The Egyptian Journal of Medical Human Genetics xxx (2017) xxx–xxx

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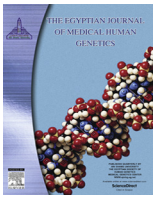
Contents lists available at ScienceDirect

The Egyptian Journal of Medical Human Genetics

journal homepage: www.sciencedirect.com



Review

Oncolytic virotherapy – A novel strategy for cancer therapy

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ARTICLE INFO

Article history:
Received 16 October 2017
Accepted 29 October 2017
Available online xxxx

Keyword:
Oncolytic virotherapy

ABSTRACT

Oncolytic virotherapy is a new modality of cancer treatment which uses competent replicating viruses to destroy cancer cells. This field progressed from earlier observations of accidental viral infections causing remission in many malignancies to virus drugs targeting and killing cancer cells. More competent and specific viruses which attack tumor cells but not healthy cells could be made with advancements in the field of genetic engineering. Studying virus as a drug has benefits of secure handling of all aspects related to this advancing field. In many ways virus given for treatment is comparable to a drug. The virus lies in the grey area of life and death and thus outside the body it is same as an unopened drug. Once inside a biological system, it starts acting targetting specific systems sine qua non as a drug. This review compares virus to a drug and deals with its pharmacokinetics, pharmacodynamics, virus drug interactions and combination virotherapy of this new treatment modality.

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1. Introduction

Cancer treatment is ever-changing, and researchers are in search of newer modalities to fight cancer. It was a known fact that certain viruses have oncolytic or cancer-killing properties. There were reports of chickenpox infection improving the WBC (White Blood cells) count and lymph node status in patients with lymphocytic leukaemia [1]. Measles caused an improvement in the case of leukemia, Hodgkin's, and Burkitt's lymphoma [2]. A lot of research is going on in this field utilizing this property of virus to make new treatment options for cancer. Using genetic engineering better virus are created which have more specificity for its action. Chinese state FDA (Food and Drug Administration) approved the first oncolytic virus-drug 'ONCORINE' an Adenovirus type 5 injection in 2005 for head and neck malignancy [3]. Many new viral drugs are on trial for metastatic malignancies like malignant melanoma. In October 2015 the US FDA approved a genetically engineered herpes virus called talimogene laherparepvec (T-VEC) to treat advanced melanoma [4]. T-VEC is genetically modified so that it

Peer review under responsibility of Ain Shams University.

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https://doi.org/10.1016/j.ejmhg.2017.10.006
1110-8630/

Please cite this article in press as: Gopisankar MG, Surendiran A. Oncolytic virotherapy – A novel strategy for cancer therapy. Egypt J Med Hum Genet (2017), https://doi.org/10.1016/j.ejmhg.2017.10.006

will not cause herpes but attacks specifically tumor cells and destroys it. More candidate viruses are under trial for its oncolytic potential. The viruses kill neoplastic cells as well as trigger immune response against the tumor. Virotherapy along with chemotherapy, i.e., combination virotherapy, may fill the lacunae of current treatment options by reducing adverse events as it has specificity for cancer cells.

2. Virus kinetics

2.1. Dosage and administration

To begin with, we need to have an idea of the dosage form of virus drug. The dosage of the virus is measured using several methods, e.g., TCID50 (50% Tissue Culture Infective Dose) a measure of the infective virus titer, plaque forming units (pfu), Focus forming assay, Haemagglutinin assay, electron microscopic methods, TRPS (Tunable Resistive Pulse Sensing), etc. Adequate dosage is required for the significant action of the virus at the tumor site. Studies in measles virus (Moraten strain) showed that for efficient antitumor activity, Moraten dose more than 10^8 TCID50 is needed, which was assessed by the prolonged survival after administration of the strain in the murine intraperitoneal model of human ovarian cancer. Therapeutic range studies of the virus can be done to determine the dose which matches the efficacy and safety of virus drug. In mice, doses up to 1×10^7 plaque forming units (pfu) of the second generation HSV inoculated into brain resulted in no adverse effects [5,6]. Measles virus given as a single intravenous dose of 4×10^6 TCID50 per kilogram caused tumor regression and prolongation of survival in KAS-6/1 myeloma model [2]. Unlike drugs which can be readily prepared in any concentrations, there is difficulty in getting a maximum concentration of virus drug to mark the actual start of toxicity. It is practically possible only in few cases. In the virus, JX-594 maximum tolerated dose was 1×10^9 pfu [7,8]. Drugs are given at lower doses and given more frequently considering the half-life so that adequate concentration is reached without causing a much toxic effect. Safer viral drugs are also available which can be provided in more massive doses. ONYX 015, even when administered up to 10^{11} pfu did not cause any dose-limiting toxicity [9]. Virus infection in cancer cells and its destruction induces an immune response against cancer cells as many tumor antigens get exposed to the immune system. There is a dose-dependent increase in levels of the inflammatory cytokines like IL-6 and IL-8 released by malignant melanoma cells upon infection with measles virus. This increase shows the need of optimal dosage for the bystander response also [9]. Threshold dose to ensure that the virus acts on tumors can be calculated by conducting dose range studies and doing tumor biopsies to recover the virus. JX594, an oncolytic vaccinia virus is under trial for non-resectable hepatocellular carcinoma appeared in tissue biopsies only when the threshold dose was more than 10^9 infectious units [10].

2.2. Distribution of virus

Viral titer, which is similar to drug concentration measures the in vivo distribution of the viral drug. As the virus causes cytolysis, it releases some detectable molecules which can be used to assess the activity indirectly. Adeno virus used in the treatment of prostatic adenocarcinoma if infects the tumor cells significantly, cause PSA (Prostate-specific Antigen) to rise by many times, which confirm its effect [11]. The virus levels may spike several times over a period due to replication [12]. Due to this; the total viral load will increase that which was introduced. There are other ways to study the in vivo monitoring of the spread of the oncolytic virus. Visual analysis of distribution can be done using fluorescent labelling of the vector with isothiocyanate [11]. By genetic engineering of the viral genome, transcription units coding for soluble marker peptides is inserted. When the virus infects the cells, this soluble substance is secreted from the cell to detect it quickly from the body fluids. In case of measles virus, β-hCG (β sub-unit of human chorionic gonadotropin) and soluble extracellular domain of CEA (human Carcino Embryonic Antigen) is used for this purpose [13]. So once a virus infects the cells, this soluble marker starts appearing in the blood and urine and thus confirms the infection and not mere excretion of the agent or destruction by the immune system.

In the case of measles virus, a recombinant version that codes human thyroidal sodium iodide symporter (NIS) is added [14]. So the infected cells, with the help of this symporter concentrates iodine in the cells. Radioactive iodine given through the intravenous route gets concentrated only in the virus-infected cells by the uptake through NIS. Radioactivity measured by serial SPECT (Single Photon Emission Computed Tomography), serial gamma camera imaging of iodine-123 or PET (Positron Emission Tomography) at the site of tumor confirms the action of a virus on the tumor. A Vaccinia virus GLV-1h153 engineered to carry the human sodium iodide symporter (hNIS), facilitated detection by PET with both intratumoral and systemic administration. Dana et al. studied the tissue distribution, spread of GLV-ih153 and timing dynamics between viral infection, uptake of radioiodine and oncolysis in human pancreatic carcinoma cells [15]. A benefit of virus drug is that its action can be confirmed by immunohistochemistry method. G207, another second generation oncolytic HSV virus is a multimutated virus with both copies of γ34.5 gene deleted and *E. coli* LacZ gene inserted. Histochemical detection of β-galactosidase helps to confirm and monitor the preferential affinity of the virus to glioma cells instead of healthy neural tissue [16]. Distribution in tissues depends on the chemical properties of the drug. More lipophilic molecules will spread easily through the body and will have a higher volume of distribution. Entry of drugs into the central nervous system is limited due to tight junctions which form the blood-brain barrier. This limitation can be circumvented by using new drug delivery methods like CED (Convection Enhanced Devices). CNS tumors can also be targeted by using a virus like Parvo virus which, unlike other oncolytic viruses crosses the blood brain barrier and attack the tumor cells [17].

2.3. Metabolism and excretion

The main route of elimination of virus drug is by the immunological mechanism. But studies have not shown much correlation between viral titers and increasing anti-viral antibody titer. Antitumor action persisted in spite of high antibody response against them [18]. O'Riordan and colleagues described PEGylation of virus that is adding polyethylene glycol covalently to the protein covering of Adenovirus. It prevents the immunogenicity of the virus, prevents antibody binding, and increases the solubility and thus the serum half-life [19]. The Virus will concentrate in the reticuloendothelial system, and from there it is slowly removed by immune-mediated mechanisms. Preconditioning the MPS scavenger receptors or by destroying the macrophage or endothelial cells can reduce this loss. In animal studies, it is seen that polyinosinic acid, which will bind to the scavenger receptors will reduce the sequestration of adenovirus [15]. Clodronate-loaded liposomes can destroy the liver Kupffer cells and splenic macrophages in mice [20]. Some cells can function as vehicles for the therapeutic virus. The cell carriers can be solid tumor cells, Hematological malignant cells, Xenogeneic/allogeneic cells, T cells, CIKs, mesenchymal stem cells, neural stem cells, etc. An efficient carrier should have a natural habit of being at the tumor site. This vehicle should pass

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