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Veterinary Viruses Used in Tumors Virotherpy

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Abstract: One of the leading causes of death worldwide is Cancer. The conservative treatment of cancer is usually amalgamation of surgical removal, chemotherapy and/ or radiation therapy but their side effects are often sever and some tumors are not accessible by surgery, resistant to radiation and chemotherapy and some of them possess the ability for metastasis. All these criteria urge the development of new treatment strategies. Oncolytic- viro-therapy is one of the most promising treatments of tumors. Oncolytic viruses selectively infect and lyse tumor cells by forcing the tumor cell to use all its power to replicate the viral genome. The new progeny viruses infect neighboring tumor cells leaving normal cell intact due to interferon blockage of virus replication in normal cells. Furthermore the lytic cells stimulate cytotoxic immune cells and the virus itself evokes systemic antivirus immune response. RNA oncolytic viruses considered safer as they are not genotoxic dropping the fear of DNA integration in patient chromosomes. Moreover, animal viruses considered safer than viruses that infect humans.

Key words: Oncolytic viruses · Virotherapy · Antitumor · Cancer treatment · Antineoplastic

INTRODUCTION

Tumor is a mass or lump of almost any type of tissue more than the normal mass. Tumors are usually divided into three groups benign, pre-malignant and malignant. Benign tumor remains in there form until it is removed because it has no ability to spread. Benign tumor terminology differs according to their location for example adenomas are tumors arise from glandular epithelial tissue while fibroid or fibroma are tumors of fibrous or connective tissue, hemangiomas consist of excessive blood vessels and lipomas arise from soft tissue. Pre-malignant tumors are not yet carcinogenic but appear to develop the criteria of cancer. For example, Actinic keratosis in which patches of skin become scaly, crusted and thick may progress to squamous cell carcinoma if not treated and with continuous exposure to sun. Another example of pre-malignant tumors are cervical dysplasia which may progress to malignant cervical tumor. Malignant tumors are cancerous tumors which grow, spread, got worst and eventually end with painful death. Unlike benign tumors, malignant tumors grow faster and have the ability to invade other tissues and spread to other parts of the body which is called metastasis. The terminology of malignant tumors differs according to cell type, for example, carcinoma is progressed from epithelial cell, sarcoma from connective tissue. Blastoma is the malignant tumor of embryonic tissue, which commonly occurs in children e.g. medulloblastoma, glaioblastoma (occur in brain), retinoblastoma (occur in the eye), osteoblastoma (in bone) and neuroblastoma (in the nervous system) [1].

Importance: Cancer is considered main death cause in developed countries and less major death cause in developing countries due to aging, increased population, unhealthy life style as increased adoption of cancer leading habits such as smoking, handling and consumption of carcinogenic material. According to GLOBOCAN estimation 2008, about 12.7 million reported cancer patient and 7.6 million reported deaths due to cancer. This statistics jumped to 18.1 million people diagnosed with cancer and the tragedy of 9.6 million deaths in 2018 from the data gathered of local registry representing 185 countries Figure 1.

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Now one case in five men is diagnosed with cancer while one in six women is diagnosed with cancer. Overall, one in eight men and one in ten women are dying because of cancer and that is frequently called premature death [2]. The conventional treatments of such cancer are usually mixture of surgical removal, radiation therapy and/ or chemotherapy. Even though these treatments has already enhanced extensively through time, but their side effects are often sever. Additionally, some tumors are not accessible by surgery, resistant to radiation and chemotherapy and some of them possess the ability for metastasis. All these criteria urge the development of new treatment strategies. Oncolytic-viro-therapy is one of the most promising treatments of tumors. Oncolytic viruses are either none engineered or recombinant viruses that selectively infect and lyse tumor cells by forcing the tumor cell to use all its power to replicate the viral genome. The new progeny viruses infect neighboring tumor cells leaving normal cell intact due to interferon blockage of virus replication in normal cells [3]. Furthermore the lytic cells stimulate cytotoxic immune cells and the virus itself evokes systemic antivirus immune response Figure 2.

Efficacy of Virotherpy: Many viruses has been commonly used in oncolytic virotherpy such as oncolytic herpes simplex virus (oHSV) which has been officially used in treatment of malignant melanoma by US food and Drug Administration (FDA) [4, 5], coxsackievirus A21 in treatment of Bladder and lung cancer [6, 7], Adenovirus for cervical carcinoma and for head and neck tumors in China in 2005 [8], while engineered viruses has been used

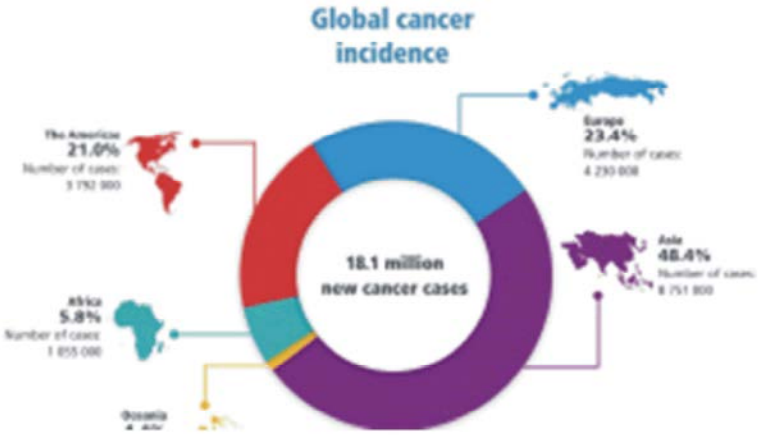

Fig. 1: Global cancer incidence in 2018. Source: UICC. https://www.uicc.org/news/new-global-cancer-data-globocan-2018

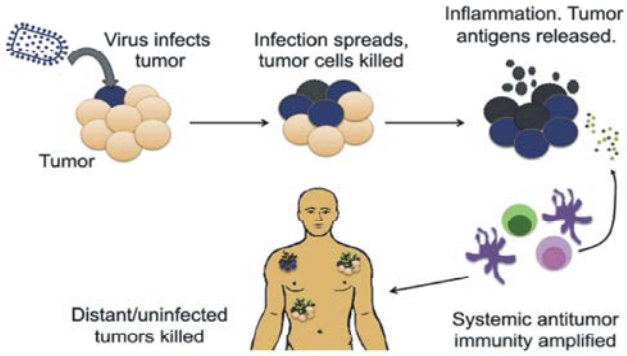

Fig. 2: Oncolytic virus in tumor treatment. High virus tittered is administered by patient with tumor resulting in intratumoral replication and subsequent cellular death. The new virus progeny attacks neighboring tumor cells. The presence of lytic virus, tumor infected cells and lytic cells will stimulate antigen-presenting cells (APC), denditric cells (DC) and T cells (TC), which collectively provide a long-lasting antitumour activity. Source: https://www.cell.com/molecular-therapy-family/molecular-therapy/fulltext/S1525-0016(17)30125-9?sf77801523=1

to express specific protein in order to provoke tumor patient`s immune response. For example vesicular stomatitis virus expressing ovalbumin (OVA) is used for treatment of OVA- expressing B12 melanoma tumors [9]. Picornavirus also has been experimentally investigated for its oncolytic activity against many types of tumors [10].

Intratumoral treatment with vaccinia vaccine strains has resulted in significant and reproducible efficacy in numerous clinical trials. In contrast to reports with adenoviruses and mumps, vaccinia-induced responses were in some cases durable, complete and distant from the site of injection. Results were published from several clinical trials. No serious adverse events were reported. Trials valuated the use of non-engineered vaccinia virus administered by intra-tumoral injection to patients with metastatic melanoma [11]. Mild flu-like symptoms were reported and objective responses, including complete regressions, occurred at the injection site.

There is a present danger for using oncolytic viruses such as the possibility that DNA viruses may integrate its genomic material with patient chromosomes. For this reason RNA oncolytic viruses are considered safer as they are not genome integrator nor toxic. Moreover, they do not encrypt cancer genes and their genomes are easily descripted as cDNA [12]. This considered as advantage of RNA oncolytic viruses like Picornavirus when compared with DNA oncolytic viruses such as Adenovirus and Herpes virus. On the other hand, this disadvantage is remunerated by DNA oncolytic viruses by high stability of their genome during replication [13].

Oncolytic viruses that infect animals considered optimal solution for the problem of infectious oncolytic virus that may cause infection to tumor patient. Bovine Enteroviruses type 1 and 2 which are endemic in cattle (i.e. can be easily isolated from cattle feces) and do not infect human, are categorized as Enterovirus E and F [14]. They were investigated in 1970 as oncolytic viruses in soft tissue and blood cancers and they met the threshold of significant killing of tumor cells in 65% of cancer cell lines [15]. Their efficacy varied according to cell type and this is thought to be based on the receptor found. Sialic acid was supposed to have a great part in virus adsorption that is dose and time dependent when used with Bovine Enteroviruses [16]. Bio-adapted viruses to cell lines also have been used successfully for eradication of sarcoma 1 Xenograft tumors as well as delayed death from leukemia in mice [17].

Table 1: Some Oncolytic viruses tested in clinical trials

Virus	Genetic target in cancers	Genetic modifications to virus backbone	Transgene encoded (rationale)
a- Non-engineered viruses			
NDV	Unknown (boosts immune response)	None	None
Reovirus	Defects in tumor PKR/interferon pathways	None	None
Mumps	Unknown	None	None
Adenovirus	NA	None	None
Vaccinia	Unknown (EGFR pathway driven)	None	None
b- Engineered, non-armed viruses			
Adenovirus dl1520 (ONYX-015)	p53 pathway defects; late RNA transport defects	E1B-55K (–), E3B (–)	None
HSV (Herpes Simplex virus) 1716	Defects in tumor PKR/interferon pathways (ICP34.5–); attenuated neurotoxicity	ICP34.5 (–)	None
Newcastle virus (NV) 1020	None (attenuated toxicity)	ICP34.5 (–), UL24 (–), UL56 (–); replaced with a fragment of HSV-2 US DNA (US2, US3, gJ and gG)	None
c- Engineered, armed viruses			
Vaccinia JX-594	Tumor cell complementation of thymidine kinase deletion; cellular thymidine kinase expression E2F pathway-driven	Thymidine kinase (–)	GM-CSF (immuno-stimulation)
Adenovirus Ad5-CD/TKrep	p53 pathway defects; late RNA transport defects	E1B-55K (–), E3B (–), CD/TK expression	CD/TK (prodrug activation)
Measles MV-CEA	Tumor-selective binding through CD46; CD46 overexpressed in most cancers	None (vaccine strain)	CEA (serum monitoring)

Abbreviations: CD/TK, cytosine deaminase and herpes virus thymidine kinase fusion gene; CEA, carcinoembryonic antigen; EGFR, epidermal growth factor receptor; GM-CSF, granulocyte-macrophage colony-stimulating factor; HSV, herpes simplex virus; MV, measles virus vaccine strain; NDV, Newcastle disease virus; NA, not applicable; PKR, double-stranded RNA activated inhibitor of translation (known as PKR); PSE1A, prostate-specific promoter-driven E1A; PSE1B, prostate-specific promoter-driven E1B. Source: Liu *et al*. [24]

Examples of Oncolytic RNA- Viruses: Bluetongue virus and Reoviruses have been used as oncolytic viruses. Bluetongue virus which infect sheep and cattle have been used in prostate cancer with radiation the results were promising. They both managed to give high rate of cytotoxicity without harming normal cells in vivo and in vitro experiments. The results of the fluoresce activating cell sorting FACS using flow cytometry showed the most prominent levels of apoptosis and the analysis of cell cycle revealed that the G2- M phase level after radiotherapy increased followed by bluetongue infection [18].

Newcastle disease virus (NDV) is of the emergent potent RNA oncolytic viruses that induces immunogenic tumor cell death and releases of danger-associated molecular pattern that result in potent anticancer immunity [19]. NDV is an avian virus affects only birds and causes no disease in human and consider safe to use. NDV, which belongs to family Paramyxoviridae, Genus Avulavirus, drew researcher attention for its antitumor activity in the mid-20th century and has proved its safety as well as its efficacy [20, 21]. Mesogenic strains of NDV exhibit antineoplastic activity against broad range of tumors of mesenchymal, neuroectodermal and epithelial origin [22]. Moreover, systemic or loco-regional treatment of mesogenic NDV leads to complete or partial regression of primary and metastatic tumors [23].

Genetically Engineered Virotherapy: Onyx Pharmaceuticals, was the first engineered replication-selective virus to be used in humans. Where deletion or addition in some genomic region/ or regions to be originally hypothesized to be replication-selective exclusively for cells and in some cases to further stimulation of the immune defense of the patients and in these cases it is called armed. The below Table 1 show more of wild type and genetically engineered viruses armed and non-armed.

CONCLUSION

Viruses have been used for cancer treatment for over a century. Virotherapy has emerged as a promising therapeutic from the early clinical studies with various wild-type viruses, to the modern trials with engineered viruses. Clinical trials to date have established the safety of this approach, as well as identifying suitable bio logical end points for therapy validation. There has been a combination regimen to enhanced efficacy. Future study should focus on the most appropriate virus species for each cancer type, optimal doses and administration routes, *in vivo* monitoring through standardized serological studies to monitor interaction with the immune system.

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