**Grant Aims to Deliver First Stem-Cell Immunotherapy in Ovarian Cancer**

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**Kunle Odunsi, MD, PhD**

The New York State Stem Cell Science Program (NYSTEM) recently awarded a 4-year $11.9 million grant to Roswell Park Cancer Institute (RPCI) in Buffalo, New York, to fund research and development of a stem-cell based treatment for ovarian cancer. Kunle Odunsi, MD, PhD, FRCOG, FACOG, executive director of RPCI’s Center for Immunotherapy, and his team are pioneers in immunotherapy research for ovarian cancer, and he spoke with Targeted Oncology about how the grant will contribute to their efforts. He also explained their progress in reengineering adult hematopoietic stem cells (HSCs) to fight ovarian cancer and the possibilities of adoptive T-cell therapy.

The American Cancer Society estimates that in 2015, more than 21,000 women will receive an ovarian cancer diagnosis and approximately 14,000 women will die of the disease.1 Ovarian cancer is aggressive, and many women have advanced disease at diagnosis.2 Approximately 85% of those who achieve remission will relapse, and median survival for patients with relapse is 12 to 24 months.2 A great need exists for new therapies, particularly for women with epithelial ovarian cancer whose disease is platinum-resistant or who relapse after treatment with a platinum-based regimen. Odunsi and his colleagues at RPCI are hopeful that the stem-cell based immunotherapy they are developing for epithelial ovarian cancer will someday help improve these dire statistics.

***OncLive*: How long have you been focused on ovarian cancer research, and what lies behind your efforts?**

**Odunsi:**For more than 10 years now, our team has been studying, in preclinical and clinical settings, several different approaches for delivering immune therapies for ovarian cancer, and we’ve made several important discoveries that we’re applying in our current projects. The desperate need for better, longer-lasting therapies to offer women with ovarian cancer has always been the driving factor behind this work.

**How will the NYSTEM grant further those efforts?**

The NYSTEM grant will support the first clinical trial to utilize adult HSCs in cancer immunotherapy. It is tremendously important support that allows us to leverage other resources and fast-track our efforts to get these therapies to patients.

**Is your stem cell approach the first immunotherapy being studied for ovarian cancer?**

This is the first study, to our knowledge, that will directly examine the potential of reprograming adult HSCs into cancer-fighting immune cells able to provide long-term control of tumor growth. Previous studies by us and others have utilized mature immune cells in adoptive cellular therapy of cancers. Our pioneering NY-ESO-1 vaccine studies were the first studies to harness the potential of the patient’s own immune system to mount a response against their ovarian cancer cells.

There are many types of immunotherapy, including but not limited to immunomodulatory agents, monoclonal antibody therapy, vaccines, and cellular therapy. Each of these therapeutic strategies is tailored for the patient depending on the type and stage of his or her disease.

**What have your studies shown so far with this approach?**

We have a lot of data on the ability of the immune system to recognize and control ovarian cancer. Data from our preclinical studies using stem cells are not yet published, but we have demonstrated that adult HSCs can be programed to mature into functional antitumor immune cells and that these mature cells persist for a long period, thereby resulting in improved tumor control.

**How are the adult HSCs obtained?**

Along with mature T cells, adult HSCs are present in blood and are drawn from patients through standard leukapheresis. Based on the expression profile of unique cell surface markers, HSCs are isolated from the blood and can be further engineered to become T cells that have the potential to recognize tumor cells and attack them. Patients receive their own reengineered stem cells.

**How do you reprogram the stem cells to identify and eliminate ovarian cancer cells?**

Our work has focused on a unique class of tumor antigens known as cancer testis antigens. These are proteins primarily overexpressed on tumor cells and in the adult male testes but not in other normal tissues. This antigen, NY-ESO-1, can be targeted for immune-mediated destruction without causing unwanted damage to normal healthy tissue.

Mature T cells with specificity for NY-ESO-1 express a T-cell receptor (TCR). Our group has identified and cloned a novel TCR with specificity for NY-ESO-1. We introduce this molecule into stem cells, effectively reprogramming them to express the NY-ESO-1 TCR. When the reengineered stem cells are infused back into the patient, a portion of the cells expand for life-long self-renewal and the remaining cells develop into mature T cells that have NY-ESO-1 specificity. These T cells represent a distinct subset of immune cells that have the capacity to recognize NY-ESO-1–expressing tumor cells and initiate a series of processes to destroy the tumor cell. This is the basis of the immune-mediated tumor debulking.

The stem cells expressing the NY-ESO-1 TCR have the potential to provide a life-long source of T cells with specificity for NY-ESO-1–expressing tumor cells.

**How would the stem cells do this? Would it be automatic? And if, for example, a patient developed another primary cancer expressing the same antigen, would the HSCs target that cancer?**

The unique aspect of HSCs is their innate capacity for self-renewal and their ability to develop into mature immune cells. The infused HSCs persist and serve as a source of mature T cells. There is the potential for the stem-cell-derived mature T cells to recognize other NY-ESO-1–expressing tumor cells and eliminate them as well.

**Would the HSC immunotherapy you are working on be offered as a frontline therapy or after remission to prevent relapse or as a salvage therapy?**

We expect that the stem cell approach will initially be used as salvage therapy. In the future, we anticipate that it may also be used after remission to minimize the risk of relapse.

**Much oncology research has focused on combining immunotherapy with other types of agents, like cytotoxics or targeted therapies; do you anticipate combining HSC immunotherapy with other types of therapy?**

In this new study, re-engineered stem cell therapy is being utilized to augment the anti-tumor response elicited by the adoptive cell therapy with mature T cells. There are studies under way by our group and others to examine outcomes in treatments that combine immunotherapies.

**Would this therapy be expected to be more effective against certain types of ovarian cancer? For example, would it matter whether the ovarian cancer was BRCA1 positive or negative?**

We expect the treatment to be effective against any type of ovarian cancer that expresses the NY-ESO-1 antigen target. While it is a personalized-medicine approach, the treatment strategy we propose is not dependent on BRCA1 or other genetic markers.

**Often, ovarian cancer is not detected until it is advanced. Would the stage of disease at the time of diagnosis be expected to effect outcomes with immunotherapy?**

Development of immunotherapies and tumor vaccines is a rapidly growing field. The various types of immunotherapies are selected based on the stage of the disease, as this will improve the likelihood of an antitumor immune response.

**Is there any possible advantage to giving immunotherapy like HSCs to prevent cancer in a woman with high-risk due to a genetic mutation or to prevent relapse in a woman who has an elevated CA-125 level after remission of ovarian cancer?**

Using immunotherapy to prevent cancer in high-risk women is conceptually appealing, but this would be a difficult study to perform. However, for a patient who develops elevated CA125 after remission, immunotherapy is an attractive strategy.

**Might the stem cell immunotherapy approach you are working on be effective against other types of cancer?**

This approach is first being tested in patients with ovarian cancer, but the biological principle is similar for other types of cancers that express a tumor antigen that is targeted by the TCR. There are a number of such cancers, including melanoma, lung, breast, and colon.

**What are the advantages of immunotherapy over traditional chemotherapy?**

Traditional chemotherapies poison the tumor cells along with healthy normal cells. The severity of this collateral damage limits the efficacy and long-term use of many types of chemotherapy. One potential advantage of immunotherapies, such as vaccines and adoptive cell therapies, is the ability to minimize unwanted destruction of healthy tissue. Specificity of responses directed against tumor cells is a hallmark of immunotherapies. With the current HSC study, an additional beneficial feature is the potential for generating a life-long source of antitumor mature T cells.

**References**

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