Journal of
Pharmacology & Clinical Research
ISSN: 2473-5574

Juniper Publishers
key to the Researchers

Letter to Editor
Volume 4 Issue 1 - October 2017
DOI: 10.19080/JPCR.2017.04.555627

J of Pharmacol & Clin Res
Copyright © All rights are reserved by Gilles Plourde

Gene Therapy in Advanced Prostate Cancer: Letter to the Editor

Gilles Plourde*

Associate Professor Department of Clinical Pharmacology and Physiology, University of Montreal, Canada

Submission: October 14, 2017; **Published:** October 24, 2017

***Corresponding author:** Gilles Plourde, Associate Professor Department of Clinical Pharmacology and Physiology, Faculty of Medicine, University of Montreal, Montreal, Quebec, Canada; Associate Professor at the Faculty of Health Sciences, University of Ottawa, Ontario, Canada;
Email: gilles.plourde@hc-sc.gc.ca; drgplourde@gmail.com

Abstract

Keywords: Advanced prostate cancer; Gene therapy; Vectors; CAR-T Therapy; Cancer Stem Cells; EpCAM

Introduction

Second to skin cancer, prostate cancer is the most common neoplastic injury in North American men. Over a lifetime, 1 out of 7 men will receive a diagnosis of prostate cancer [1-3]. Current treatments for prostate cancer includes surgery, radiotherapy, and androgen-deprivation therapy. Prostate cancer can eventually transform to an advanced castration-resistant prostate cancer that becomes a systematic disease with metastasis which is incurable. Therefore, identifying cellular components and molecular mechanisms that promotes aggressive prostate cancer at early stage is critical for stopping disease prognosis and for therapeutic intervention. Cancer in general including prostate cancer is considered as a disease caused by mutations and or epigenetic changes in tumor suppressor genes and oncogenes that populate the host genome. It is well established that most of the genetic events in cancer result from a series of accumulated, acquired genetic lesions [4]. These gene alterations involved structural changes such as mutations, insertions, deletions, amplifications, fusions and translocations, or functional changes such as heritable changes without changes in nucleotide sequence [4-6].

However, very often no single genomic change is found and multiple changes are commonly found in most cancer including prostate cancer. Approaches to cancer gene therapy include three main strategies: the insertion of a normal gene into cancer cells to replace a mutated (or otherwise altered) gene, genetic modification to block a mutated gene, and genetic approaches to directly kill the cancer cells [4-6]. In this letter to the editor, with the use of a case report, I will summarize some of the main components associated with gene therapy in order to be able to answer questions raised by many patients and clinicians dealing with patients suffering from advanced prostate cancer where treatment options become limited. Obviously, in the context of this letter limited aspects of gene therapy will be discussed.

Case Report

A 61 year-old patient known for an undifferentiated and an invasive stage IV prostate cancer came to your office. He was treated with Zoladex and Casodex for 3 years. Recently, Casodex was interrupted because his PSA level has started to increase significantly and he was then put on Zytiga, a second line hormone therapy in combination with Zoladex and prednisone. He is also known for bone metastasis for which he received Xgeva once a month. Since he is not much interested by chemotherapy, he wants to know what should be the best treatment approach for him when he will no longer be responsive to this second-line hormone therapy. He was looking at the medical literature and from what he has read; it seems that gene therapy may be an appropriate option for him. Among the following items, which one(s) is/are considered the main elements involved in the comprehension of gene therapy that you should discuss with your patients. Considering the context of this letter I will only discuss some of the main elements.

a. Prostate Cancer can be considered a genetic disorder;

b. Gene Therapy Vectors;

c. CAR-T Therapy;

d. Cancer Stem Cells (CSCs).

e. All the above item are considered relevant

Answer : E

a. Prostate Cancer Can Be Considered A Genetic Disorder

Several genes and chromosomal regions have been found to be associated with prostate cancer in various linkage analyses, case-control studies, genome-wide association studies (GWAS), and admixture mapping studies [4-6]. By acting at an earlier, upstream step in disease pathogenesis we increase the potential to induce important changes in the phenotypic patterns of cancer, with a more favorable clinical outcome. Considering the great availability of gene transfer systems, or vectors, we increase our chance for definitive therapeutic interventions in advanced prostate cancer [4-6].

b. Gene Therapy Vectors

With the gene therapy approach, different vectors both viral and non-viral vectors are employed. The six most frequently used viral vectors include those derived from adenovirus, retrovirus, poxvirus, adeno-associated virus, herpes simplex virus and lentivirus while the non-viral approaches includes calcium based molecular compounds, lipofection, and direct injection of naked DNA or RNA [4-6]. Furthermore, gene therapy vectors can be engineered to produce a variety of therapeutic proteins, and researchers are investigating the safety and effectiveness of different types of vectors in hundreds of clinical trials in the United-States. For more information please consult the clinical trials. One of the most commonly used vectors in gene therapy is the adenovirus vector. While adenovirus vectors are very efficient at delivering genes, adenovirus vectors can cause toxic effects that limit the amount of vector that clinicians can give to patients. New adenovirus gene therapy vectors are currently tested in animals before human clinical trials begin. It is important for both researchers and the Regulatory Agencies including the FDA, the EMA and Health Canada to know how well these animal studies can predict safety in humans.

This new knowledge will enable researchers to design safer and more effective gene therapy vectors for treating prostate cancer. The objective is to improving the safety and efficacy of adenovirus and other vectors, especially when administered through the vascular system. Researchers are studying additional novel mediators and pathways that control innate immune responses, and how this contributes to toxicity caused by adenovirus and other vectors. Understanding these mediators and pathways is an essential step toward our goal of developing safer vectors and new ways to limit vector-induced toxicity.

c. Chimeric Antigen Receptor (CAR) Therapy:

With the FDA approval of the first gene therapy (Kymriah) in the United-States, we are entering a new era in medical innovation with the ability to reprogram a patient's own cells to attack a cancer (personalized medicine). Kymriah is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory to chemotherapy. The concept is that by engineering the T cells to recognize antigens on the surface of the tumours, we can bypass the normal antigen presentation by peptide and HLA Class I/II and engage T cells (or NK cells) to kill the tumor targets.

Kymriah is a personalized treatment that uses a patient's own T cells. In CAR-T therapy a patient's T cells are extracted and cryogenically frozen. Then, the cells are genetically altered to have a new gene that codes for a protein called a chimeric antigen receptor (CAR). This protein directs the T cells to target and kill ALL cells with a specific antigen on their surface. The genetically modified cells are then infused back into the patient. In a pivotal clinical trial of 63 children and young adults with ALL, 83 percent of patients that received the CAR-T therapy had their cancer go into remission within three months. At six months, 89 percent of patients who received the therapy were still living, and at 12 months, 79 percent had survived. These results confirmed that this treatment is really efficient in humans.

CAR-T therapy is also associated with life-threatening side effects in some patients, including neurological toxicity and cytokine release syndrome. Furthermore, another company ended a CAR-T study earlier this year after patients died from cerebral edema. However, no patients treated with Kymriah have died from that complication. The approval of Kymria as lead the International Society for Cellular Therapy (ISCT) to confirm that this approval increased enthusiasm in the field of cell therapy by boosting investment in products at all stages of drug development. This approval creates also optimism in clinicians and researchers working on cancer including prostate cancer.

d. Cancer Stem Cells (CSCs)

Another potential strategy for aggressive prostate cancer is to target cancer stem cells (CSCs) (7-8), that can originate in any cell type of a particular tumor. CSC is believed to be a major factor contributing to resistance to radiotherapy, conventional chemotherapies, most probably hormone therapy and for the development of metastasis. Therapeutic strategies aimed at targeting specific surface markers of CSCs, the key signaling pathways in the maintenance of self-renewal capacity of CSCs such as the ATP-binding cassette transporters that mediate the drug-resistance of CSCs, dysregulated microRNAs expression profiles in CSC sand immunotherapeutic strategies developed against pre-cancerous stem cells (PCSCs) surface markers are also promising [7,8].

In a recent study [9], using a human prostate cancer cell line (PC3), the authors targeted the epithelial cell adhesion molecule (EpCAM), a protein that is over expressed in CSCs from breast, colon, pancreas, and prostate cancers. The results demonstrated that higher levels of EpCAM correlated with the proliferation and metastasis potential of prostate cancer cells. To produce CSCs-specific T cells, the researchers isolated human

How to cite this article: Gilles Plourde. Gene Therapy in Advanced Prostate Cancer: Letter to the Editor. J of Pharmacol & Clin Res. 2017; 4(1): 555627. DOI: 10.19080/JPCR.2017.04.555627.

peripheral blood cells (PBLs) and enriched them in T cells. Using retroviruses, these researchers genetically engineered T cells to have an EpCAM-specific CAR. These new T cells were able to kill human prostate cancer cell lines in culture (ex vivo) [9].

Furthermore, when mice were injected with tumor cells, followed by administration of T cells bearing. EpCAM-specific CAR, tumors did not metastasize. In contrast, mice that did not receive these modified cells, had tumor metastasis after 27 days. In addition, treated mice showed prolonged survival, as animals treated with CAR-expressing PBLs were alived 80 days after treatment, whereas only 1/3 of non-treated mice survived. These data indicate that PBLs targeting EpCAM can have significant anti-tumor effects in prostate cancer. The authors concluded that, despite the low expression of EpCAM on PC3tumor cells, EpCAM-specific PBLs had significant anti-tumor activity against PC3, probably by targeting the CSCs of prostate cancer. These data suggest that adoptive transfer of T cells targeting CSC antigens is a promising therapeutic approach for treating prostate cancer.

These are only few examples to demonstrate how the field of gene therapy is progressing in the treatment of prostate cancer. If you take a look, you will find that there more than 50 studies that are completed but not published, that others are in phases I, II, III in their development or are currently recruiting suggesting a great interest for gene therapy in the treatment of advanced prostate cancer. However, before gene therapy becomes available to our patient, further development is required. We should expect that this therapy would be available for our patients in the next few years. But patients can have access to this therapy throughout the Special Access Program or by being involved in clinical studies.

Conclusion

Recent developmentshave increased enthusiasm among cancer researchers; many now usetherapeutic approaches in genetic manipulation to improve cancer regression and find a potential cure for the disease. As stated these therapies include transferring genetic material into a host cell through viral (or bacterial) and non-viral vectors, immunomodulation of tumor cells or the host immune system, and manipulation of the tumor microenvironment, to reduce tumour vasculature or to increase tumor antigenicity for better recognition by the host immune system [4-6].

It is anticipated that gene therapy will play an important role in future cancer therapy as part of a multimodality treatment, in combination with, or following other forms of cancer therapy, such as hormonal therapy as in in our patient. Gene therapy is already determined based on an individual's genomic constituents, as well as his or her tumor specifics, genetics, and host immune status, to design a multimodality treatment that is personalised to each individual's specific needs. Finally, for our patient we can be reassuring that gene therapy will represents a very interesting option for him when he will become resistant to the second-line hormone therapy. Gene therapy is very efficient, but it is still concerning from the safety point of view. Even considering the latter aspect, gene therapy has already a favourable risk/benefit ratio.

References

1. Canadian Cancer Society, What is prostate cancer (2017).
2. American Cancer Society, Key Statistics for Prostate Cancer (2017).
3. Canadian Task Force on Preventive Health Care, Screening for Prostate Cancer with the Prostate Specific Antigen (PSA) (2014).
4. Anand C Annan, Paul B Fisher, Paul Dent, Gene P Siegal, David T Curiel (2016) Gene Therapy in the Treatment of Human Cancer. The Molecular Basis of Human Cancer pp. 811-841.
5. Magid H Amer (2014) Gene therapy for cancer: present status and future perspective. Amer Molecular and Cellular Therapies 2(27): 1-19.
6. Macpherson JL, Rasko JE (2014) Clinical potential of gene therapy: towards meeting the demand. Intern Med J 44(3): 224-233.
7. Eun Jin Yun, U Ging Lo, Jer Tsong Hsieh (2016) The evolving landscape of prostate cancerstem cell: Therapeutic implications and future challenges. Asian Journal of Urology 3: 203-210.
8. Norman J Maitland, Anne T Collins (2008) Prostate Cancer Stem Cells: A New Target for Therapy. J ClinOnco 26(17): 2862-2870.
9. Zhenling Deng, Yanhong Wu, Wenbo Ma, Shuren Zhangand, Yu Qian Zhang (2015) Adoptive T-cell therapy of prostate cancer targeting the cancer stem cell antigen EpCAM. BMC Immunology 16: 1.

This work is licensed under Creative Commons Attribution 4.0 License
DOI: 10.19080/JPCR.2017.04.555627

Your next submission with Juniper Publishers will reach you the below assets

- Quality Editorial service
- Swift Peer Review
- Reprints availability
- E-prints Service
- Manuscript Podcast for convenient understanding
- Global attainment for your research
- Manuscript accessibility in different formats
  (Pdf, E-pub, Full Text, Audio)
- Unceasing customer service

Track the below URL for one-step submission
_ https://juniperpublishers.com/online-submission.php

How to cite this article: Gilles Plourde. Gene Therapy in Advanced Prostate Cancer: Letter to the Editor. J of Pharmacol & Clin Res. 2017; 4(1): 555627. DOI: 10.19080/JPCR.2017.04.555627.