vaccines stimulate T cells in pancreatic cancer. Nature. 2023 Jun 1;618(7963):144–50.
28) Palmer DH, Valle JW, Ting Ma Y, Faluyi O, Neoptolemos JP, Jensen Gjertsen T, et al. TG01/GM-CSF and adjuvant gemcitabine in patients with resected RAS-mutant adenocarcinoma of the pancreas (CT TG01-01): a single-arm, phase 1/2 trial. Br J Cancer. 2020 Mar 31;122(7):971–7.
29) Muscarella P, Bekaii-Saab T, McIntyre K, Rosemurgy A, Ross SB, Richards DA, et al. A Phase 2 Randomized Placebo-Controlled Adjuvant Trial of GI-4000, a Recombinant Yeast Expressing Mutated RAS Proteins in Patients with Resected Pancreas Cancer. J Pancreat Cancer. 2021 Mar 1;7(1):8–19.
30) Le DT, Picozzi VJ, Ko AH, Wainberg ZA, Kindler H, Wang-Gillam A, et al. Results from a phase IIb, randomized, multicenter study of GVAX pancreas and CRS-207 compared with chemotherapy in adults with previously treated metastatic pancreatic adenocarcinoma (ECLIPSE study). Clin Cancer Res. 2019 Sep 15;25(18):5493–502.
31) Noonan AM, Farren MR, Geyer SM, Huang Y, Tahiri S, Ahn D, et al. Randomized Phase 2 Trial of the Oncolytic Virus Pelareorep (Reolysin) in Upfront Treatment of Metastatic Pancreatic Adenocarcinoma. Mol Ther. 2016 Jun 1;24(6):1150–8.
32) Abdel-Wahab R, Varadhachary GR, Bhosale PR, Wang X, Fogelman DR, Shroff RT, et al. Randomized, phase I/II study of gemcitabine plus IGF-1R antagonist (MK-0646) versus gemcitabine plus erlotinib with and without MK-0646 for advanced pancreatic adenocarcinoma. J Hematol Oncol. 2018 May 30;11(1).
33) Lim SH, Yun J, Lee MY, Kim HJ, Kim KH, Kim SH, et al. Gemcitabine and Erlotinib with or without Oxaliplatin in previously untreated advanced pancreatic cancer: A randomized phase ii trial. Yonsei Med J. 2021 Aug 1;62(8):671–8.
34) Halfdanarson TR, Foster NR, Kim GP, Meyers JP, Smyrk TC, McCullough AE, et al. A Phase II Randomized Trial of Panitumumab, Erlotinib, and Gemcitabine Versus Erlotinib and Gemcitabine in Patients with Untreated, Metastatic Pancreatic Adenocarcinoma: North Central Cancer Treatment Group Trial N064B (Alliance). Oncologist. 2019 May 1;24(5):589-e160.
35) Mettu NB, Niedzwiecki D, Rushing C, Nixon AB, Jia J, Haley S, et al. A phase I study of gemcitabine + dasatinib (gd) or gemcitabine + dasatinib + cetuximab (GDC) in refractory solid tumors. Cancer Chemother Pharmacol. 2019 Jun 1;83(6):1025–35.

36) Sinn M, Liersch T, Riess H, Gellert K, Stübs P, Waldschmidt D, et al. CONKO-006: A randomised double-blinded phase IIb-study of additive therapy with gemcitabine + sorafenib/placebo in patients with R1 resection of pancreatic cancer – Final results. Eur J Cancer. 2020 Oct 1;138:172–81.
37) Wei AC, Ou FS, Shi Q, Carrero X, O'Reilly EM, Meyerhardt J, et al. Perioperative Gemcitabine + Erlotinib Plus Pancreaticoduodenectomy for Resectable Pancreatic Adenocarcinoma: ACOSOG Z5041 (Alliance) Phase II Trial. Ann Surg Oncol. 2019 Dec 1;26(13):4489–97.
38) Tempero M, Oh DY, Tabernero J, Reni M, Van Cutsem E, Hendifar A, et al. Ibrutinib in combination with nab-paclitaxel and gemcitabine for first-line treatment of patients with metastatic pancreatic adenocarcinoma: phase III RESOLVE study. Ann Oncol. 2021 May 1;32(5):600–8.
39) Bendell J, Sharma S, Patel MR, Windsor KS, Wainberg ZA, Gordon M, et al. Safety and Efficacy of Andecaliximab (GS-5745) Plus Gemcitabine and Nab-Paclitaxel in Patients with Advanced Pancreatic Adenocarcinoma: Results from a Phase I Study. Oncologist. 2020 Nov 1;25(11):954–62.
40) Davis SL, Cardin DB, Shahda S, Lenz HJ, Dotan E, O'Neil BH, et al. A phase 1b dose escalation study of Wnt pathway inhibitor vantictumab in combination with nab-paclitaxel and gemcitabine in patients with previously untreated metastatic pancreatic cancer. Invest New Drugs. 2020 Jun 1;38(3):821–30.