Immunotherapy Cancer Treatment

Introduction

Cancer is the second leading cause of death in the United States according to the American Cancer Society (1). Treatments for this disease are often harsh, involving multiple rounds of toxic chemicals to enter the patient for months, even years on end. A lot has been learned on cancer in recent decades with new theories of treatment arising. Immunotherapy is one new treatment plan being used in modern day cancer treatment. Immunotherapy is the use of a patient's own immune system to detect and fight off cancer cells. The immune system is one of the human body's greatest advantages against illness and harnessing it to fight disease could be the next major step in "curing" cancer.

What Exactly Is the Immune System?

The human immune system is composed of tissues, cells, and organs that all work together to detect, recognize, and fight off foreign invaders of the body. The human body has organs that house the machinery to make the cells to fight off invaders. The spleen, tonsils, thymus, skin, bone marrow, and mucosal membranes are all organs that are members of the immune system which produces cells to detect invaders. (See Fig.1.1)

The organs of the immune system produce what are called natural killer (NK) cells, T-cells, and B-cells, which are from our adaptive immunity, meaning that as the body encounters pathogens or foreign invaders they can better recognize them if they see them again.

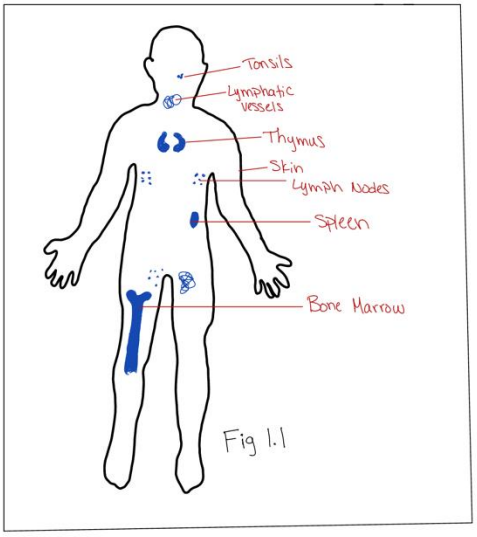

Fig. 1.1: The location of all the immune systems organs are listed. These organs play a role in producing the cells needed to detect abnormal invaders of the body.

NK-cells are sent out to kill cells that are marked as foreign by markers called major histocompatibility classes (MHC). MHC-1 places receptors on cells for NK cells to detect and come destroy cells that have been signaled via MHC. B-cells create antibodies that are used to detect pathogens or foreign invaders of the body once they enter again. Antibodies are proteins of the immune system that bind very specifically to a type of antigen, each antibody only binds to one type of antigen. The pairing of these antibody-antigens in the immune system helps to send signals that target specific cells for death; this is one way the immune system is able to remove foreign invaders. T-cells are made to orchestrate the body's cell mediated immunity as well as help regulate B-cell response. T-cells are most important in the idea of treating cancer with immunotherapy.

Immune Checkpoints

The immune system is capable of detecting a lot of invaders, cancer is difficult though because the cells come from the persons own body, making it harder to detect. There are things called "checkpoints" in the immune system; the checkpoints use proteins on T-cells to bind to proteins on other cells that have their "partner protein" which can be used to signal to kill the cell. Cancer is an ever-adapting disease, it finds ways to adapt and outsmart current treatments, even the body's own immune system. Cancer is able to take immune checkpoints, bind to the partner proteins and make the signal that is usually sent to T-cells "too strong" so that it sends an "off" signal to the T-cell. Once signaled "off", the cancer cell is able to avoid being killed by the T-cell and even avoid detection. Checkpoints such as Cytotoxic T lymphocyte associated protein-4 (CTLA-4), Programmed death-1 (PD-1), and programmed death lymphocyte-1 (PD-L) are currently being used to target cancer cells via checkpoint inhibitors. Immune checkpoint inhibitors are able to engage with the proteins on the T cells, recognize, and bind to the partner proteins of other cells, such as tumor cells which would signal to kill tumor cells (See Fig 2.1).

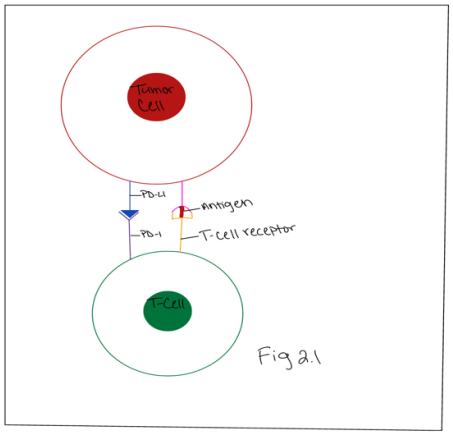

Fig 2.1: The binding of partner proteins of T-cell and tumor cell turn the "off" signal to the T cell avoiding tumor cell death. Activation of antibody such as nivolumab or avelumab blocks binding, allowing T-cells to kill tumor cells.

Antibodies for the three checkpoints have been made so that at each checkpoint, the binding can block inactivation of cytotoxic T-cells. CTLA-4 uses ipilmummab, PD-1 uses nivolumab, and PD-L1 uses avelumab (3). Immune checkpoints are able to be administered to patients intravenously. Immune checkpoints exist in the everyday immune system but are being used to patients advantages for cancer treatment. There is large room for improvement in immune checkpoint treatment, however, it currently is serving a small percentage of cancer patients well. The statistics for immune checkpoint therapy working are small, but those that it does work for take very well to it.

Tumor Infiltrating Lymphocytes

Tumor infiltrating lymphocytes (TILs) show promise of another immunotherapy for cancer. Lymphocytes are a part of the immune system that recognize cells and invaders as foreign and penetrate them, killing them off. TILs are lymphocytes taken from a tumor of a cancer patient, grown in a lab, and put back into the patient (4). Lymphocytes are capable of marking cells as cancerous, as they came from the tumor itself and are now better capable of recognizing and killing the cancerous tumor quickly. The increased number of lymphocytes are better able to fight off the tumor in patients thanks to their increased numbers. See Fig. 3.1 for depiction of TILs attacking solid tumor mass in tissue.

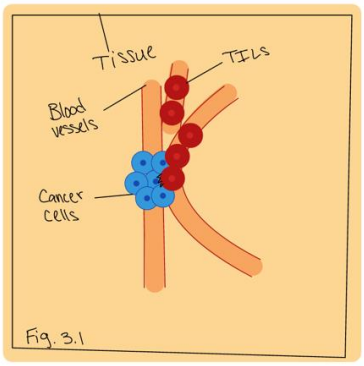

Fig 3.1: TILs are entered back into the patient after being grown in a lab. Solid mass of tumor cells is identified in a tissue and TILs travel to clump of cancerous cells through blood vessels.

The downfall with TILs is that the treatment is only an effective option with solid tumors and may pose lack of treatment options for those with more developed stages of cancer. Along with other forms of immunotherapy, cancer is constantly looking for ways to downregulate the immune systems signals to kill cancerous cells, when these signals are downregulated, the TILs are not as capable to make or kill the tumor.

Monoclonal Antibodies

Monoclonal antibodies serve as another option of immunotherapy for cancer patients. As mentioned before, there are antibodies in the immune system that bind to one particular antigen per antibody type. Monoclonal antibodies are lab made proteins that bind to specific cancers, acting like human antibodies. There are four types, each with a special ending that would indicate the protein is lab made. Murine comes from mouse proteins with a -inomab ending, Chimeric is part mouse and part human protein with -ximab ending, Humanized is small mouse proteins attached to a human protein with -zumab ending, and finally human which is human proteins with -umab ending (5). This is not a common type of immunotherapy used for cancer as each antibody that's made, there first needs to be a specific antigen for a specific cancer found first. The specificity of antigen-antibody binding is already very high, therefore the difficulty of finding particular antigens that work to target specific cancers is extremely high. While some monoclonal antibodies have been found, this is still a fairly new development in cancer immunotherapy and will likely take multiple more years of dedicated research before anything new arises from the developmental stages that have been given.

Cancer Genetic Biomarkers

Biomarkers have the ability to be a measurable mechanism of detecting cancer in a quicker and more effective way, which could lead to cancers being caught in earlier stages. Genetic motifs are in all cells, including cancerous ones; if particular motifs can be found for certain cancers, then they can serve as biomarkers. The main problem with biomarker motifs is that each person and each person's cancer has unique biomarker patterns. Biomarkers may not in itself be an immunotherapy treatment, however, it can be analyzed by a patients doctor to help them better determine a method of treatment. It may soon be found that certain biomarkers on certain cancers may react better to particular immunotherapies, such as immune checkpoints, or monoclonal antibodies. As of now, less than half of patients respond to immunotherapy in a positive manner. Some amino acid sequences (101 found) may have a link to who may or may not benefit from immunotherapy (6). Genomic characteristics that are in human tumors have the potential to be biomarkers for immunotherapy; 1/13 of the 101 tetra-peptide amino acids identified in an experiment by Robins etal. have neo-antigen markers that could identify patients for the best treatment option (6). Immunotherapy treatment of cancer is

diverse and complicated, as cancer is constantly finding ways to turn off the immune system from attacking it. Biomarkers in cancer immunotherapy are still in the infancy stage with much to be learned in coming years.

What Are the Side Effects of Immunotherapy Treatment?

Many current cancer treatments are harsh on the patient's overall health. Toxic chemicals and radiation are used to kill cancerous cells and are also killing healthy parts of the immune system. Many types of immunotherapies are a lot less damaging to the patients already fragile health. Some side effects of immunotherapy treatments include fever, chills, diarrhea, fatigue, rash, weakness, or low blood pressure. The comparative side effects of radiation and chemotherapy for cancer patients include fatigue, hair loss, skin changes, nausea and vomiting, loss of appetite, bladder issues, diarrhea, memory trouble, and fertility issues (7). Immunotherapy has the capability of using the body's own defense system on cancer cells comparative to radiation and chemicals being inserted into a patient's body. Immunotherapy comes with side effects; however, this is to be expected with any sort of medication or treatment. The other downside to immunotherapy related to side effects is the long-term effects of this treatment. Immunotherapy is fairly new, therefore not a lot is known regarding the long-term side effects. Only time will be able to reveal whether or not immunotherapy holds long term health effects on cancer patients. There also is no current data on the relapse percentage with immunotherapy treatment.

What Types of Cancer Can Be Treated with Immunotherapy Treatment?

With such a new and promising cancer treatment, the big question is what kinds of cancer can be treated? All cancers can be attempted to be treated with immunotherapy; however, it does not show promise for all cancers as a lot still remains unknown. There are some cancers though that show more promise in successful treatment with immunotherapy. Cancer types with FDA approval include bladder cancer (the first FDA immunotherapy cancer approved), colorectal cancer, and leukemia (8). Other cancers also have promise in being more successful with immunotherapy treatment, though they may not have an FDA approval or current FDA trials. Other cancers with promise in treatment are brain cancer, breast cancer, childhood cancer, kidney cancer, advanced lung cancer, and melanoma. Immunotherapy has shown long term promise in breast cancer treatment, childhood cancer has shown promise to avoid long-term damage, kidney cancer treatment has shown overall positive correlation to overall survival, advanced lung cancer has promise in pairing with chemotherapy and radiation, and immunotherapy has overall changed the way melanoma cancers are treated (8). There are many types of cancer and not all have success in treatment with immunotherapy, however the current list is beginning to grow on the cancer types that show promise with positive treatment correlations.

Looking To the Future

Immunotherapy is a new and exciting cancer treatment that holds the potential to change the way cancer is treated. Current immunotherapy treatments are in their infancy to beginning stages. The treatments being used and monitored currently are so new that only short-term treatment success and effects are known. The future holds lots of room to grow the knowledge that is immunotherapy treatment. The coming

years will offer more insight to the long-term effects of immunotherapy as well as expand the knowledge over which cancers respond best to this treatment type. The future is bright, hopefully the need for harsh chemicals and radiation treatments on patients who are already in compromised health will decrease.

Summary

Immunotherapy is a new treatment having only been used in the recent decades. The treatment option is exciting as it holds the potential to avoid treating cancer patients with toxic chemicals and radiation which can lead to long term side effects and are extremely harsh on the body. Multiple genres of immunotherapy exist ranging from immune checkpoints and immune checkpoint inhibitors, tumor infiltrating lymphocytes (TILs), monoclonal antibodies, and even genetic biomarkers. Each immunotherapy has its pros and cons as is the case with many treatments. This new opportunity for cancer patients' treatment plans offers reduced invasiveness with a more "natural" look to cancer treatments. The body possesses well equipped machinery to combat illness- the immune system; immunotherapy offers cancer patients a third treatment option to chemo and radiation. Only time will tell now on the effectiveness and long-term effects, or lack of, with immunotherapy cancer treatments.

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