The Uses of Immunotherapy in Epithelial Ovarian Cancer

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Introduction

Cancer is the uncontrolled growth of abnormal cells in the body. There are many different types of cancer that affect different parts of the body. The immune system is the network of cells, tissues, and organs that help fight off foreign invaders in the body such as infections and harmful pathogens. The immune system, in the case of cancer, is responsible for recognizing the cells that are infected and killing them. The cancer cells are killed by cytotoxic T cells and NK cells and the immune system is responsible for activating such cells. Immunotherapy is a type of cancer treatment that involves treating a patient's immune cells so it's ability to recognize and kill the infected cells are enhanced. Immunotherapy is an attractive option to many cancer patients due to its many potential benefits. Immunotherapy does not have the side effects that traditional cancer treatments, such as radiation and chemotherapy, have. Immunotherapy also has potential for long term effectiveness. This review paper will focus on immunotherapies associated with epithelial ovarian cancer and future directions for immunotherapy treatments.

Understanding Epithelial Ovarian Cancer

Epithelial ovarian cancer is the most common type of ovarian cancer, making up about 90% of ovarian cancers among women (Gubbels 2010). The exact cause of epithelial ovarian cancer is not clear; however, there are certain factors that put someone at higher risk for developing this disease in their lifetime, such as age and family history. Some patients diagnosed with epithelial ovarian cancer have a genetic predisposition of specifically the *BRCA1* or *BRCA2* gene mutations which is linked to heredity. This can increase one's risk of developing epithelial ovarian cancer. About 90% of people diagnosed with epithelial ovarian cancer carry this gene mutation (Gubbels 2010). Epithelial ovarian cancer mostly affects postmenopausal women but it can still affect younger women as well though it is less common. This type of cancer is extremely aggressive as the tumor cells will metastasize and spread to other organs. Early detection methods for epithelial ovarian cancer are currently not very successful; however, different methods are being tested but none of them have proven to be successful yet. Hence, epithelial ovarian cancer is often detected at late stages when the cancer has already metastasized and spread from the ovaries to other parts of the body. Patients with stage 1 epithelial ovarian cancer that are older will often undergo a hysterectomy and oophorectomy since the cancer is contained to those organs. However with younger patients who wish to preserve their fertility, other treatment routes will be taken. Patients with epithelial ovarian cancer will usually go through a treatment combination of surgery and chemotherapy. The stage of the cancer cannot be determined without an examination surgery hence patients will often undergo a surgical examination during which the surgeon will remove as much of the tumor as possible from the affected tissues. After the surgery, patients will often have to follow up with chemotherapy to eliminate remaining cancer cells that could not be removed in the surgery. Epithelial ovarian cancer has a high rate of recurrence with at least 50% of patients experiencing recurrence (Gubbels 2010).

Pre-Clinical Data on Adoptive Cell Therapy for Epithelial Ovarian Cancer

One method cancer employs to evade the immune system is by downregulating MHC molecules in the cancer cells (Gubbels 2010). This works well for the cancer cells as killer T

cells are the immune system's main defense against pathogens and other infections, such as cancer, but they require MHCI in order to be activated. When the cancer cells downregulate MHCI, they become almost invisible to the immune system which will, as a result, not recognize the cells. Therefore, the cancer cells will evade the immune system as a result of killer T cells not being activated. In epithelial ovarian cancer, adoptive cell therapy is commonly used as treatment though. There are many types of immunotherapies used to treat epithelial ovarian cancer, one of which is CIK cell therapy. Doctors will use cytokine induced killer or CIK cells which are a type of T lymphocyte which are expanded *ex vivo.* The first step in adoptive cell therapy is to collect the patient's T cells from their bloodstream. These collected cells are then cultured and treated with cytokines such as IL-2 that will help activate the T cells. The treated immune cells are now better able to recognize cancer cells as the treatment has increased their cytotoxicity, as IL-2 will promote T cell activation and proliferation. Through this treatment, the CIK cells multiply and divide and are then reintroduced back into the patient's body. The released CIK cells then move through the body and recognize the cancer cells and activate immune responses to kill them. Although further research is needed to determine the true success of this type of immunotherapy for epithelial ovarian cancer, the preclinical data shows promising results as the treated CIK cells were able to successfully kill cancer cells *in vitro*. However, the cost for the adoptive cell treatment can become quite expensive as they have to be done individually and tailored for each patient and cannot be mass produced. Patients may also have the need to undergo multiple adoptive cell treatments as this could have a stronger effect (Capallero 2020). Epithelial ovarian cancer also has a high rate of recurrence which may call for more than one round of treatment.

Immunotherapy Clinical Trials for Epithelial Ovarian Cancer

One ongoing immunotherapy clinical trial for epithelial ovarian cancer studies the effect of Durvalumab (NCT04918186) Durvalumab is a monoclonal antibody that targets a protein called programmed death-ligand 1 (PD-L1) that is often found on the plasma membrane of certain cells including cancer cells. PD-L1 is used by the immune system to regulate immune responses. By binding to PD-L1 the programmed cell death protein 1 (PD-1), used by cancer cells to evade the immune system, is blocked. This trial uses DCVAC/OvCa to stimulate the immune system's ability to detect and kill cancer cells. DCVAC/OvCa are cancer treatments made from the patient's own cells. Once the cells are collected from the patient the cells are cultured and treated. These cells, which are now called DCVAC/OvCa, are then released back into the patient's body and are able to regulate immune responses to cancer. The treatment is combined with standard chemotherapy in hopes of being able to effectively get rid of the cancer. This clinical trial is in phase 2 and currently has twenty two patients enrolled with indications of relapsed platinum resistant epithelial ovarian cancer. The inclusion criterion states patients must be females eighteen years or older with stage III or IV epithelial ovarian cancer that have not reached full remission yet with platinum based chemotherapy. The exclusion criteria include prior or current systemic anti-cancer therapy for ovarian cancer, previous radiotherapy to the abdomen and pelvis or having received a stem cell transplant. Such pre-existing conditions would not be ideal in showing if the treatment alone is effective for the cancer.If the patient also has any history of cardiovascular disease or any immune disease that required treatment such as immunosuppressive treatment, they would not be an ideal candidate for this trial as it could pose some potential safety risks. This combination therapy utilizes immunotherapy and chemotherapy to overcome limitations of previous therapies. The chemotherapy will work to kill

cancer cells and the immunotherapy can then be used to keep the disease from recurring and maintain the effect of the chemotherapy. Future directions for the trial include refining the therapy to better target the PD-L1 protein. Another ongoing clinical trial for epithelial ovarian cancer examines the efficacy and safety of using ITIL-306 in patients with advanced solid tumors such as epithelial ovarian cancer (NCT05397093). This clinical trial is based on TIL therapy. TIL, or tumor infiltrating lymphocyte therapy, is used when the T cells are unable to respond sufficiently to the cancer cells and eliminate them. The T cells are taken out of the patient's body to be grown and expanded *ex vivo*. The T cells are then reinfused into the patient and are now able to respond to the cancer more effectively due to their growth *ex vivo*. This trial is in phase 1. There are about 51 participants enrolled in this trial. Inclusion criteria for this trial includes having histologically documented advancement of the disease, adequate organ function and, the disease having unequivocally progressed during or after at least on prior line of systematic treatment. Exclusion criteria include having another primary malignancy within the last three years, receiving a stem cell transplant, previously receiving TIL therapy or, having any cardiac or autoimmune disease. This trial aims to address previous limitations by providing a treatment option for advanced solid tumors that have proven hard to treat. Future directions for this clinical trial include refining the therapy based on results from the trial and exploring how it can be more effective.

Conclusion

Epithelial ovarian cancer remains one of the most threatening types of cancer due to its late stage detection and high recurrence rate. Immunotherapy has shown to be a promising treatment method through adoptive cell therapy and enhancing the immune system's ability to detect and fight the cancer cells. Researchers continue to refine these therapies as well work on early detection methods as the late detection of the disease is a factor that makes the cancer significantly harder to treat. Immunotherapy has shown to hold great potential to improve the survival rate of epithelial ovarian cancer.

References:

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