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Gene Therapy for Treatment of Various Types of Cancers: A Review.

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ABSTRACT

Due to high prevalence of cancer deaths and difficulty in success of present methodologies including chemotherapy, radiotherapy ***etc***., it is now the need of the hour to understand and exploit better technologies to succeed in the control cancer deaths. At this context the mechanism and use of gene therapy is expected as very promising approach for total cure of cancer the present paper presents the updates on gene therapy for treatment of various types of cancer and the status of success of gene therapy techniques.
Keywords: cancer, chemotherapy, gene therapy.

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INTRODUCTION

Cancer, the heterogeneous deadly disease characterized by uncontrolled proliferation of tumor cells in the body which will invade normal tissues with significant individual differences. [1,2]. It is due to disrupting the normal cell proliferation and apoptosis process. The treatment depends upon the type of cancer, grade, prognosis and the individual. Advances in cancer therapy need a novel therapeutic agent with novel mode of action, several mechanisms of cell death, and synergy with conventional management. Treatment options are chemotherapy, surgery, radiotherapy, hormone treatment, photodynamic therapy, hyperthermia, immunotherapy, stem cell transplantation and targeted therapy [3] and including Gene therapy.

Gene therapy is a method of novel treatment in which genes or short oligonucleotide sequences are used as therapeutic molecules, rather than conventional drug substances [1]. Human gene therapy is a method of insertion of new genetic material into the cells of an individual to produce the therapeutic effect [4]. The gene therapy works by having the ability to manipulate cell physiology at genetic and epigenetic levels. Gene therapy experiment was first approved on September 14, 1990 in US for treatment of ADA-SCID on patient when Ashanti DeSilva [5].

Genes can be introduced into the cell of patients by direct and indirect routes & inserted genes can integrate into the chromosomes or remain extra chromosomal [6]

Gene therapy is different from traditional therapy methods as it does not have side effects compared to traditional therapy [7,8]. Gene therapy is applicable for with all these profiles. There are numerous gene therapy approaches which are applicable for the management of cancer

Understanding the promising results of gene therapy for treatment of cancer, this paper presents the various types of gene therapy techniques with their success and methodologies etc.

As of November 2017, more than 2597 clinical trials were conducted on gene therapy all around the world. Among these trials, greater than 65% are associated with cancer, followed by cardiovascular diseases [9]. The CAR T cell therapy showed promising results for the management of both myeloid and lymphoid leukemia. Until August 2019, only 22 gene products were approved for the treatment of different disorders. Immuno-gene therapy is a prominent treatment approach for the treatment of p53 deficient tumors (Imlygic, Gendicine, Yescarta, and Kymriah [10].

Table: 1 Gene Therapies products approved for therapeutic use [11]

Trade Name	Date of approval & Approving agency	Vector & Modified gene	Indication	Route of Administration
Gendicine	2003 State Food and Drug Administration of China	Adenoviral vector P53	Head and neck squamous cell carcinoma	*In vivo*
Oncorine (Recombinant Human Adenovirus Type 5 Injection)	2005 State Food and Drug Administration of China	Adenovirus Type 5	Head and neck and esophagus cancer, Nasopharyngeal cancer, etc.	*In vivo*
Kymriah™ (tisagenlecleucel)	August 2017 FDA	CD19-specific CAR T Lentiviral vector	Acute lymphoblastic leukaemia	*Ex vivo*
Yescarta™ (axicabtagene ciloleucel)	October 2017 FDA	CD19-specific CAR T Y-Retroviral vector	Non-Hodgkin lymphoma	*Ex vivo*
Imlygic (talimogene laherparepvec, T-Vec)	2015 FDA	GM-CSF HSV-1	Melanoma	*In vivo*

Various Gene Therapy Techniques

The various gene therapy techniques include gene replacement therapy, gene silencing (RNA interference or siRNA), immunomodulation, suicide gene therapy, oncolytic virotherapy, gene editing etc. [12].

Gene Replacement Therapy

Some cancers are caused by mutations in tumor-suppressor genes (like TP53 or BRCA1). The aim of gene replacement therapy is to replace these defective genes with functional versions to maintain normal cell control mechanisms. This can inhibit or slow down the growth of cancer cells [13].

Gene Silencing (RNA Interference Or SiRNA) Technique

Gene silencing is a technique in which small interfering RNA (siRNA) are used to turn off genes which are responsible for the cancer growth, such as oncogenes (e.g., RAS or MYC, the most commonly activated oncogenes in tumorigenesis). This mechanism prevents the expression of proteins that is accountable for tumor growth. Gene silencing therapy is knockdown of specific genes in tumor cells through RNA interference (RNAi). RNAi is single or double-stranded noncoding RNAs (21 ribonucleotides) that induce sequence-specific degradation of complementary mRNAs via the cell's internal machinery [14]. siRNA is essential because mostly genes does not have inhibitors due to the lack of ligand binding sites and amino acid sequence homology with other proteins which limits their target selectivity. RNAi generally contains microRNA (miRNA), Small Interfering RNA (siRNA) and short hair pin RNA (shRNA). After the discovery of RNAi, ONPATTRO™ (patisiran) for the first time management of the polyneuropathy of hereditary transthyretin-mediated (hATTR) amyloidosis [15]. Tumor suppressor genes, oncogenes, genes involved in cancer progression, and drug-resistance are promising tar gets for gene silencing by RNAi based cancer treatment due to selective gene silencing effect and relatively fewer adverse effects than conventional chemotherapy [16]. The advantage of RNAi in cancer treatment is gene targeting of several of different cellular pathways involved in cancer progression and develop a drug for a specific patient [17]. Several studies conducted on animals revealed that targeting vital proteins in the cell cycle, such as Protein kinase N3 (PKN3), kinesin spindle protein (KSP), and polo-like kinase 1 (PLK1) by siRNA displayed a potent antitumor effect. Several liposomal siRNA dose preparations are in Phase 1 trials, such as treatments for pancreatic cancer (PKN3 siRNA), liver cancer (CEBPA siRNA), and neuroendocrine tumors (PLK1 siRNA) [18].

Immunomodulation (Enhancing Immune System Responses)

Gene therapy can be used to enhance and boost the ability of the immune system to identify and destroy cancer cells. This method involves inserting genes which code for immune-stimulating molecules (e.g., cytokines like IL-12 or GM-CSF), or engineering T cells (like in CAR-T cell therapy) which will specifically target cancer cells. T cells destroy infected and tumor cells by identifying non- self-antigens with the T cell receptor (TCR). CAR is described as "chimeric" because it consists of the antigen-binding site of the B cell receptor and an intracellular TCR activation domain. CAR has three domains, an extracellular domain that has cancer-specific epitopes made from light (V L) and heavy (V H) chains of immunoglobin that target antigen (such as CD19), a transmembrane domain, and intracellular TCR derived stimulatory domain. The component binds to the target antigen in the MHC independent way leading to CAR clustering and stimulating T-cell via intracellular region that possess the TCR- derived CD3 chain, with or without co-stimulatory domains. Stimulated CAR T-cells give target-specific memory cells that inhibit tumor relapse [19]. Second-generation CARs have a costimulatory domain with the CD3 activation domain show enhanced T cell activity. Two second-generation, CD19-targeted CARs are in clinical use contain a 41BB costimulatory domain (19-BBz) and a CD28 costimulatory domain and those with more than one additional co-stimulatory molecule are known as third-generation CAR [20].

Kymriah (Tisagenlecleucel) 38%

Kymriah is the first FDA approved CAR T-cell-based gene product to treat relapsed B-cell acute lymphoblastic leukemia. Kymriah has autologous T cells modified with lent virus to encode a CAR having murine single-chain antibody fragment selective for CD19, an intracellular domain 4-1BB (CD137), and CD3 zeta with CD8 transmembrane hinge. Kymriah initiates the antitumor effect via the CD3 domain after

binding to CD19 antigen- expressing cells. The intracellular 4-1BB co- stimulatory domains increase antitumor activity. The CD19 antigen is a 95-kD glycoprotein encoded as a surface antigen in diffuse large B-cell lymphoma (DLBCL) and other B-cell lymphomas [21].

Yescarta (Axicabtagene Ciloleucel)

For the management of aggressive non-Hodgkin lymphoma Yescarta is another CAR T-cell therapy. It is CD19 antigen- specific *ex-vivo* modified autologous T cells infected with a gamma-retroviral [22]. It encodes a CAR comprising an extracellular murine anti-CD19 single-chain variable fragment fused to a cytoplasmic domain that possesses CD28 and CD3-zeta co-stimulatory domains [23].

Zalmoxis (Allogenic T Cells Encoding LNGFR and HSV-TK)

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) uses for the management of several hematopoietic graft-versus-host-disease (GvHD) and the major demerit that has emerged is Graft rejection to its success. After stem cell infusion, the therapeutic approach for haplo-HSCT relies on T-cell depletion or the use of lymphotoxin drugs such as cyclophosphamide to specifically decrease activated alloreactive lymphocytes, although this results in prolonged immunodeficiency post-transplantation. Thus, treatment to enhance immune reconstitution after trans plantation is necessary [24]. Zalmoxis is a genetically modified allogeneic T cell that utilizes a retroviral vector to express a human low-affinity nerve growth factor receptor and HSV-TK Mut2, enabling T cell tracking and the potential to mitigate Graft Versus Host Disease in transplant patients while enhancing immunity against infections and improving outcomes post-transplant [25].

Suicide Gene Therapy

This approach involves introducing a gene into cancer cells that converts a non-toxic prodrug into a toxic compound, killing the cancer cells selectively. A common example is the herpes simplex virus thymidine kinase (HSV-TK) gene, which makes cells sensitive to the antiviral drug ganciclovir. Suicide gene therapy involves introducing viral or bacterial genes into cancer cells, enabling them to convert harmless prodrugs into harmful compounds, with notable systems including HSV-thymidine kinase paired with ganciclovir and cytosine deaminase paired with 5-fluorocytosine [26]. Gene-mediated cytotoxic immunotherapy is one strategy where an adeno viral vector possessing the herpes virus thymidine kinase gene is administered locally into the tumor site that causes local expression of the herpes simplex virus thymidine kinase gene to the synthesis of viral thymidine kinase that converts GCV to GCV monophosphate. Next is the administration of GCV, the substrate of HSV-TK and phosphorylated to produce GCV monophosphate. Subsequently cellular kinases metabolize GVC monophosphate into GVC triphosphate. GCV triphosphate is a deoxyguanosine triphosphate analog, incorporated into the DNA chain causing chain termination and tumor cell death [27].

Oncolytic Virotherapy (OV)

Some gene therapies use genetically modified viruses like oncolytic viruses specifically infect and kill cancer cells. These viruses can also be engineered to carry additional therapeutic genes boosting their ability to combat cancer. Oncolytic virotherapy (OV) is very promising that uses replication-competent viruses which will proliferate selectively at tumor cells. Oncolytic viruses are divided as naturally occurring and genetically modified viruses. Natural occurring viruses like parvoviruses, and Newcastle disease viruses selectively replicate in tumor cell without genetic modification. GM viruses such as vesicular stomatitis viruses, adenoviruses, measles viruses, HSV and vaccinia viruses, genetically modified to improve the safety, tumor-specificity, and decrease virus pathogenicity [28]. Ovs for therapeutic use is an immune- related treatment alternative.

Gendicine (Recombinant Human P53 Adenovirus [Ad5RSV-P53])

Gendicine was the first approved gene for management of neck and head squamous cell carcinoma in 2003. It is a non-replicative an adenoviral vector where E1 gene is replaced with the tumor suppressor p53 cDNA gene. The expression of p53 triggers antitumor effect by activating the apoptotic pathway, inhibit damaged DNA repair and anti-apoptotic activity. p53 gene mutation is prevalent in many cancers and gendicine induces the expression of p53 and restores its activity and destroys the tumor cells. Gendicine

management revealed 30-40% complete response and 50-60% partial response with a total response rate of 90-96% in different therapeutic use. Up to date greater than 30,000 patients managed by Gendicine [29].

Oncorine (rAd5-H101)

Oncorine is the first replicative, oncolytic recombinant ad5 (rAd5-H101) approved to treat refractory nasopharynx geal cancer. Oncorine is an ad5 virus with a deletion in the E1B 55K gene [30]. Host cell p53 gene inactivation plays an important role for wild-type to block the activation of apoptotic pathway. Removal of E1B 55K gene inhibits viral proliferation in normal cells and allows proliferate in p53-deficient host cells. Viral proliferation in tumor cells causes oncolysis which is the mechanism to treat solid tumors. Following cancer cell lysis, adenoviruses release and infect another cell activating a serious of Oncorine-mediated cell death [31].

Imlygic (Talimogene Laherparepvec)

Imlygic is genetically modified oncolytic HSV-1 approved in Europe in 2015 for the management of non-respectable metastatic melanoma. It is the first oncolytic virus for management of advanced melanoma [32]. Replacement of γ34.5 and α47 genes with human granulocyte- macrophage colony-stimulating factor (GM-CSF) gene modifies the HSV-1 gene. γ34.5 gene deletion results tumor cell-selective replication and suppression of pathogenicity. γ34.5 blocks protein synthesis of the host cell during viral infection. Thus, suppressing γ34.5 seizes the virus proliferation in normal cells. In tumor cells, the γ34.5 gene deleted HSV-1 can replicate. Besides, two human GM-CSF genes inserted into the virus providing high levels of GM-CSF production, and stimulate immune responses [33]. Administration of Imlygic causes apoptosis of tumor cell enhanced antigen presentation and increased antitumor response [34].

Gene Editing (CRISPR-CAS9)

The CRISPR-Cas9 technology is used to precisely edit cancer-causing genes in cells. By correcting or inactivating mutations that lead to cancer, CRISPR holds potential for permanent treatment. CRISPR is a heritable, adaptive immune system of bacteria that provides them with the memory of previous virus infections and defends against reinfection. Not like human adaptive immune system, CRISPR possess on to next generation of bacteria making the colony immune to future virus infections. CRISPR immunity depends on the integration of the invader's DNA (virus or plasmid) into the bacterial genome [35]. CRISPR makes bacterium to recognize viral sequences and break. These spacer sequences are viral sequences integrated during past viral infections when transcribed into short RNA sequences and are capable of guiding the Cas endonuclease to complementary sequences of viral DNA. During target identification, Cas binds to the viral DNA and cleaves it and then protects the prokaryotic cell aginst infection [36]. CRISPR immune system changed to create a gene-editing tool that can target changes to the DNA. The most common is CRISPR/Cas9, which possess the Cas9 endonuclease and a short noncoding guide RNA (gRNA) that contains two components: a target-specific CRISPR RNA and a helper trans-activating RNA. The gRNA unit guides Cas9 to a specific genomic locus via base pairing between the crRNA sequence and the target sequence [37]. CRISPR-Cas- mediated gene repair, disruption, insertion, or deletion are thus finding applications in several areas of biomedical research, medicine, agriculture, and biotechnology [38].

CONCLUSION

Efficiently delivering genes to the tumor cells, especially through gene therapy and advancement in gene therapeutic techniques will act as definitely as promising methodologies to tackle the current high prevalence of this hazard.

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