IMPACT REPORT

Preston Robert Tisch Brain Tumor Center at Duke University Medical Center

Activity Summary 2016

Uncle Kory FOUNDATION

We've got brain cancer surrounded.

IMPACT REPORT: THE PRESTON ROBERT TISCH BRAIN TUMOR CENTER AT DUKE UNIVERSITY

THE PRESTON ROBERT TISCH BRAIN TUMOR CENTER

In 2015 the Uncle Kory Foundation (UKF) made a financial contribution to support brain cancer research to the Robert Tisch Brain Tumor Center at Duke. The foundation contributed $100,000 in funding to be applied to their genetically modified poliovirus trial in recurrent glioblastoma patients. This grant helped advance the "immunotoxin guided missile" approach to the treatment of malignant brain tumors, especially glioblastoma multiforme. These funds were specifically designated to help cover patient expenses in order to expand the trial.

CLINICAL TRIALS

To bring the drug to clinical trial, Duke had to prove the immunotoxin called D2C7-PE38-KDEL could effectively kill glioblastoma cells. They found that human glioblastomas have two primary genes that drive the malignant process and when infused directly with this immunotoxin, could have uniform destruction. They also had to develop a methodology to produce a high quality clinical grade immunotoxin. This was done in the Duke laboratories. After determining the safe beginning dosage, they began working with the FDA to begin treating patients that had recurring glioblastoma, and had failed all previous trials. To begin this trial on a new patient, the doctors worked with the BrainLab in Germany to work up a computer algorithm to show their neurosurgeons how to stereotactically, with a needle biopsy, remove a piece of the tumor to verify its recurrence. Then they use the same coordinates to insert one to four catheter tubes to slowly pump the immunotoxin over a 72-hour period into the tumors.

In conjunction with this study, they also explored the action of this agent. Specifically, the white blood cells that infiltrate the tumors are measured. Their studies have shown that the infusion of D2C7 converts the tumors from having a low level of white blood cells to having an extensive amount of white blood cells. First, the toxin kills all tumor cells that it comes into contact with and a sea of inflammation is created by the potent bacterial toxin. Then, inflammatory cells invade the rest of the tumor and a "secondary immune response" is initiated. This type of response is capable of moving over the entire brain and seeking out and killing remaining tumor cells.

Uncle Kory FOUNDATION

These researchers will continue to work on this process by including a new agent called "checkpoint inhibitors." This is a newly discovered class of drugs, which restore the normal immune system function in patients with brain tumors. It has been known for many years that GBM and other primary brain tumors paralyze the immune system. It has recently been discovered that these checkpoint inhibitors are capable of restoring normal immune function. The combination of these two factors is very promising; one process to kill the tumor cells and another to foster normal immune function.

FINDINGS

The researchers are learning many things from this trial and have had many successes. They have had two complete responders who are alive four years out from treatment, and a third patient who is more than three years out from treatment. The median survival in all of the patients is 15 months compared to 10.5 months in historical controls matched for eligibility.

As with all clinical trials, they are having an issue that they are trying to overcome. There has been significant inflammation after the initial dosing, that causes brain swelling and requires treatment. To combat this swelling, they have lowered the dose of the virus to a -1 dose level in some trials, and are now lowering the dose again to -2 level. Although the patients initially have an inflammatory response, over time it diminishes. In the most recent patients, their neurosurgeons have determined that corticosteroids, which are used to treat brain swelling, can be eliminated after infusions with the immunotoxin. It is their belief that eliminating these harsh steroids, which downregulate white blood cells, will eventually increase the efficacy of the treatment.

RECOGNITION

There were two important recognitions by the U.S. Food and Drug Administration during the last year for these trials and drugs. The FDA granted the recombinant poliovirus therapy developed at Duke with the "Breakthrough Therapy Designation." This means that the therapy will be fast tracked within the FDA to develop the fastest and most efficient way to ultimately get approval as a treatment for recurrent glioblastoma. To

obtain "breakthrough status," the preliminary evidence must show that the treatment may be a substantial improvement over standard therapy. Although this designation does not mean the approach or drug has been approved for clinical use, it is being tested in clinical trials in adults with advanced glioblastoma tumors.

The second designation Duke received was the drug PVS-RIPO was granted Orphan Drug Status. This status is given to drugs that are intended for the treatment of diseases that will affect less than 200,000 people in the U.S.; or for more than 200,000 people, but the developers are not expected to recover the costs of developing and marketing the treatment. This status helps the makers qualify for grants and may include tax credits to continue the development of their treatment. The preliminary findings and results of these trials have led them to receive these prestigious recognitions.

NEXT STEPS

With these new designations comes new trials and future additions to the treatment. The first step is to determine the adequate dosage of the virus. Once they have treated approximately 12 patients at the -2 Dosage Level they will do a trial of 62 patients. In this trial they will add a chemotherapeutic agent Lomustine to the virus. They have seen massive tumor destruction in multiple patients after adding this agent.

These designations are extremely important to the path of this trial. This fast track can help get this therapy efficiently to FDA approval. Once FDA approves one indication for the drug use, a prescribing physician can use it in any other indication. In fact, some estimates are that 70%+ of all cancer treatments are done as off-label indications.

The $100,000 contribution provided by the Uncle Kory Foundation allowed this program to expand their trials to include additional patients and continue their ever important findings on the path to eliminating Glioblastoma. These increased patients would not have had the opportunity to participate in this trial were it not for this generous donation as a direct result of Uncle Kory Foundation.

Uncle Kory
FOUNDATION

THE UNCLE KORY MISSION

The Uncle Kory Foundation looks forward to collaborating with like-minded individuals and organizations to inspire and bring hope to those who are facing such life-altering challenges. GBM accounts for approximately 17 percent of all brain tumors and increases in frequency with age, affecting more men than women. Unfortunately for all of them, the prognosis is grim, as few will live to see 3 years after diagnosis. Most patients will live only 6-18 months. The entire family is affected by the devastating news. The Uncle Kory Foundation's mission is to advance innovative and collaborative brain cancer research to specifically improve the survival rate and treatment of those diagnosed with Glioblastoma (GBM).

For more information or to make a donation, please visit **UNCLEKORY.ORG**

Uncle Kory
FOUNDATION