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A Critique of mRNA Vaccine for Pancreatic Cancer

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KOKILAVANI S *, APARNA S, DR. V. DHANAPAL, MANASA C, BHUVANESHWARI, SWEETHA V

Department of Pharmacology, Sree Sastha Pharmacy College Chembarambakkam Chennai.123 India.

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ABSTRACT

Pancreatic cancer also called pancreatic ductal adenocarcinoma (PDAC) is a common type of cancer that affects the pancreas. An mRNA vaccine is a type of vaccine that contains messenger RNA and helps to produce an immune response in patients with cancer. Dr. Vinod Balachandran from Memorial Sloan Kettering Cancer Centre (MSKCC) was involved in the development of individualized mRNA vaccine immunotherapy. Chemotherapy shows no response in pancreatic cancer patients. Immunotherapy shows a promising result for patients with pancreatic cancer. The mRNA vaccine triggers the immune system. It can recognize and attack infectious antigens. It was the best idea to use mRNA vaccine shows an amazing result, after surgical removal of the cancerous cells, individualized vaccines are prepared for every individual patient that is called a personalized vaccine. The mRNA vaccine immunotherapy for pancreatic cancer showed reduced reoccurrence of tumour. This article reviewed the mRNA vaccine against pancreatic cancer, the mRNA vaccine development history, and clinical trials of the vaccine.

INTRODUCTION:

Pancreatic cancer is the deadliest type of cancer. Diabetes mellitus, inflammation in the pancreas, obesity, liver cirrhosis, and smoking are also some of the factors for Pancreatic cancer. The treatment usually involves surgical removal of tumour cells. Chemotherapy is the choice of treatment for all types of cancer. However, chemotherapy failed in pancreatic cancer patients. After a long study, researchers found that immunotherapy gives an exciting result against pancreatic cancer. The vaccine is made of a specific protein called neoantigen that alerts the body's immune system against the cancer cells. It plays a role in delivering the antigen-encoding mRNA into the immune cells, which helps to stimulate the B & T cell production. The vaccine made of specific protein, which is responsible for stimulating the adaptive immune response in the body helps to recognize the cancer cells and destroy them. It helps to prevent the reoccurrence of cancer. The phase 2 clinical trial of this vaccine development is completed, and further research is in progress to make the vaccine available to patients.

HISTORY OF VACCINE:

The mRNA was discovered in 1961. The mRNA-based drug concept was proposed in 1989 and the approach was made in 1990. In 1993 the study reported the mRNA vaccine can stimulate cell-mediated immunity and humoral-mediated immunity. The first mRNA vaccine encoded in a cancer antigen was discovered in 1995. The first clinical trial on the mRNA vaccine was held in 2001 and the study was reported in 2008. In 2009, the first mRNA vaccine used in 2009. BioNtech in 2008 and Moderna in 2010 were involved in the development of mRNA-based biotechnologies. In 2013, the first clinical trial was conducted against rabies using mRNA vaccine. After a few years, many mRNA vaccine clinical trials were initiated against various infectious viruses. In March 2022, Moderna announced the mRNA vaccines developed for about 15 diseases such as COVID-19, MERS, Nipah viruses, etc.

DEVELOPMENT OF mRNA VACCINE AGAINST PANCREATIC CANCER:

Dr. Vinod Balachandran and his team in collaboration with BioNTech, which is known famous for its contribution to COVID-19 vaccine development, and GENENTECH, a pharmaceutical company that was already involved in the development of individualized

mRNA vaccine therapy. They started the development of mRNA vaccine immunotherapy against pancreatic cancer.

During the COVID-19 pandemic situation, researchers engaged in the development of mRNA vaccines against novel pathogens accelerated the development of mRNA vaccine technology.

Since there is a failure of chemotherapy for treating pancreatic cancer. They showed interest in immunotherapy. The research takes about 8 years to get promising results on immunotherapy. Now various mRNA vaccines are developed against various types of viruses that can produce chronic or repeated illnesses such as HIV have been under clinical trial research.

CLINICAL TRIALS:

Clinical trials are research studies to test new treatment procedures to see the action of vaccines.

PHASE 1: The phase 1 clinical trial was conducted in 16 MSK patients with pancreatic cancer. The clinical trial report was published on May 10, 2023. The mRNA vaccine was given in 9 doses. The first dose of the vaccine was given to the patient after nine weeks after the surgery (removal of the pancreatic tumor). Before the first dose of mRNA vaccination, the drug Atezolizumab was given to the patients. These drugs act as an immune checkpoint inhibitor. The first 8 doses are chemotherapy for pancreatic ductal adenocarcinoma and the 9^{th} dose will be given as a booster dose. The vaccine was administered to 16 volunteers. Those volunteers are the patients with Memorial Sloan Kettering Cancer Centre (MSK) pancreatic cancer. The vaccine was administered to 8 patients out of 16 patients, and they have a strong immune response with activated T cells. The remaining patients do not have a strong immune response to this vaccine. The result of the phase 1 clinical trial recommends that the mRNA vaccine is safe and effective, it produces an immune response. In phase 1 clinical trial studied 8 patients out of 16 patients, and the vaccine stimulates the immune T cells, which will recognize the pancreatic neo antigens in individuals.

Barbara Brigham one of the Memorial Sloan Kettering Cancer Centre (MSK) patients doing well 2 years after receiving the mRNA vaccine.

PHASE 2: After the success of the phase 1 clinical trial, the phase 2 clinical trial is in progress to analyse the potential of the vaccine to fight against neoantigens. This trial was conducted on newly diagnosed pancreatic cancer patients, in those who hadn't taken chemotherapy or surgery before. It investigates the therapeutic efficacy of the vaccine to reduce the cancer severity after the removal of the tumor. About 260 patients enrolled at Memorial Sloan Kettering Center approximately from 80 places around the world. In this phase of a clinical trial, the patients are grouped into two randomly. one of the two groups will receive standard treatment which is surgery followed by chemotherapy and another group will get the experimental treatment, which involves surgery followed by individual mRNA vaccines an immunotherapy drug they called a checkpoint inhibitor. The mRNA vaccine is provided in two phases. Initial doses are used to stimulate the immune system and the latter are booster doses.

The researchers are presently planning to conduct a large clinical trial, expected after 2 years.

MECHANISM:

The ultimate target of the vaccine is to stimulate the immune system. The mRNA vaccine encoded the surface antigens presenting in tumor cells. The mRNA vaccine follows the process of normal cellular protein synthesis. Once the mRNA vaccine is administered to an individual the mRNA fragments are taken up by dendritic cells through phagocytosis. The ribosomes in the dendritic cells read mRNA and produce viral antigens which encode mRNA. The mRNA fragments are degraded by the body after a few days of vaccine administration. The personalized mRNA vaccine contains the genetic code of a specific antigen in an individual. When the adaptive immune system once stimulated by the viral antigen, it follows the normal immune processes. Proteosomes degrade the viral antigens. The MHC molecules attach to the antigens and are transported to the cellular membrane, where they activate the dendritic cells. DC cells migrate to the lymph nodes and trigger the T cells and B cells for the production of antibodies specific to the antigens.

FUTURE PROSPECTS:

The mRNA vaccines are custom-made for every person. Pancreatic cancer is one of the deadliest of all cancers. They use proteins in the pancreatic tumor called neo-antigens, which alert the immune system that the cancer cells are foreign. In this way, the new mRNA vaccine

could prevent tumors from returning after surgery, which trains the body to protect itself against cancer cells.

MRNA-based therapy has a wide range of applications and is a promising therapeutic method for both the treatment and prevention of diseases. Genetic diseases are treated and prevented using mRNA vaccine.

Some other applications of mRNA therapy:

- Protein replacement therapy
- Immunotherapy
- Genome editing
- Cellular reprogramming
- Vaccines

CONCLUSION:

The mRNA vaccine has promising results for the development of personalized vaccines for pancreatic cancer. However, the development of individualized vaccine development is a challenging process. Presently, phase 1 and phase 2 clinical trial reports are published. From the results of phase 1 and 2 clinical studies, the vaccine was found to be safe and potentially effective against pancreatic cancer. The complex nature of the cancer cells depends on the patient's genome, it may cause the evolution of the tumor cells, and consequent therapeutic failure may occur. There is another strategy against PDAC is the development of a prophylactic mRNA vaccine, but there is also a consequence due to the complexity of pancreatic cancer. The mRNA vaccine clinical test is currently under process.

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