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Immunotherapy Treatment on Pancreatic Cancer in Adults

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ABSTRACT

Pancreatic cancer has claimed thousands of lives across the world and currently is one of the most prevalent challenges overtaking the medical community. The cancer once known to only appear in child-related cases has increasingly been affecting middle aged adults. With no defining symptoms, the cancer escapes early detection allowing for the strengthening of the tumor's microenvironment. Pancreatic cancer is highly malignant, spreading rapidly throughout the body and uses the body's own immune system to feed its attack. Current modes of treatment include radiation therapy, chemotherapy, and surgery, none of which have been found to be consistently successful. With the number of deaths rising, innovative treatment options, such as immunotherapy, are of interest to the medical community. Immunotherapy, which targets the body's natural processes to attack cancerous cells, has been successful in various clinical trials. Further investigation into the biomarkers, mechanisms, and drug combinations to be used in the varying immunotherapy treatments is required.

Keywords

Pancreatic cancer, Tumor microenvironment, Early detection, Immunotherapy, Biomarkers, Chemotherapy.

Abbreviations

CTLs: Cytotoxic T lymphocytes, DC: Dendritic Cells, FOXP3: Forkhead Protein 3, GEM: gemcitabine, IFN-Gamma: interferon gamma, MUC1: Mucin, NEK2: Never in mitosis gene A (NIMA)-related kinase 2, PDAC: Pancreatic ductal adenocarcinoma, PD-L1: Programmed cell death ligand 1, TME: Tumor Microenvironment, Treg Cells: Regulatory T-Cells.

Introduction

With only a 10% survival rate, pancreatic ductal adenocarcinoma (PDAC) is on the rise to being the leading cause of cancer-related deaths in adults [1]. Typically, common only in children, pancreatic cancer cases have shifted towards affecting middle-aged adults, often going unnoticed due to the asymptomatic nature of the cancer. Most times, pancreatic cancer is found too far into the progression of the disease, presenting a median overall survival of less than six months [2]. The pancreas exhibits both endocrine and exocrine functions, aiding in biological processes such as digestion, glucose levels, and metabolism. Pancreatic cancer infiltrates both the organ's endocrine and exocrine cells, and the subtypes are denoted by their histological appearance [2]. PDAC arises from the epithelial cells of the pancreatic duct and is the most common subtype across pancreatic cancer cases [2]. With high malignancy rates, PDAC is known for rapidly spreading throughout the body, infecting nearby organs such as the liver and kidneys, and then traveling further throughout the body via the lymph nodes. Symptoms of the cancer are rarely noticed until the internal damage becomes detrimental to the survival of the patient, which is, in most cases, too late for a treatment to be effective [1]. The rapid growth of pancreatic cancer is attributed to the TME the tumor establishes. The immunosuppressive environment surrounding the tumorous mass deters normal body functions from attacking the cancerous cells, thus facilitating uncontrolled growth [3]. Upon the discovery of the TME, researchers have been developing treatment methods of immunotherapy that target the patient's own biological systems to infiltrate the immunosuppressive barrier and attack with anti-tumor properties.

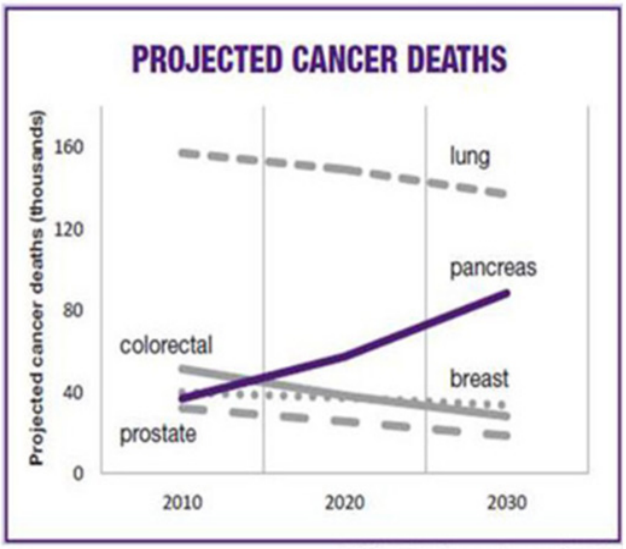

Figure 1: Graph displaying projections of cancer-related deaths across various forms of cancer [4].

Tumor Microenvironment

A TME is the environment created surrounding a cancerous tumor in which the tumor has manipulated and reprogrammed the body's natural immune system to work against itself. Within this TME, the tumor can continuously grow without attack and uses the normal T cells, along with other regulatory molecules, to fight against the normal cells trying to arrest the tumor's growth [5]. Various studies have been conducted to determine the leading cause of the TME, one noted factor being FOXP3. FOXP3 regulates the production of Treg cells, which are defined as white blood cells with the responsibility of preventing autoimmune responses in the body [6]. The TME reprograms the role of the Treg cells to benefit the tumor, enhancing immunosuppressive effects and allowing growth to continue in an uncontrolled environment. In most cases, the Treg cells have been noted to inhibit the cytotoxic T cells of the body, which are typically used to attack a cancerous tumor. The alteration of the mechanisms typically used to prevent an autoimmune attack is therefore used to attack the body to protect the tumor [5]. Pancreatic cancer patients have elevated FOXP3 and Treg cell levels, which correlate to larger tumor volume, metastasis, and immune suppression [6]. The FOXP3 pathway, along with other related mechanisms, is the source of various clinical studies in a search for an immunotherapy treatment focused on preventing the formation of the TME through reprogramming the body's T-cells [1].

Current Treatments

The current treatment protocol for patients diagnosed with pancreatic cancer entails a combination of chemotherapy, radiation, and surgery to remove the tumor [8]. To shrink the mass, chemotherapy and radiation will be administered, and treatment is then followed by surgical resection of the tumor. Prior to the surgery, patients often experience adverse side effects in the presence of chemotherapy drugs and radiation, such as hair loss, fatigue, vomiting, and low blood count [9]. Removal of the tumor in pancreatic cancer patients has further been denoted as a cause of metastasis. The immunosuppressed TME feeds off the depleted immune system following surgery, creating an environment for rapid growth and invasion of nearby organs [8]. In most cases, patients experience further weakness and immune suppression, falling ill and having their quality of life in a constant decline.

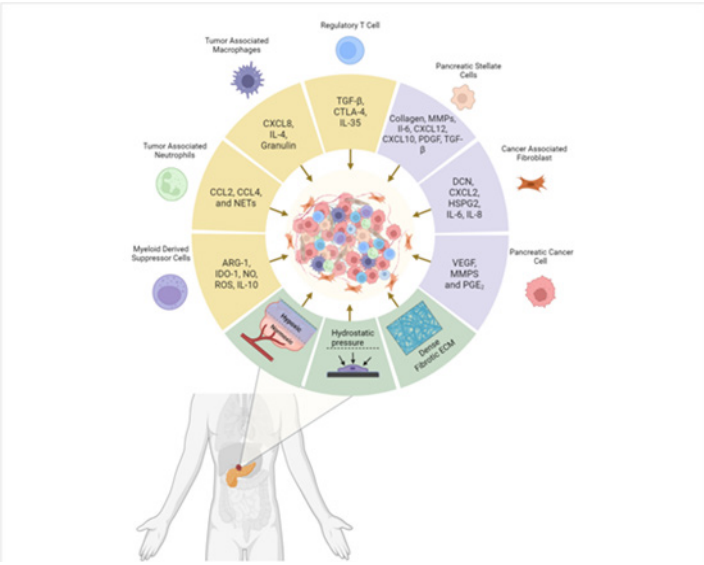

Figure 2: Image portrays the different cells and conditions of a pancreatic TME [7].

Immunotherapy

Immunotherapy is a treatment that utilizes a person's immune system to target infiltrated cells and cellular pathways to stop the growth of cancerous tumors and eradicate the disease from the body. Immunotherapy aims to enhance the body's ability to attack cancer cells by bringing mutated mechanisms back to their normal function, such as FOXP3, or altering a current pathway to focus on preventing tumor growth [10]. An additional method of immunotherapy includes the introduction of neoantigens into the body of the patient to induce a strong immune response against cancerous cells [11]. Neoantigens are defined as unique antigens created by the mutations found in cancerous tissues. Vaccinations with these specific antigens have been administered in patients to elicit an anti-tumor T-cell response [12]. This method of immunotherapy is considered a form of personalized treatment as the patient's tumor tissue is harvested to culture the specific neoantigens found within the tumor. These neoantigens are then inserted into the body to induce the immune response [11]. These vaccinations allow for the penetration of the TME as the T cells can recognize the cancerous cells as being foreign and can overcome the tumor-infiltrated T cells, working in favor of the tumor.

Immunotherapy Targets

The most significant obstacle in treating pancreatic cancer is surpassing the immunosuppressive environment created by the TME, and it is through immunotherapy that the pathways responsible for the TME formation can be targeted and shut down. Amongst the targets is the protein NEK2 [13]. In pancreatic cancer,

the cancerous cells of the TME produce mutated NEK2, which does not phosphorylate PD-L1. The PD-L1/PD-1 is known as an immune checkpoint complex in normal functioning cells, and when unphosphorylated, it leads to the instability of the complex, and there is an overexpression of PD-L1 in cancer cells [13]. The overabundance of PD-L1 prevents the body's cells from attacking itself and creating an autoimmune response. When there is an overexpression of PD-L1, it binds to its ligand PD-1 on the body's T cells and prevents the attack of the cancerous cells, allowing for the evasion of the tumor and continued growth. The overexpression of PD-L1 is additionally correlated with the overexpression of FOXP3, which further prevents the body from performing normal immune functions [11]. The PD-L1 pathway and FOXP3 gene are potential biomarkers/targets in immunotherapy. By reverting the pathways to their normal function by inhibiting NEK2 or FOXP3, the TME can be weakened, allowing for penetration of anti-tumoral drugs or resection of the tumor.

It was recently discovered that dendritic cells enhance the anti-tumor response and have been the focus of a new type of immunotherapy [14]. Dendritic cells are antigen-presenting cells found within the body that are responsible for activating the innate and adaptive immune system. In one study, it was found that higher levels of dendritic cells were associated with higher survival rates in cancer patients [15]. DC vaccinations harness these cells to present an antigen, specifically a neoantigen, which leads to a significant increase in the amount of tumor-specific T cells [14]. One neoantigen used is MUC1, which demonstrated an increase and a hypersensitivity of mucin-specific IFN-gamma-secreting CD8+ T cells within the patient [16]. DC vaccinations are personalized forms of treatment that display immunotherapeutic effects, using the body's own natural defense system to attack the tumor.

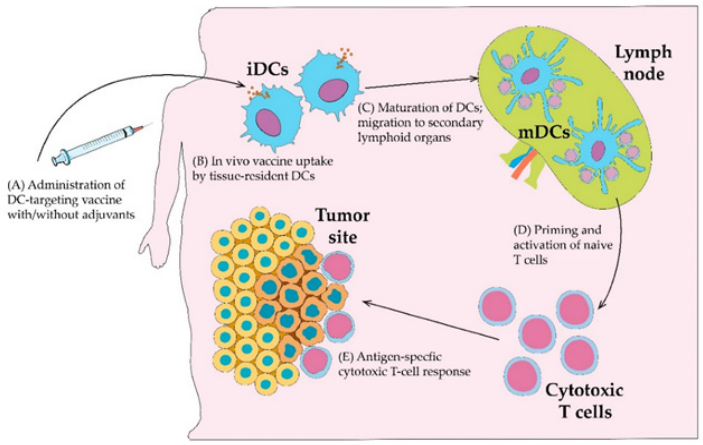

Figure 3: Illustration demonstrating the pathway of a DC vaccination on a pancreatic tumor [17].

Clinical Trials

Clinical trials have been performed to observe anti-tumoral responses, shrinkage of the tumor, and overall survival of the patients to determine the success rates of the various methods and targets of immunotherapy. In a recent study conducted at Memorial Sloan Kettering Cancer Center, 16 patients with pancreatic cancer were administered the immunotherapy drug atezolizumab along with a personalized vaccine targeting the neoantigens of the patient's tumor [18]. The ideology behind this approach is that Atezolizumab works to inhibit the PD-L1 complex of the cells, allowing the immune system to recognize and attack the cancer, at the same time as the neoantigen vaccination works to increase the number of T-cells [18]. This combination of weakening the TME and increasing the body's natural defense showed a complete success rate for six of the patients (who have not seen their cancer since starting the trial), a partial response in two other patients, and a delayed recurrence of cancer in the other eight patients. Before and after the trial began, blood samples were taken, and across all 16 patients, T-cell production had been induced and persisted beyond two years after the vaccination was administered [18]. Although only successful for half the patients treated, the coupling of a neoantigen vaccination with an immunotherapy regimen demonstrated a favorable combination that, with time, could lead to an even higher success rate.

Another clinical trial focused on a form of adoptive immunotherapy that used dendritic cells pulsed with the MUC1 peptide [19]. Dendritic cells were used for their antigen-presenting properties and were cultured with MUC1 to ensure that MUC1 was the protein presented to the T-cells to attack. MUC1 is overexpressed in patients with cancer, specifically pancreatic cancer, which makes it an accessible target on the tumor cell for the T-cells to attack. Alongside the administration of GEM, a chemotherapeutic drug that sensitizes the cancerous pancreatic cells to a T-cell attack, forty-two patients with unresectable pancreatic cancer were treated with the dendritic cell vaccination and immunotherapy [19]. Results from the study indicated a 61.9% disease control rate with one patient who made a full recovery despite experiencing liver metastasis [19]. The combination of the dendritic cell vaccine, GEM, and immunotherapy left promising results for being a safe and effective treatment regimen.

Further confirming the results of the previous study conducted by [19], a case study is noted of a fifty-two-year-old female with pancreatic cancer and liver metastasis treated with GEM and MUC1 peptide-pulsed dendritic cell vaccination. The patient received six rounds of the GEM and nine rounds of immunotherapy [20]. After these rounds of treatment, the patient demonstrated a complete response, eradicating any forms and signs of pancreatic cancer. This combination has continued to be administered, and the complete response is still persistent [20].

In an additional case study, a 62-year-old female who was diagnosed with metastatic pancreatic cancer is now 12 years cancer-free after being treated with an immunotherapy regimen consisting of an SVN-2B peptide vaccination [21]. The SVN-2B peptide is derived from the Survivin protein, a protein that promotes cell survival and is overexpressed in cancer cells. In the trial, CTLs were cultured to be specific to the SVN-2B peptide and were thus administered to the patient. The patient, who was

unable to continue with chemotherapy due to adverse side effects, tolerated the SVN-2B peptide vaccination immunotherapy well and demonstrated increased numbers of CTLs targeting the cancerous cells. Despite being administered the vaccination ten years prior, SVN-2B peptide-specific CTLs continued to circulate throughout the patient's body, indicating the body's induction of memory T cells [21]. Based on the extended survival rate and full recovery of the patient, additional trials were conducted with similar patients, concluding with results that indicated tumor shrinkage and increased immune response. Overall, the response to the SVN-2B peptide vaccination was positively correlated with an increased survival rate, and it was concluded that the longer the vaccination was administered, the longer the survival rate/disease-free period [21].

Potential Plan of Action

Based on the results of clinical trials and case studies, innovative treatment regimens for pancreatic cancer are on the rise. Personalized immunotherapy vaccinations have been proven by these trials to be feasible, safe, and effective in most cases of pancreatic cancer and open the door to a new alternative to traditional practices [22]. With more in-depth research, specific biomarkers and targets can be confirmed, allowing for a wide variety of options when it comes to customizing a patient's treatment. These biomarkers also serve as preventative measures, allowing for earlier screening and detection of the disease [23].

In addition to the future use of vaccinations, the immunotherapy methods tested have also been seen to work well when in combination with certain chemotherapeutic drugs. This has been observed to enhance the immune system, slow or stop the growth of the cancer, and lead to a safer resection procedure [8]. In one study conducted, the number of dendritic cells was seen to increase when paired with chemotherapy. This combination, as seen with GEM, has the chemotherapy drug and immunotherapy regimen complement one another, allowing both pathways of treatment to benefit the patient to the best of their abilities. This combination of treatments has been coined with the term chemoimmunotherapy and holds great potential in treating pancreatic cancer [15].

Additionally, in cases where surgery is required, preoperative administration of immunotherapeutic drugs has had a positive effect on postoperative complications [8]. Immunotherapy can be tailored to fit the needs of the patient's case in various ways by priming the body's immune system to make an attack, supporting it during a stressful operation, and/or working with other anti-tumoral drugs to elicit the most effective response. The treatment options for pancreatic cancer continue to grow, but looking forward, the malleability of immunotherapy may be the best chance at fighting the aggressive disease of pancreatic cancer.

Conclusion

Pancreatic cancer has quickly become one of the most lethal cancers worldwide, posing one of the most significant medical challenges in the 21st century [22]. With limited success with current treatments, there is no other option but to look for alternative options. Though substantial research is still ongoing, immunotherapy provides promising evidence for treating pancreatic cancer. With several strong candidates and successful trials, new options may be available for patients suffering from this disease. With further study into biomarkers to target and personalized vaccinations, cancer treatment is on its way to a whole new level, allowing one life at a time to be set free from the grasp of this deadly disease.

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