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Pancreatic Cancer: An Emphasis on Current Perspectives in Immunotherapy

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Abstract

Pancreatic cancer affects both male and female individuals with higher incidences and death rates among the male population. Detection of this malignancy is delayed due to the lack of symptoms in the early-stage cancer, which makes it extremely difficult to treat. Identifying effective strategies has been a challenge for improving the survival rates in pancreatic cancer patients. Resistance to chemotherapy is often developed in pancreatic cancer treatment. Although many strategies are under clinical trials to target certain markers associated with cancer, immunotherapeutic approaches are currently gaining importance. Immunotherapy for pancreatic cancer is in the limelight after preclinical research showed some promise. Immunotherapy approaches were tested along with other treatment options to enhance the treatment effect. Adoptive cell transfer and immune checkpoint inhibitors are currently in clinical trials. The Food and Drug Administration approved pembrolizumab in a fast-tracked review for advanced pancreatic cancer patients. Pembrolizumab blocks the checkpoint protein, programmed cell death protein 1 (PD-1), on T cells to boost the response of the immune system against cancer cells, thereby shrinking tumors. The recent developments in immunotherapy and the early success in other cancers are encouraging to further test immunotherapy in pancreatic cancer. The combination of pembrolizumab and pelareorep, an isolate of human reovirus, is in phase II clinical study in metastatic disease. Depending on the results of current clinical trials and testing, the strategies in the pipeline are expected to increase the use of immunotherapy in the clinical testing setting. Success in immunotherapy is urgently needed to address the side-effects, treating patients with advanced disease and reducing metastasis for increasing the survival rate in pancreatic cancer patients.

Keywords

pancreatic cancer; immunotherapy; clinical trials; programmed cell death protein 1

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I. INTRODUCTION

Pancreatic cancer is one of the deadliest cancers for both men and women, with exocrine pancreatic ductal adenocarcinoma (PDAC) making up 85% of the cancers and endocrine pancreatic cancers making up less than 5%.[1-6] Pancreatic cancer is the fourth leading cause of death in both genders, and survival for all stages combined is 9%.[7] There were 56,770 new cases in the United States in 2018, with an estimated 45,750 deaths.[8] The highest prevalence is in the male population of the developed world. Pancreatic cancer is considered one of the deadliest cancers because of its late detection. Currently, no tests are available for the early detection of pancreatic cancer, and thus, there have been minimal advances in treatment.

Many risk factors can contribute to the development of pancreatic cancer, some of which include tobacco use, obesity, exposure to certain chemicals, diabetes, and chronic pancreatitis. Genetic syndromes can also be risk factors that can contribute to the development of pancreatic cancer (Table 1).

II. TYPES OF PANCREATIC CANCER

A. Exocrine Tumors

Pancreatic cancer is divided into two types: exocrine and endocrine. Exocrine cancers, such as PDAC, are formed in glands that secrete fluids and make up the majority of pancreatic cancer. The most common site for exocrine tumors of the pancreas is in the pancreatic duct. Patients with early stages of PDAC present with general symptoms such as fatigue, weakness, and loss of appetite. Later stages of the disease may present with more common symptoms such as jaundice and severe abdominal pain.[9] However, these symptoms are very vague and as a result, pancreatic cancer is typically not diagnosed until it is already in the later stages.

B. Endocrine Tumors

Endocrine tumors are not as common as exocrine tumors and are usually benign. Because these tumors effect hormone production, they are called pancreatic neuroendocrine tumors (PNETs). PNETs develop from multipotent stem cells in the pancreatic epithelial lining.[10] They are categorized as nonfunctional or functional. Nonfunctional pancreatic neuroendocrine tumors (NF-PNET) do not cause symptoms because they do not cause the production of hormones, or the hormones they secrete do not cause symptoms. On the other hand, functional pancreatic neuroendocrine tumors (F-PNET) produce hormones that cause symptoms.[11]

Because NF-PNETs do not cause the emergence of specific syndromes, they are diagnosed incidentally or because the tumor mass is causing symptoms. Common symptoms are weight loss, abdominal pain, a palpable mass, and jaundice.[12] Hormones that can be secreted by NF-PNET include chromogranin A, ghrelin, HCG subunits, neurotensin. Levels of chromogranin A are the most widely used test for NF-PNET.[13,14]

Two of the most frequently occurring F-PNET tumors are insulinomas and gastrinomas. Insulinomas are the most common F-PNET and they secrete excess of insulin. Symptoms include hypoglycemia, visual disturbances, headaches, weakness, sweating, palpitations, and tremors.[15] The next most common F-PNET is gastrinomas. Most of these are found in the duodenum, then the pancreas, and surrounding tissues.[16] Gastrinomas can cause the Zollinger-Ellison syndrome due to the high production of gastrin. Also, because of this, patients can develop peptic ulcers and gastroesophageal reflux disease (GERD). Approximately 20%–30% of gastrinomas have been associated with the gene Multiple endocrine neoplasia type 1 (*MEN1*)[17] In addition, several laboratory exams that can be performed to confirm the diagnosis of gastrinoma: FSG levels, basal acid output, stomach pH, and secretin levels.[18]

III. DIAGNOSIS

A. Imaging

Different imaging and screening modalities can be used as diagnostic tools for pancreatic cancer. Computed tomography (CT) scans are usually the first line of diagnostic imaging used when pancreatic cancer is suspected. Multidirectional CT scans can determine the size of the tumor and how far it has spread due to its ability to reconstruct 3D images. In addition, CT scans have advanced spatial resolution and sensitivity of up to 96% and accuracy of 86.8%. The lower cost and easy accessibility of CT scans make them the preferred choice over other diagnostic methods such as magnetic resonance imaging (MRIs). CT scans should be performed with IV contrast agents in both the pancreatic parenchymal phase and the portal venous phase.[19]

Endoscopic ultrasound (EUS) is one of the most sensitive techniques in pancreatic cancer detection; it has a higher sensitivity for detecting solid lesions that are smaller than 2 cm when compared to CT scans. EUS also has the option to be combined with fine-needle aspiration (FNA) to obtain tissue samples.[20-25] With EUS, patients are able to avoid unnecessary exposure to ionizing radiation. However, advanced training is needed to operate the ultrasound, and there is significant variability among operators of the device.[19]

MRIs have a similar sensitivity for the detection of pancreatic cancer compared to CT scans. However, they have the advantage of being able to image larger areas of the abdomen at one time and not exposing the patient to ionizing radiation. Pancreatic cancer is shown on MRIs as a hypointense mass on T1-weighted MRIs and a slightly hyperintense mass on T2-weighted MRIs. When looking at the diffuse weighted images (DWIs), the apparent diffusion coefficient (ADC) is low in pancreatic cancer due to the increased cellularity and fibrotic changes that occur at sites of the cancer.[20-25] These changes prevent the free movement of water, which results in a low ADC.

B. Biomarkers

The most common biomarker screened for in pancreatic cancer is the serum carbohydrate antigen 19-9 (CA 19-9). Although this is the only biomarker approved by the FDA, its specificity and sensitivity for pancreatic cancer are 77.6% and 75.4%, respectively. CA 19-9

can also be present in other gastrointestinal cancers. Carcinoembryonic acid (CEA) and CA 242 are two other biomarkers that can be tested for pancreatic cancer; however, they are not highly sensitive and specific for pancreatic cancer. CEA has a specificity of 81.3% and a sensitivity of 39.7%, whereas CA 242 has a specificity of 83% and a sensitivity of 67.8%. Therefore, CA 19-9 has the highest sensitivity and CA 242 has the highest specificity for pancreatic cancer.[26]

IV. PANCREATIC CANCER TREATMENT

A. Current Treatment Options

Surgical resection and adjuvant therapy involving chemotherapy alone or alongside radiation are the widely used options for the treatment of this malignancy. The chemotherapy regimen is planned typically using the chemotherapeutic agents, capecitabine, erlotinib, fluorouracil, gemcitabine, irinotecan, leucovorin and oxaliplatin.

V. IMMUNOTHERAPY

Immunotherapy is a heavily emerging science founded on the idea of manipulating the mechanisms of the body's immune system to allow for recognition of antigens of our choosing. Currently, the three most significant approaches to immunotherapy are checkpoint inhibitors, vaccination, and adoptive T-cell transfer.

A. Checkpoint Inhibitors

In an effort to avoid autoimmunity and immunopathologic conditions, the immune system contains various fail-safe type mechanisms to regulate the development and function of its effector cells.[27-31] Exploiting such a mechanism has brought about the concept of immune checkpoint therapy, a treatment that has shown promise in clinical settings and has brought much attention to the field of cancer immunotherapy. The belief is that the ability of the tumor to gain control over these inhibitory pathways gives it the power to suppress the action and development of immune cells before they have the chance to carry out their anti-tumor functions. The process of T-cell suppression in regard to tumors is most notable via interactions between the activated T-cell cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and the dendritic cell CD 80/86. Another way is through T-cell programmed cell death protein 1 (PD-1) binding to PD-L1, which resides on tumor cells. In a healthy individual, both of these processes are normal physiologic mechanisms to avoid autoimmunity and immune system dysfunction. In cancer patients, the tumor has seized control of these T-cell suppressive mechanisms to promote its survival.[32-37] The emergence of checkpoint inhibitors such as anti-CTLA-4, anti-PD-L1, and anti-PD-1 antibodies allows for the disinhibition of the tumor override mechanisms, reinstalling the antitumor T-cell effector functions (Fig 1).[29,38-41]

B. Preclinical Research

Several checkpoint inhibitors have been developed to target the previously described interactions. One of which is ipilimumab (YERVOY®), a humanized antibody that prevents the interaction between CTLA-4 and B7, and thereby enables increased T-cell activity.

Preclinical evidence for CTLA-4 blockade has emerged primarily from prostate cancer murine models, which have demonstrated a five-fold reduction in tumor incidence when combined with an irradiated tumor vaccine.[11,42-50]

1. **Clinical Trials—**The success in preclinical studies led to the development of a human CTLA-4 antibody, which eventually underwent a double-blind, placebo-controlled phase III trial that compared the standard treatment of dacarbazine alone, to treatment in combination with ipilimumab in patients with metastatic melanoma. Ipilimumab gained FDA approval for use in metastatic melanoma in March 2011, after phase III studies showed a significant increase in survival with the addition of ipilimumab in patients.[51-54]

VI. VACCINATION

The idea behind vaccination in the setting of cancer involves tumor-associated antigens (TAAs), which are molecular components of the tumor cells. Although TAAs can vary in identity, the therapeutic benefit comes from using TAAs to incite the immune system against the tumor. TAA vaccines can be in the form of DNA, protein (antigen), DCs, or even whole cancer cells that are used to inoculate the immune system against the cancer. TAAs can even be derived from cancer-cell DNA mutations that differentiate the tumor cells from the normal cells of that tissue (Fig. 2). More specific and effective TAAs are constantly being researched. The more specific the TAA is to the cancer, and different it is from the normal tissue, the safer the treatment should be.[55-59]

A. Preclinical Trials

Preclinical trials have shown early success in the development of functional cancer vaccines. Gomez et al. showed this success in a B16 melanoma murine model.[60-65] Melanoma cell lines were transduced with the gene coding for the MCPyV small T (ST) antigen, an antigen critical to the pathogenesis of Merkel cell carcinoma. From this antigen, they produced a DNA-coated particle vaccine (pcDNA3-MCC/ST). They administered the vaccine to ST-expressing cancerous mice and recorded significant levels of an ST-targeted T-cell immune response. Upon completion of a strict vaccination schedule, the tumor volumes of pcDNA3-MCC/ST vaccinated mice were significantly lower than that of the control.

1. **Clinical Trials—**Success in preclinical trials, such as those previously mentioned, have led to clinical trials and even to the development of Sipuleucel-T, the first ever FDA-approved cancer vaccine for the treatment of prostate cancer.[66] Sipuleucel-T is a cellular vaccine consisting of serum mononuclear cells and antigen presenting cells (APC) activated against the prostate-specific PA2024 fusion protein. In a randomized double-blind placebo-controlled phase III trial concerning metastatic castration-resistant prostate cancer patients, 512 patients received either Sipuleucel-T or a placebo. The Sipuleucel-T group showed a significant immune response to the antigen of vaccination along with a 22% decrease in risk of death or 4.1-month increase in median survival time over the placebo.[67] Receiving FDA approval for this new class of treatment shines a light on the enormous potential for cancer vaccination therapy and has broadened the field of immunotherapy in general.

VII. ADOPTIVE T-CELL TRANSFER (ACT)

ACT involves the identification and collection of T-cells based upon their specific antigen-recognition capabilities, or for the purpose of modification of receptor function. The two main methods for achieving these are the collection of tumor-infiltrating lymphocytes (TILs) and the engineering of chimeric antigen receptor (CAR) T cells.

Tumor-infiltrating lymphocytes are lymphocytes that have migrated out of the bloodstream and to the site of the tumor. These lymphocytes are obtained from the patient along with dendritic cells (DCs) and tumor DNA. The tumor DNA will be sequenced for the identification of mutations. Once identified the mutations, or neoepitopes, they are exposed to the DCs for uptake. These primed DCs are cultured together with the TILs and undergo expansion *ex vivo*. The TILs are then administered to the patient along with the cytokine interleukin-2 (IL-2) to enhance anticancer immunity.

CAR T-cells, are an emerging therapy with a similar mechanism. However, these T cells are extracted from the peripheral blood. The T cells undergo a modification process that yields an engineered T-cell receptor allowing the cells to bind a specific antigen residing on the surface of the tumor cells. These cells are expanded *ex vivo* and administered to the patient (Fig. 3).[55-59,68]

A. Preclinical Research

Early in the CAR T-cell development, the first-generation cells resulted from the cloning of the intracellular CD3-zeta chain domain. Upon fusion with CD8, CD4, or CD25 extracellular domains, evidence of T-cell activation was apparent following antigen stimulation. Despite this early success, in murine models, the CD3-zeta fusion chain in CAR T-cells failed to significantly inhibit tumor growth due to suboptimal production of IFN-γ leading to eventual anergy. Although these CAR T-cells were equipped to initiate antigen-specific cytotoxicity, they failed to sustain significant T-cell expansion.

The second-generation CAR T cells combatted the issue of anergy or activation-induced cell death (AICD) with the addition of a CD28-based chimeric costimulatory receptor (CCR). This second-generation T-cell was able to mediate IL-2 synthesis, to support T-cell expansion following antigen interaction, and to improve tumor rejection function overall in murine models. These second-generation T-cells were then engineered to target CD19 surface antigens due to the presence of CD19 presence in the majority of B-cell malignancies. This first occurred nearly 20 years ago. Since then, clinical trials have shown significant results.[69-74]

1. Clinical Trials—In refractory B-cell lymphomas, CD19 targeting CAR T-cells (CTL019) showed promising results.[15] In a study of 28 lymphoma patients administered CTL019 cells, a significant response was noted in 64% of the cohort. It was reported that 57% of patients underwent complete remission, and patients in remission at the 6-month mark remained so at 39.7 months. Due to these and other supporting results, CTL019-directed T cells received unanimous approval from the FDA advisory committee for the treatment of relapsed or refractory B-cell acute lymphoblastic leukemia (ALL).[75-80]

Currently, in pancreatic cancer research, no treatment regimens offer long-term benefits for late-stage patients. This may be due, in large part, to the uniquely suppressive tumor microenvironment (TME) of pancreatic cancer. Pancreatic tumors contain a dense desmoplastic stroma that limits blood and drug deliveries, enhancing immune escape of the tumor. Also, a severe combination of hypoxia, decreased pH, and significant interstitial fluid pressure contribute to tumor survival and downregulation of antitumor immune cells. This TME is thought to be a major limiter of pancreatic-based immunotherapy. Another major hindrance to the use of immunotherapy in pancreatic cancer is the uniquely low level of mutation and neoantigen formation in tumors. The mutation quantity may be correlated with increased potential for immunotherapy effectiveness. This also leads to lower levels of TILs, which combat the effectiveness of drugs, such as checkpoint inhibitors that exert their effects by promoting TIL activity.[81-85]

VIII. IMMUNOTHERAPY IN PANCREATIC CANCER

A. Checkpoint Inhibition

Although checkpoint inhibitors have shown efficacy in immunotherapy in some cancers, pancreatic cancer remains largely unsusceptible to their lone effects. This is likely due to the low levels of tumor-infiltrating lymphocytes and immunogenicity in pancreatic cancer as mentioned previously. A 0% overall response rate (ORR) was found in patients treated with an anti-PD-L1 monoclonal antibody, further demonstrating the ineffectiveness of checkpoint inhibition monotherapy.[60-64] New PD-1 inhibitors pembrolizumab and nivolumab have received approval for therapy in melanoma, but they remain in the clinical trial phase of testing for pancreatic cancer. The most hopeful advances to checkpoint inhibition in pancreatic cancer seem to be combination therapy with chemotherapeutic agents. In a recent phase I study, the safety profile of the chemotherapeutic agent gemcitabine and CTLA-4 checkpoint inhibitor tremelimumab was examined. This combination showed success in the production of tolerable side effects, with 7 of 28 patients showing relatively stable disease for over a 10-week period. Despite these minor progressions, much work is yet to be done to find more efficacious treatments regarding checkpoint inhibition in PC.

B. Vaccines

Cancer vaccines have also been limited in their effectiveness due to the reasons previously mentioned. However, some progress has been seen in a preclinical murine model using the GVAX vaccine in combination with a checkpoint inhibitor. This vaccine is comprised of PC cells that have been irradiated and engineered on a genetic level to produce granulocyte macrophage colony-stimulating factor (GM-CSF). GM-CSF is a cellular signaling molecule that initiates the priming of T cells, presentation of antigens, and tumor-directed cytolytic action. In this study, GVAX was combined with an anti–PD-1 checkpoint inhibitor. The therapy promoted the secretion of IFN-γ and expansion of activated T-cells within the tumor microenvironment of mice receiving the combination therapy.[81-85] Mice that were administered either treatment alone did not show these results, indicating that it was the synergistic effect of the combination therapy that was responsible. Combination therapy seems to be a growing idea at this point; however, more research needs to be done to develop vaccinations with increased specificity and potency.

C. Adoptive T-cell Transfer

Adoptive T-cell transfer (ACT) is made difficult in PC by the immunosuppressive TME along with previous lack of a suitable antigen for the CAR. The latter issue has recently been overcome by engineering the CAR T cell to recognize mesothelin, a protein with minimal expression in normal cells but with significant expression in pancreatic cancer cells. Mesothelin is thought to play a part in tumor aggressiveness, malignancy, and potentially metastasis. A concluded phase I clinical trial with mesothelin-targeted CAR T cells accomplished disease stability in two of the six patients who underwent therapy. The results showed that the treatment was well-tolerated and pointed toward evidence of antitumor effects in pancreatic cancer. A study of the usefulness and safety of using antimesothelin CAR T-cells in conjunction with chemotherapeutic drugs (e.g., cyclophosphamide) in metastatic pancreatic cancer patients is currently ongoing as a nonrandomized phase I/II clinical trial (Table 2).[81-85]

IX. RECENT ADVANCEMENTS

Recent therapy options for pancreatic cancer are aimed at reducing the immunosuppressive TME. By targeting the immunosuppressive cells within the TME, immunotherapy options for treatment are more likely to be effective. The first of these targets is CSF1R. CSF1R is located on the tumor associated macrophages (TAM). The binding of CSF1 to CSF1-R allows for TAMs to proliferate and survive longer which then aids in tumor growth, resistance to treatments, and tumor metastasis. When CSF1-R is inhibited, fewer TAMs are present. This allows for a higher immune response, increases tumor regression, and increases survival.[86]

Another therapy option is targeted at the JAK/STAT pathway. Overactivation of this pathway by interferons upregulates the expression of PD-L1, as well as suppresses cytotoxic T-lymphocytes, in tumor cells. The use of JAK/STAT inhibitors can not only reduce the overexpression of PD-L1 but also reduce the growth of tumors and increase survival rates. This therapy can increase the response to anti–PD-L1 immunotherapies.[82]

X. FUTURE PERSPECTIVES

Pancreatic cancer is one of the most fatal cancers due to its late detection and aggressiveness. Therapeutic advancement in immunotherapy, such as vaccines and adoptive T-cell inhibitors, give hope to the future prognosis of pancreatic cancer. However, due to the highly immunosuppressive tumor microenvironment (TME) of the cancer, even these advances are proving to be of minimal help. Combination treatments of chemotherapy, immunotherapy, and radiation therapy work best to induce long-term antitumor activity and increase the body’s T-cell response. More research needs to be done into the optimal timing, order, and dosing of the different treatment options to best fight the disease.[86]

Research is being conducted on altering the TME to make the tumor more susceptible to treatment. The TME is a barrier to pharmacological intervention, increases the tumors progression, and increases tumor angiogenesis and stromal formation. Therapies targeted at inhibiting TGF-β, which aids in immunosuppression and stroma formation, are being further

developed as a way to weaken the tumor defenses and allow drugs to enter the TME.[87-92] Additionally, new technology is being developed that looks into T-cell receptor gene sequencing. This technology allows for a more detailed look into the number of T cells that are attacking the tumor as well as the specificity of those T cells.[57,93-97] Much more research needs to be done to investigate whether this is an effective antitumor treatment method.

XI. CONCLUSION

Pancreatic cancer continues to be one of the leading causes of cancer-related deaths in both males and females. The development of new therapies has been slow due to the continual late diagnosis of pancreatic cancer. Immunotherapy has shed a light on a very dim future for many individuals. The use of checkpoint inhibitors diminishes the ability of cancer cells to downregulate T-cell proliferation. Vaccinations and adoptive T-cell transfer both increase the specificity of T cells to attack specific cancer cells. However, the use of these therapies alone is not enough. Although not completely treatable, combinations of immunotherapy, chemotherapy, and radiation therapy have proven to be the most effective method in the treatment of pancreatic cancer. In addition, altering the TME to be less immunosuppressive could lead to more successful treatments. Ultimately, immunotherapy has offered new and exciting opportunities for the treatment of pancreatic cancer, but much more research still needs to be done to ensure a higher success rate.

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ABBREVIATIONS:

ACT	adoptive T-cell transfer
ADC	apparent diffusion coefficient
AICD	activation-induced cell death
ALL	acute lymphoblastic leukemia
APC	antigen presenting cells
CA	carbohydrate antigen
CAR	chimeric antigen receptor
CCR	chimeric co-stimulatory receptor
CEA	carcinoembryonic acid
CSF1R	colony-stimulating factor 1 receptor
CT	computed tomography

CTLA4	T-cell cytotoxic T-lymphocyte-associated protein 4
DC	dendritic cells
DWI	diffuse weighted images
EUS	endoscopic ultrasound
FDA	Federal Drug Administration
ENA	fine-needle aspiration
F-PNET	functional pancreatic neuroendocrine tumors
GERD	gastroesophageal reflux disease
GM-CSF	granulocyte macrophage colony-stimulating factor
IFN-γ	interferon gamma
MEN1	multiple endocrine neoplasia type 1
NF-PNET	non-functional pancreatic neuroendocrine tumors
ORR	overall response rate
PD-1	programmed cell death protein 1
PDAC	pancreatic ductal adenocarcinoma
PNET	pancreatic neuroendocrine tumors
TAA	tumor-associated antigen
TAM	tumor-associated macrophage
TGF	transforming growth factor
TIL	tumor-infiltrating lymphocyte
TME	tumor microenvironment

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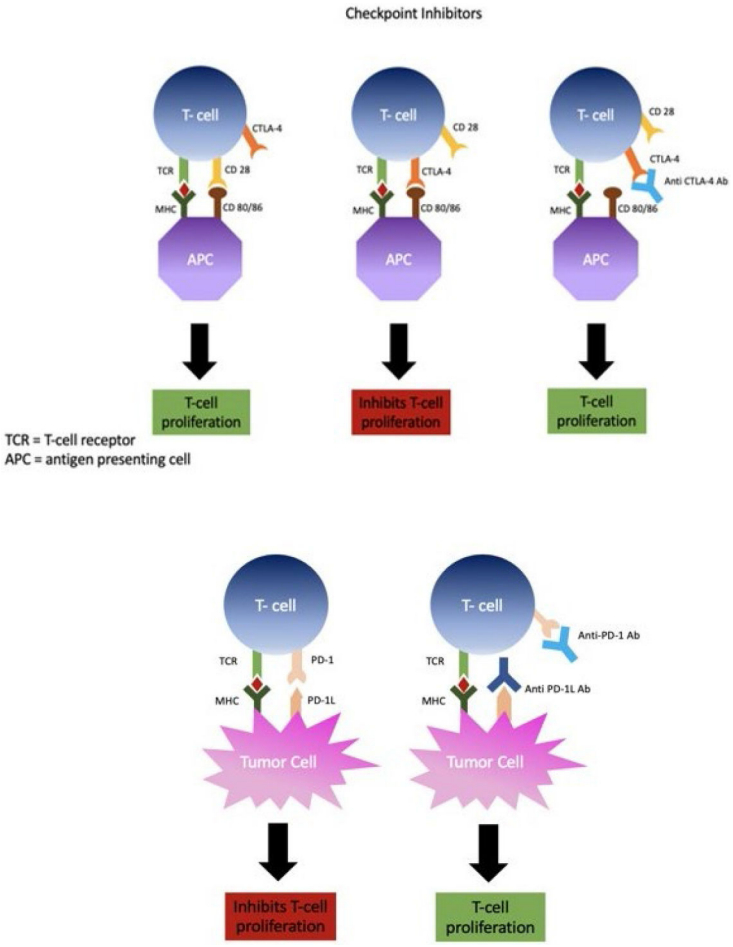

FIG. 1:

Checkpoint inhibition. Antibodies are created against specific receptors or ligands that prevent T-cell proliferation.

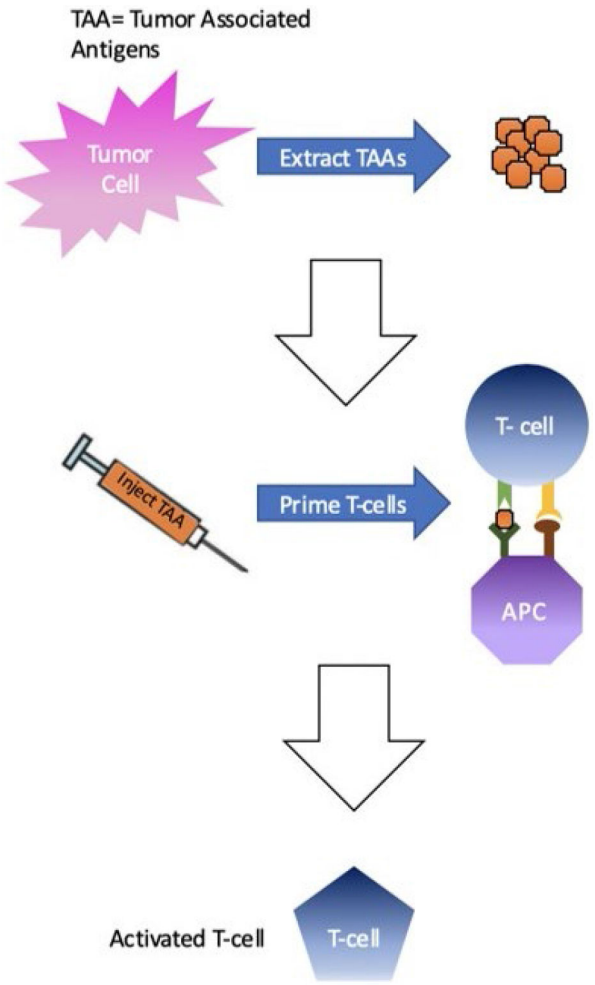

FIG. 2:

Vaccines against tumor cells. Tumor associated antigens (TAAs) are extracted from tumor cells and used to create vaccines. Once injected, the TAAs in the vaccine activate T-cells specifically against the tumor cells.

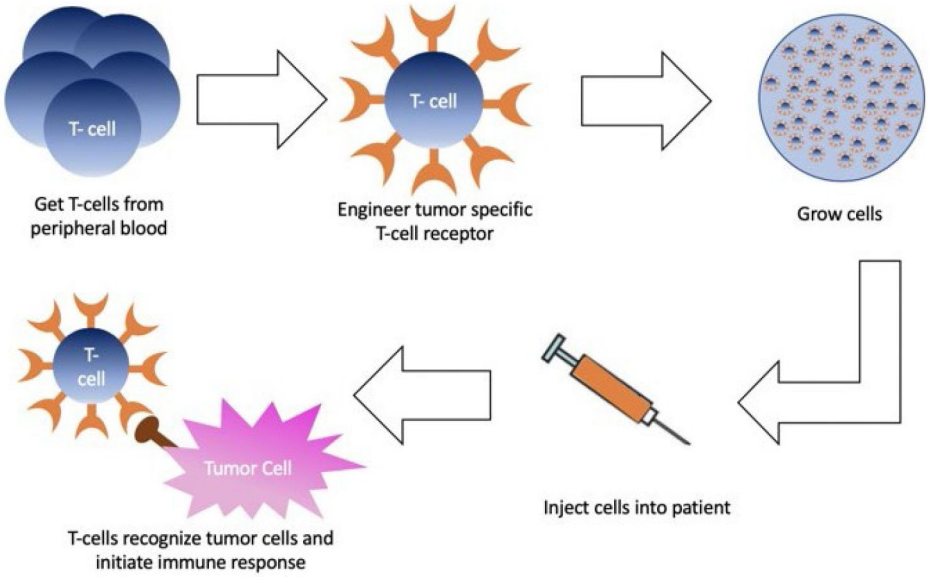

FIG. 3:

Adoptive T-cell transfer. T cells are removed from the peripheral blood and engineered to have tumor specific receptors.

TABLE 1:

The genetic syndromes and associated genes that are mutated

Genetic Syndrome	Gene Mutation
Hereditary breast and ovarian cancer syndrome	Breast cancer genes (BRCA1/BRCA2)
Hereditary breast cancer	Partner and localizer of BRCA2 (PALB2)
Familial atypical multiple mole melanoma (FAMMM) syndrome	Cyclin-dependent kinase Inhibitor 2A (P16/CDKN2A)
Familial pancreatitis	Cationic trypsinogen (PRSS1)
Lynch syndrome	MutL homolog 1 and 2 (MLH1/MLH2)
Peutz-Jeghers syndrome	Serine/threonine kinase 11 (STK11)

TABLE 2:

Adoptive T-cell transfer preclinical research and clinical trials

Preclinical Trial Focus	**Target Cancer**	**Results**	**Preclinical Trial Focus**
Apoptosis and anergy of T cell induced by pancreatic stellate	Pancreatic Cancer	High expression of galectin-1 was associated with short survival as was low expression of CD3.	Apoptosis and anergy of T cell induced by pancreatic stellate
Virus-specific T cells engineered to coexpress tumor-specific receptors	Neuroblastoma	Infusion of these genetically modified cells was associated with tumor regression or necrosis in half of the subjects tested	Virus-specific T cells engineered to coexpress tumor-specific receptors
Tumor-infiltrating lymphocytes	Large pulmonary and hepatic metastatic tumors	100% of mice (n = 12) bearing the MC-38 colon adenocarcinoma were cured of advanced hepatic metastases, and up to 50% of mice were cured of advanced pulmonary metastases.	Tumor-nfiltrating lymphocytes
Clinical Trial Focus	**Target Cancer**	**Results**	**Trial Identifier**
B-cell malignancies can be effectively treated with autologous T cells expressing an anti-CD19 chimeric antigen receptor.	B-cell lymphoma	Of 15 patients, eight achieved complete remissions (CRs), four achieved partial remissions, one had stable lymphoma, and two were not evaluable for response.	NCT00924326
Anti-tumor effect of B7-H3-blocking monoclonal antibody	Pancreatic Cancer	T-cell infiltration into the tumor and induced a substantial anti-tumor effect on murine pancreatic cancer	
T cells for the treatment of metastatic ovarian cancer	Ovarian Cancer	An inhibitory factor developed in the serum of three of six patients tested over the period of treatment, which significantly reduced the ability of gene-modified T cells to respond against FR+ tumor cells.	