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An evaluation of chemotherapy, surgery and immunotherapy's effectiveness in tackling pancreatic cancer

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Abstract. Statistics show that among malignant tumors, pancreatic cancer has the poorest prognosis. Cancer has a low likelihood of survival, and early cancer diagnosis is challenging. The major therapies currently used include surgery, chemotherapy, and radiation, although the outcomes are not optimal. Treatments for pancreatic cancer using immunotherapy now appear more promising because to developments in molecular biology. The primary pancreatic cancer treatments will be analyzed and evaluated in this study, and it will be concluded that immunotherapy is the most promising course of action. The usage of patient range, toxicity, and other side effects are some of the difficulties, although it is still in the research and development stage.

Keywords: Pancreatic Cancer, Immunotherapy, Immune Checkpoint Inhibitor Drugs, CAR-T Cell Immune Therapy, PD-1/PD-L1

1. Introduction

In recent years, immunotherapy has become one of the hottest research fields in molecular biology. Immunotherapy pertains to a medical intervention that exploits the immunological capabilities of the body to combat various ailments, including cancer, autoimmune conditions, and allergic reactions. It involves the use of substances that stimulate or suppress the immune system in order to prevent, slow down, or treat diseases. Pancreatic cancer is considered to be one of the most lethal forms of cancer, with projections indicating that it will ascend to the position of the second most prevalent cause of cancer-related mortality by the year 2025. At present, surgery, chemotherapy and radiotherapy are the main treatment methods, however, the effect is not effective. In contrast, immunotherapy is more promising, with higher survival rates. It can be administered through various methods such as injections, oral medications, or topical creams, and the type of therapy used will depend on the disease being treated and the patient's individual needs. Currently, the comprehensive approach to complete treatment mostly relies on surgical intervention, with additional utilization of radiation and chemotherapy. Furthermore, there is ongoing investigation into novel strategies that involve the integration of immunological and molecular biological therapies. This essay focuses on immunotherapy as the best treatment for pancreatic cancer. To establish the optimal solution, UCD's OneSearch search engine was used to find relevant scholarly and peer-reviewed articles having keywords. The purpose of the essay is to evaluate three treatments for pancreatic cancer: chemotherapy, surgery, and immunotherapy, and to conclude the best treatment. It will begin by analyzing three treatments respectively. It then compares and evaluates

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the treatments mentioned. It concludes with suggestions for pancreatic cancer and the best treatment, immunotherapy.

2. Problem

There are two main causes of human death: disease and degeneration. Cancer is one of the most deadly diseases. For pancreatic cancer, five to six million people are dying of it every year. Especially there were 10 million people died of pancreatic cancer in 2020. The overall five-year survival rate for pancreatic cancer in the United States is only 8% [1]. Pancreatic cancer is characterized by a significant level of malignancy, a subtle and gradual beginning, a quick rate of advancement, and a very limited period of survival. This particular neoplasm exhibits a rather unfavorable prognosis. Referred to as the "King of cancer," this particular kind of cancer exhibits a significant degree of morbidity and mortality, placing it inside the top ten most lethal tumors on a global scale. There are three main pathogeneses of pancreatic cancer. The first is precancerous etiology. For example, atypical ductal hyperplasia of the pancreas is a precancerous lesion of pancreatic cancer. The second is the gene. There has been a lot of research on genetic abnormalities in pancreatic cancer. From research, it has been found that individuals with mutations in genes such as BRCA1 have a significantly increased risk of pancreatic cancer. Furthermore, a history of pancreatic cancer in a first-degree relative is associated with a significantly increased risk. Lifestyle factors also play a role in the risk of pancreatic cancer. People who smoke or have a poor diet are more likely to have pancreatic cancer.

3. Main therapys

3.1. Chemotherapy

Chemotherapy is one of the most effective methods to treat cancer at present, and together with surgery and radiotherapy, it is called the three major treatment methods for cancer. Chemotherapy mainly uses chemical drugs to kill cancer cells. Both the modified FOLFIRINOX and gemcitabine chemotherapy regimens have demonstrated efficacy in enhancing clinical outcomes among individuals diagnosed with pancreatic cancer [2]. Chemotherapy is a means of systemic treatment. Most pancreatic cancer patients are diagnosed as an unresectable disease. These patients who do not benefit from local treatment could improve their condition with chemotherapy. However, chemotherapy drugs are cytotoxic. This toxic effect is non-selective, in consequence, drugs will not only kill tumor cells but also cause damage to the group of normal cells. On the other hand, the metabolic process of chemotherapy drugs in the body needs to pass through the liver or kidney, then it may also cause certain damage to these organs [3]. The effectiveness of chemotherapy in treating pancreatic cancer is limited. The majority of pharmaceutical agents have little or negligible efficacy in combating pancreatic cancer. Several medications that have demonstrated efficacy in treating other malignancies, including breast cancer, exhibit limited effectiveness in combating pancreatic cancer [3]. In conclusion, although gemcitabine as the main drug chemotherapy is currently an effective method for the treatment of pancreatic cancer, the chemotherapy process is long and the efficacy is limited.

3.2. Surgery

Surgery is the main treatment for pancreatic cancer and the basis of comprehensive treatment for pancreatic cancer. Surgery remains the preferred treatment for most early and relatively early solid tumors. Furthermore, surgery is the only possible cure for pancreatic cancer. Especially minimally invasive surgery, whose significant advantages are less postoperative wound, faster recovery time, and less intraoperative interference to the abdominal cavity. The survival rate of pancreatic cancer patients after surgery is 4% to 40% [4]. The survival rate is generally referred to as five-year survival. If pancreatic cancer is diagnosed at an early stage and surgically removed, the survival rate after surgery is significantly improved, reaching 20% to 40% [4]. Cure is rare, even if the patient has a complete surgical excision, by reason that pancreatic cancer surgery is complex, invasive and has a high incidence of complications. The risks of surgery could not be underestimated. It is known that the risk of

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complications is approximately 50% [5]. The main intraoperative risk is hemorrhage, and the main postoperative complication is pancreatic leakage [5]. Consequently, this increases the probability of patients being admitted to the intensive care unit (ICU). Similar to chemotherapy, the high cost of surgery can also increase the financial burden on patients and their families [5]. Surgery is targeted but limited and high-risk. It is necessary to do more evaluation before surgery.

3.3. Immunotherapy

At present, the immunotherapy of pancreatic cancer mainly consists of the following two types, immune checkpoint inhibitor drugs and CAR-T cell immune therapy.

3.3.1. Immune checkpoint inhibitor drugs. Pancreatic cancer often develops mechanisms to evade the immune system, prompting the development of immune checkpoint inhibitors with the objective of counteracting this phenomenon. Immune checkpoint inhibitors are drugs that target specific proteins on immune cells or cancer cells, known as checkpoint proteins. These proteins regulate the immune response and prevent immune cells from attacking healthy cells, including cancer cells. By blocking these checkpoint proteins, immune checkpoint inhibitors unleash the immune system's ability to recognize and attack cancer cells. In the context of pancreatic cancer, immune checkpoint inhibitors have been studied in combination with standard chemotherapy or other therapies. One of the checkpoint proteins targeted is PD-1 (Programmed Cell Death Protein 1) or PD-L1 (Programmed Cell Death Ligand 1). When the interaction between PD-1 on T cells and PD-L1 on cancer cells is blocked, it allows T cells to recognize and attack the cancer cells more effectively. By interacting with the PD-1 receptor, PD-L1 allows T lymphocytes to recognize tumor cells as normal cells and no longer attack them, allowing tumor cells to evade attack by the body's immune system. In simple terms, the combination of PD-1 and PD-L1 initiates the programmed death of T cells, allowing tumor cells to obtain immune escape. Clinically, PD-L1 expression levels are often screened to determine whether patients can benefit from immunotherapy. When the expression level of PD-L1 is at a high level, it is often suggested that patients may be better off with immunotherapy. PD-1/PD-L1 immunoblocking therapy has attracted so much attention because of its three advantages. The first is that it has durability, and the average time for patients who are effective in PD-1 inhibitors is long, and some patients even maintain the effect for 5-10 years. PD-L1 tumoral expression has been found as a biomarker linked to improved overall survival across a variety of tumor types and a greater likelihood of tumor response in patients receiving anti-PD-L1 antibodies [6]. The second advantage is broad spectrum. Although the effective rate is lower than that of targeted drugs, the vast majority of tumors can be tried. One of the most important advantages is its low toxicity. It is much smaller than traditional chemoradiotherapy, and the incidence of grade 3-4 adverse reactions is reduced by half or more. However, pancreatic cancer tissue is different from other common tumors in that there are a large number of tumor-associated fibroblasts in the tumor tissue, which can lead to ischemia and hypoxia. Cancer is distributed in the tumor tissue in the shape of an island. In the ischemic environment, drugs are difficult to penetrate, and in the case of hypoxia, the tumor cells are relatively dry, and the immune cells around the tumor tissue are relatively few. Therefore, the basic effect of conventional PD-1 monoclonal antibody immunization drugs is poor. The lack of immunogenicity of this type of tumor is another factor contributing to the poor efficacy of immunotherapy in pancreatic cancer [6]. Poor antigenicity is the cause of the absence of immunogenicity in the pancreatic tumoral microenvironment [6]. Nevertheless, PD-1/PD-L1 blocking treatment seems to work in pancreatic cancer patients who have an MMR deficit. These individuals exhibit a heightened response to PD-1/PD-L1 blockade therapy due to the presence of MMR deficiency, which significantly elevates the rate of somatic mutations. Consequently, this increased mutation rate leads to the generation of neoantigens that may be identified and targeted by the immune system. Immune checkpoint inhibitors are promising for cancer treatment, but more research is needed in the treatment of pancreatic cancer because of the specificity of the tumor microenvironment.

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3.3.2. CAR-T therapy. Chimeric antigen receptor T-cell therapy (CAR-T therapy) is considered as the most promising immunotherapy approach for pancreatic cancer. CAR-T therapy is a form of immunotherapy wherein the genetic modification of a patient's T cells, a subset of immune cells, is undertaken to enable the expression of a chimeric antigen receptor (CAR) on their cellular surface. The present study focuses on the development of a Chimeric Antigen Receptor (CAR) that exhibits the ability to identify and selectively attach to distinct antigens present exclusively on malignant neoplastic cells. After the genetic modification of T cells to incorporate the chimeric antigen receptor (CAR), these modified cells are reintroduced into the patient's organism. Subsequently, they are capable of selectively identifying and eliminating cancerous cells that exhibit the specific antigen of interest. The fundamental concept underlying CAR-T therapy involves the introduction of genetic material containing a distinct antigen recognition domain and T cell activation signal into T cells via gene modification techniques. This process enables the direct activation of T cells upon interaction with specific antigens present on the surface of tumor cells. Consequently, the activated T cells effectively eliminate tumor cells by releasing cytotoxic substances such as perforin and granzymin B. At the same time, human endogenous immune cells are recruited to kill tumor cells through the release of cytokines, so as to achieve the purpose of tumor treatment, and immune memory T cells can be formed, so as to obtain a specific long-term anti-tumor mechanism. A typical CAR-T treatment process is mainly divided into the following five steps. The first step is to isolate and purify their own T cells from peripheral blood of cancer patients. The second step is the grooming process. After T cells are activated, the CAR structure that can specifically recognize tumor cells is genetically engineered into T cells. The third step is amplification. The engineered CAR-T cells are cultured and allowed to multiply in the laboratory to produce a larger population of modified T cells. This step ensures that there are enough CAR-T cells to effectively target the cancer cells once they are infused back into the patient's body, which is mainly determined by the patient's weight and treatment cycle. The fourth step is the feedback process. CAR T cells were injected back into the patient after pretreatment with chemotherapy. The ultimate phase involves the monitoring of the patient, the observation of the effectiveness, and the close monitoring of any adverse responses. The entire duration of the treatment regimen spans approximately three weeks, with the process of "separation - modification - expansion" of cells including approximately two weeks, therefore requiring a relatively longer period of time. Possible adverse effects may encompass cytokine release syndrome (CRS) and neurological toxicity, both of which are effectively addressed by healthcare practitioners. CAR-T treatment possesses several notable advantages. It is more lethal to tumor cells, and is more targeted, and the treatment is more durable. Every chimeric antigen receptor T-cell (CAR-T) therapy is custom-engineered to specifically recognize and bind to the surface antigen present on the tumor cells of individual patients, hence enhancing its targeting specificity. Experiments have shown that when cancer cells rekindle in the body, these genetically modified T cells can still exert anti-tumor activity. Take precision targeting for an example, CAR-T therapy can be engineered to target specific antigens present on the surface of pancreatic cancer cells. This targeting could potentially spare healthy cells and tissues from damage, leading to a more targeted and effective treatment approach. However, the therapy has not been widely used in clinical practice cause it still has some challenges in treatment of pancreatic cancer. On one side, the process of preparing CAR-T cells is intricate and requires a high level of technical expertise. However, the effectiveness of chimeric antigen receptor T (CAR-T) cells in treating solid malignancies is currently suboptimal, and secondly, the metabolic environment of the tumor microenvironment is not conducive to the persistence of car-t cells. In contrast to liquid tumors, solid tumors have a different dominant CAR T cell toxicity [7,8]. On-target and off-tumor effects are the primary adverse effects so far seen in solid tumor investigations. The most frequent significant adverse effects are neurotoxicity and cytokine release syndrome (CRS) [7]. Patients treated with CAR-T cell therapy showed significant improvement, but were at risk of the serious adverse events mentioned above [9]. Disease severity, CAR-T cell dosage, and treatment outcome are related to cytokine release syndrome. Low blood pressure, fever, blood coagulation issues, respiratory or renal insufficiency, myalgia, and neurological issues are some of its symptoms. A significant challenge of CAR T cell therapy is the inherent histological characteristics and immunosuppressive capacity of this tumor type.

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Stromal responses are present in most pancreatic tumors, which can promote tumor growth and act as a barrier to effective drug delivery [10]. Despite the promising potential of CAR-T cell therapy and obvious progress over the past decade, there are still targeted challenges for its application as a pancreatic cancer treatment.

4. Evaluation and Comparison

The three most commonly used treatments for pancreatic cancer are chemotherapy, surgery and radiotherapy. According to the pathological diagnostic result of pancreatic cancer, different treatment priorities are adopted. For early pancreatic cancer patients, surgery is a better treatment. Although patients with early stage pancreatic cancer have the opportunity to have the lesion removed by surgery, unfortunately, most patients relapse within one year after surgery. Chemotherapy is the main treatment for those patients with pancreatic cancer that cannot be treated surgically due to its low resection rate. Although chemotherapy is the main treatment, the disadvantages of chemotherapy are limited efficacy and expensive drugs. Immunotherapy, by contrast, are more promising. It has fewer side effects and is more targeted to cancer cells and oncogenes on account of immunotherapy's specific characteristics. Immunotherapy has a relatively low complication rate compared to other anti-cancer therapies [6].

Here is a set of data on five-year survival rates for pancreatic cancer. The survival rate for untreated pancreatic cancer patients is less than 5%. The average survival rate with chemotherapy is 27%, while patients with early pancreatic cancer treated with surgery are 7% lower, with a recurrence rate of 85% after one year. Obviously, chemotherapy works better than surgery. Gene therapy like immunotherapy for pancreatic cancer is considered to be a new mode of cancer treatment following traditional therapies such as surgery, radiotherapy and chemotherapy. The combination treatment used of RNAi-Mediated PD-L1 is effective in the treatment of pancreatic cancer by using comparison with chemotherapy and detailed experimental data to support it [1]. Traditional tumor surgery and chemotherapy cannot be expanded due to their limitations. Surgery and chemotherapy have high recurrence rates, whereas immunotherapy has fewer side effects and higher survival rates. In conclusion, immunotherapy is the most promising and effective treatment for pancreatic cancer, followed by chemotherapy and surgery.

5. Conclusion

In this essay, three treatments of pancreatic cancer have been analyzed and compared with each other. Based on the above analysis, immunotherapy has been recognized as the most promising and best treatment for pancreatic cancer. Pancreatic cancer is recognized as a prevalent malignancy affecting the gastrointestinal system. The condition presents with insidious and atypical clinical manifestations, posing challenges in both diagnosis and therapy. With more and more people suffering from pancreatic cancer worldwide, finding an effective treatment is urgently needed. immunotherapy can be the best and the most promising treatment of pancreatic cancer since it has the characteristics of specificity and high efficiency. Although chemotherapy and surgery have shown some success in treating pancreatic cancer, they still have the disadvantages of limitations like high risk and high cost. immunotherapy, as a new and efficient technology for the treatment, has extremely broad prospects for development. Immunotherapy especially CAR-T therapy could potentially offer a long-term, effective solution to cancer, but there may be doubts about its safety. In the design of drug delivery strategies, some drugs tend to endanger life and cause adverse toxicity when accumulated. However, the development of biotechnology will still advance biology and medicine. It is well suggested to understand the pathogenesis of pancreatic cancer and find more promising treatments using biotechnology such as genetic engineering. With biotechnology, the researchers will be able to better understand the biological behavior such as lesions of cancer in further research. In conclusion, immunotherapy can be considered as the best treatment of cancer.

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