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INTRAVESICAL IMMUNOTHERAPY WITH A GM-CSF ARMED ONCOLYTIC VESICULAR STOMATITIS VIRUS IMPROVES OUTCOME IN BLADDER CANCER.

Context

Bladder cancer is the 5th most common cancer in North America. Approximately 12,000 Canadians and 81,180 Americans are diagnosed with bladder cancer each year (The American Cancer Society,2022). The majority of these cases (80%) are nonmuscle invasive bladder cancer (NMIBC). The standard treatment for NMIBC is transurethal resection (TUR) followed by intravesical chemotherapy. Despite these treatments, approximately 60-70% of these cases will recur or spread to other organs.

For these high-grade cases, intravesical Bacillus Calmette-Guerin (BCG) immunotherapy will be used. Treatment options are limited in patients who fail chemotherapy and BCG. Cystectomy (bladder removal) remains the standard of treatment for high-grade patients who have failed chemo- and BCG therapy. For those who receive cystectomy before their bladder cancer progresses to muscle invasive disease have shown good disease-free survival. However, cystectomy comes with significant morbidity and diminished quality of life.

Bladder cancer is also the most expensive cancer to treat (specialized surveillance tools, highly trained medical personnel). We propose to evaluate a novel virus as an alternative bladder-sparing treatment option for bladder cancer. This engineered virus forms the hypothesis that it may be used as a better alternative to BCG and for bladder cancer patients who have failed current treatment options and are recommended for bladder removal (cystectomy). The use of this virus may delay or potentially prevent cystectomy for bladder cancer patients. This virus may also be used in combination with checkpoint inhibitors to work synergistically against bladder cancer.

TECHNOLOGY

The present invention involves administering a virus (vesicular stomatitis virus, VSV) that is not a common human pathogen to reduce the viability of bladder cancer cells, while leaving normal cells largely unharmed. The virus has been engineered to contain a special human growth factor called hGM-CSF that will stimulate an immune response by attracting and promoting the development of antigen presenting cells and effector immune cells. The immune response will help with the local removal of bladder cancer cells as well cancer cells that may have spread to regional lymph nodes or other organs.

In fact, *in vitro* assays with human bladder cancer cell lines showed that VSVd51-hGM-CSF released danger signals (calreticulin, HMGB1, ATP) and immunogenic cytokines/chemokines that were detected in the infected cell lines. The same results were observed in mouse bladder cancer cell lines using the mouse virus VSVd51-mGM-CSF. As proof of concept using the mouse virus, intravesical instillation of VSVd51-mGM-CSF increased the activation of natural killer (NK) cells and peripheral cytotoxic CD8+ T cells present in the bladder. The increased functionality of NK cells and CD8+ T cells was associated with improved survival as determined by *in vivo* depletion studies. Using human bladder cancer patient derived tissue grown as 3D organoids, biomarkers of immune cell activation were detected following treatment with VSVd51-hGM-CSF. These preclinical *in vivo* and translational human cell culture experiments demonstrated the potent immune-stimulating capacity of VSVd51-hGM-CSF as intravesical therapy for bladder cancer.

Preliminary results in *in-vitro* human tumors cells and in *in-vivo* mice with endogenous tumors demonstrate significant increased effectiveness compared to BCG. Models treated with the virus have a stronger and faster reduction of tumors compared to the ones treated with BCG. The number of cancer relapses also appear to be lower compared to BCG treatment.

ADVANTAGES

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TECHNICAL ADVANTAGES

- It may be use as a form of treatment for bladder cancer patients who have failed current treatment options and are recommended for a cystectomy. This virus may delay or potentially prevent the intervention for bladder cancer patients.
- It may be combined with immune checkpoint inhibitors to treat bladder cancer.
- The bladder is easily accessible by the urethra for intravesical instillation of the invention, thus delivery is easy.
- VSVd51 is non-pathogenic in humans.
- Preliminary results in human in-vitro cells and endogenous tumors models.
- Preliminary results show a significant increased effectiveness compared to BCG.
- Preliminary results seem to show that cancer relapses are lower compared to BCG treatment.

COMMERCIAL ADVANTAGES

There is an urgent need for bladder-sparing therapies for patients failing frontline therapies. In fact, there are very limited treatment options for high-grade patient who have failed chemotherapy and BCG.

Bladder cancer represents 3% of all the cancer cases and its treatment was a 9.4 billion dollars endeavour in 2020 in the United States alone. Up to 40-50% of patients diagnosed with bladder cancer will fail BCG and will need an alternate treatment before cystectomy.

APPLICATIONS

May be used as a form of non-toxic intravesical therapy for bladder cancer patients who have failed chemotherapy/surgery/BCG and to prevent cystectomy (bladder removal)

Technology Readiness Level (TRL)

Technology is at TRL stage 2-3.

It is currently being tested in multiple *in vivo* mouse models of bladder cancer, including an orthotopic model and carcinogen-induced model. In addition, improved survival and reduced bladder tumor volume were observed in mice treated with this agent. Following *in vitro* testing, biomarkers of immunogenic cell death and immunogenic cytokines/chemokines were detected in infected mouse and human bladder cancer cell lines. Also, this immune response was detected in human's cells, in organoids derived from tissues of treated bladder cancer patients.

Seeking

Seeking a partner to make an option/licensing/collaboration with the technology.

Intellectual property

A provisional patent and a PCT Patent application has been filed.

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