Advances in Life Science and Technology
ISSN 2224-7181 (Paper) ISSN 2225-062X (Online)
Vol.79, 2020

Review on Application of Oncolytic Virotherapy of Cancer Cells in Veterinary Medicine

Tamirat Demissie Sultan Abda*
Hawassa University, Faculty of Veterinary Medicine

Abstract
Oncolytic virotherapy is using oncolytic viruses (OVs) which selectively infect and kill cancer cells. Oncolytic viruses represent a highly targeted approach to established cancer that brings a multimechanistics approach and an acceptable safety profile to patients with a variety of cancers. A variety number of viruses have been developed as oncolytic virotherapeutics, including *Adenovirus, Vaccinia virus, Herpesvirus, Measles, Coxsackie A virus, Newcastle disease virus, and Reovirus*. Anticancer viruses can now be engineered to selectively attack cancer cells, spare normal tissue, awaken the host immune system and reverse immunosuppression in the tumor microenvironment. But virotherapy is not a cure on its own. Research suggests that virotherapies will serve to supplement chemotherapy, radiation therapy or immunotherapy. Combinations of OV with cytotoxic agents are feasible and safe, with the potential of transient immune supperssion of the host in order to increase viral access to the tumor and provide time for viral oncolysis to exceed the tumor's replicative potential. Granulocyte macrophage colony stimulating factor as an immune-stimulatory cytokine boosts host immune activity through the infiltration of dendritic cells and CD4+ and CD8+ T cells at tumor sites. Concomitants to human, cancer is the leading cause of death in companion animals such as dogs and cats. The most important challenges for the successful clinical use of OVs in veterinary practice are reduction of viral toxicity, optimization of virus delivery to tumor, and enhancement of viral spread throughout the tumor mass. The multifactorial, interplay can be determined by the complex interactions between the tumor and its microenvironment, the virus, and the host immune response. Yet, there is promise that OVs will soon be a new, powerful treatment option for veterinary patients with cancer. Hence, sound understanding of the biology of OVs and its application in veterinary medicine require.
Keywords: *Cancer, Combination-therapy, Oncolytic virotherapy*, *Virus.*
DOI: 10.7176/ALST/79-04
Publication date: March 31st 2020

1. INTRODUCTION

The potential of viruses as anti-cancer agents was first realised in the early twentieth century, although coordinated research efforts did not begin until the 1960s (Alemany, 2013). Oncolytic virotherapy is an emerging anti-cancer treatment modality that uses OVs. One of the most attractive features of the OVs is that they are either naturally occurring or genetically engineered to selectively infect, replicate in and damage tumor cells while leaving normal cells intact (Workenhe and Mossman, 2014; Guo *et al.,* 2008). In the 1920s animal experiments confirmed that viruses were capable of infecting and lysing experimental murine tumors and several studies followed in the 1950s demonstrating potent oncolysis of murine tumors by Newcastle disease virus and Influenza virus (Kelly and Russell, 2007).

A mouse was considered the first animal model to demonstrate full regression through viral oncolysis (Nicholas *et al.,* 2003). Incidence of cancer ranges from 1 to 2 percent in the canine population and currently accounts for about half of the deaths in dogs older than 10 years (Merlo *et al.,* 2008). A number of viruses including *adenovirus, reovirus, measles, herpes simplex virus, Newcastle disease virus*, and *vaccinia* have been clinically tested as oncolytic agents (Donnelly *et al.,* 2012). Most current OVs are engineered for tumour selectivity, although there are naturally occurring examples such as *reovirus* and the *senecavirus* (Roberts, 2006).

Cancer is one of the most common causes of natural death in dogs in both developed and developing countries. It is among the top deadly diseases in dogs and cats (Merlo *et al.,* 2008). In contrast to the progress of human oncolytic virotherapy, there are very few clinical trials using OVs for canine or feline cancer patients (Patil *et al.,* 2012). The most common forms of cancer in dogs and cats are skin, lymphoma, mammary, bone, connective tissue, and oral cancers (Paoloni and Khanna, 2008; Tang *et al.,* 2010). Oncogenic viruses can establish a chronic infection allowing them to escape from the host's immune-system while producing proteins that control cell death and proliferation. Chronic infection also leads to inflammatory reactions promoting cancer development (McLaughlin-Drubin and Munger, 2008).

To potentiate their immunogenic effects, genetic engineering strategies have been used to encode OVs with various cytokines, immunomodulators, and tumor associated antigens (Melcher *et al.,* 2011). Clinical evaluation of adoptive T cell transfer and OVs are currently underway as mono- therapies (Patel and Kratzke, 2013). Viral oncolysis directly destroys tumor cells through either their lytic replication cycle or the expression of endogenous cytotoxic gene products (Chu *et al.,* 2004). To further enhance their oncolytic effects, transgenes encoding pro-

apoptotic proteins are inserted into OVs to subvert cell death machinery. These proteins include various death inducing ligands such as TNF-related apoptosis inducing ligand (Wohlfahrt *et al.,* 2007; Zhao *et al.,* 2006).

Through transgene insertion, OVs can serve as directed gene delivery vehicles, and thus accommodate a diverse array of therapeutic strategies. Arming OVs with additional weaponry, such as pro-apoptotic genes, tumor suppressors, or genes stimulating antitumor immunity, can enhance their killing capacity. With a broad arsenal, modified OVs have the potential to target a wide spectrum of different cancer types. Moreover, administration of OVs as a monotherapy has demonstrated varying degrees of success in clinical trials (Vacchelli *et al.,* 2013; Buonaguro *et al.,* 2012).

Over an extended period, selective pressure on heterogeneous tumor populations can also lead to therapeutic resistance to OVs via receptor loss or mutation of essential signaling pathways required for viral replication (Moerdyk-Schauwecker *et al.,* 2013). NDv binds cells via the hema gglutinin neuraminidase (HN) protein (Park *et al.,* 2003). PV701 and MTH68/H are live attenuated oncolytic viral strains of NDv, which have the capacity to selectively replicate in and lyse tumor cells and to cause immune-stimulation (Fournier *et al.,* 2012) and become one of the promising new therapeutic approach of oncolytic virotherapy. OVs exhibit selective viral replication in tumors and metastases resulting in the killing of cancer cells and the initiation of tumor-specific immunity (Liu *et al.,* 2007; Chen and Szalay, 2011).

Canine cancers share many features in common with human cancers including histological appearance, tumor genetics, molecular targets and response to conventional therapy (Al-Dissi *et al.,* 2010; Mederle *et al.,* 2010; Amorim *et al.,* 2010). In both species, tumor initiation and progression is influenced by similar factors like age, nutrition, sex and environmental exposure (Hlavaty *et al.,* 2011). One reason for the lack of efficient therapeutic response associated with early conditionally replicative adenoviruses can be the absence of the primary canine adenovirus receptor (CAR) on some cancer cells, as has been reported in gastrointestinal, pancreatic, ovarian, and hormone refractory prostate cancers. Specific strategies to enhance CAR-independent transduction of conditionally replicative adenovirus refractory cancer cell types and improve tumor-specific immunity have utilized modifications to the viral coat to induce better cancer selectivity and provide proinflammatory signals. Adenovirus-35 is a strain that utilizes CD46, rather than CAR, as the primary receptor for initial adsorption and entry (Gaggar *et al.,* 2005; Sirena *et al.,* 2004). This vector demonstrated enhanced selectivity and stronger adenovirus affinity for the targeted cell (Tanaka *et al.,* 2006). Moreover, control mechanisms have been added to adenoviruses to ensure cancer cell specificity, and arming the virus with suicide genes has also been explored to improve therapeutic effects (Liu *et al.,* 2005). Adenoviruses are also being tested as therapeutic agents for canine cancers. Human adenovirus 5 has been shown to productively replicate in canine osteosarcoma and canine mammary carcinoma cells (Ternovoi *et al.,* 2005).

Herpes simplex virus tumor selectivity is enhanced further by gain of function mutations occurring in given oncogenes of the Ras-signaling pathway of transformed cells, whereby tumor cells with augmented Ras activation are significantly more susceptible to oncolytic herpes simplex virus infection than healthy cells with normal Ras signal transduction pathway physic- ology (Pan *et al.,* 2009). Recruitment of innate immune cells associated with direct lysis of tumor cells and priming of adaptive immunity was seen, including an accumulation of activated natural killer cells and immunogenic dendritic cells (Benencia *et al.,* 2005).

Coxsackie virus could also activate neutrophils to release interferon-β and antigen-presenting cel ls and to induce cytotoxic T lymphocytes (Jablonska *et al.,* 2010). Coxsackie virus B3 exhibit ed potent tumor cell lysis in a number of non-small cell lung cancer cell lines, even in cancer cells refractory to conventional radiotherapy and molecular targeted therapies (Prestwich *et al.,* 2009). OVs induces oncolytic-mediated tumor regression, insertion of the gene encoding *GM-CSF* resulted in rejection of distant noninjected A20 tumors in mice, suggesting the vector could induce potent local oncolytic effects and generate systemic antitumor immunity (Liu *et al.,* 2003). Reovirus oncolysis of cancer cells is mediated mainly via the extrinsic apoptosis pathway (Clarke *et al.,* 2007; Smakman *et al.,* 2006). Depending on the tumor cell infected, reovirus induced apoptosis uses different proapoptotic molecules to activate apoptosis. For example, the HeLa cell line requires NF-κB for apoptosis, while specific ovarian, breast, and lung cancer cell lines activate death receptor pathway of apoptosis (Clarke *et al.,* 2007).

Reovirus, like other oncolytic vectors, is subject to immune recognition and rapid clearance. Use of immune suppressant drugs, such as cyclophosphamide and cyclosporine A, has been shown to potentiate oncolysis and increase reovirus replication in injected tumor tissue with enhanced reovirus-mediated tumor clearance (Qiao *et al.,* 2008). An oncolytic measles virus armed with genes coding for antibodies against inhibitory immune checkpoints has been shown to have improved antitumor activity compared to control virus. It appears to be a synergistic effect between oncolytic measles virus and immune checkpoint inhibitors (Engeland *et al.,* 2014).

Although, a lot of studies have been done over the causes of cancer, there is still the paucity of information regarding to virotherapheutic efficacy and associated factors in animal cancer. Therefore, the objectives of this review are:

- To give the base line overview on oncolytic virotheraphy for cancer cells.

- To describe the major OVs utilized with various tumor cells.
- To describe the mode of actions, advantages and limitations of some of the viral vectors commonly used for oncolytic virotherpy incompnien animals.

2. ONCOLYTIC VIROTHERAPY FOR CANCER CELLS IN VETERINARY MEDICINE

An OVs is a virus that preferentially infects and kills cancer cells. As the infected cancer cells are destroyed by oncolysis, they release new infectious virus particles or virions to help destroy the remaining tumour (Ferguson *et al.,* 2012; Casjens, 2010). OVs are thought not only to cause direct destruction of the tumour cells, but also to stimulate host anti tumour immune system responses (Melcher *et al.,* 2011; Lichty, 2014). Adenovirus 5 (Ad5) subtype has been extensively used in oncolytic virotherapy as a vector (Ginsberg, 2013).

Herpes simplex virus (HSV) was one of the first viruses to be adapted to attack cancer cells selectively, because it was well understood, easy to manipulate and relatively harmless in its natural state (merely causing cold sores) so likely to pose fewer risks. The herpes simplex virus type 1 (HSV-1) mutant 1716 lacks both copies of the ICP34.5 gene, and as a result is no longer able to replicate in terminally differentiated and non-dividing cells but will infect and cause lysis very efficiently in cancer cells, and this has proved to be an effective tumour targeting strategy(van den Hengel *et al.,* 2013). In a wide range of in vivo cancer models, the HSV1716 virus has induced tumour regression and increased survival times (Allen *et al.,* 2013; Josupeit *et al.,* 2016).

The current trend is to use recombinant strains with decreased pathogenicity and improved antitumor effect. However, naturally occurring oncolytic NDV strains are also observed. The oncolytic potential of NDV strains circulating in wild migratory birds of Russia remains poorly understood. The oncolytic wild-type NDVs from natural reservoirs obtained in 2008–2014 in Russia. They are demonstrate the *in vitro* ability of NDVs to influence the viability of tumor cells after infection and evaluate in vivo efficiency of NDV strain against non-small cell lung carcinoma (li *et al.,* 2011, Song *et al.,* 2010, Bai *et al.,* 2014, Elankumaran *et al.,* 2010, Zamarin *et al.,* 2009 and An *et al.,* 2016).

Canine lymphoid cell lines and B and T lymphocytes established from dogs with lymphoma have been shown to express CD150 receptors. Attenuated CDV has been tested for oncolytic property in the lymphoma cells and was able to infect and induce apoptosis in these cells (Suter *et al.,* 2005). The molecular mechanisms underlying virus induced carcinogenesis are diverse and complex. In addition to causing direct effects such as induction of genomic instability, DNA damage, and viral oncogene triggered cell transformation (Chen *et al.,* 2014).

2.1 Mechanisms of Oncolytic Virus-mediated Tumor Ablation

2.1.1 Tumor tropism and oncolysis

Oncolytic virotheraphy have the ability to establish a niche of continuous viral replication within the tumor, recruit uninfected cells in proximity creating syncytia, infect dividing and non-dividing cells, and be stable *in vivo*, yet lack chromosomal integration and do not result in major disease (Verheije and Rottier, 2012). OVs, like reovirus (Prestwich *et al.,* 2012), vaccinia virus (Thorne *et al.,* 2008), can induce tumor specific adaptive immune responses and indirectly cause malignant cell death. Adenovirus (Diaconu *etal.,* 2012),Coxsackie B3(Miyamoto *et al.,* 2012)and measles virus (Donnelly *et al.,* 2013), can lead to endoplasmic reticulum stress and cause immunologic cell death a type of cell death that leads to release of danger association molecular patterns, like adenosine triphosphate, calreticulin and high mobility group box-1, which attract immune cells (Kepp *et al.,* 2011).

OVs can also selectively target tumor neovasculature. Vesicular stomatitis virus (VSV) can selectively infect endothelial cells in the tumor microenvironment and cause thrombosis in the tumor vessels (Breitbach *et al.,* 2011). HSV and vaccinia virus can also selectively damage tumor endothelium(Benencia *et al.,* 2005; Breitbach *et al.,* 2013); preferential replication in tumor vessels may be secondary to the dependence on high vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) levels for replication in normal endothelium (Breitbach *et al.,* 2013) .

Therefore, instead of relying on receptor specificity, tumor tropism of vesicular stomatitis virus is dependent on the permissiveness of malignant cells to viral infection. VSV belongs to a class of interferon (IFN) sensitive viruses, which preferentially infects tissues exhibiting reduced or absent IFN responsiveness (Krishnamurthy *et al.,* 2006; Stojdl *et al.,* 2003; Noser *et al.,* 2007). Selective retargeting of viruses to tumor cells can also be generated in viruses without innate oncolytic abilities. Adenovirus based vectors are a good demonstration of this approach, since they possess a wide tropism, but a lytic life cycle that can be exploited for oncolytic virotherapy (Kruyt and Curiel, 2002).The pathogenicity and tissue tropism are similar within the subgroups (Wold and Toth, 2013).

Viruses are small passive particles that reach their target cells via either radial cell-to-cell spread or diffusion across concentration gradients in soluble matters, such as blood, and propagate infection. They are higher the number of infectious virions at the tumor territory, the higher the probability of infecting and destroying every single tumor cell (Miller and Russell, 2014; Smith *et al.,* 2014). It is important to investigate how infection of the host normal cells by the OVs can enhance the oncolytic virotherapy. To normal cells, such as liver, that can be

quickly self regenerated after a trauma or disease, infection of normal cells could be tolerable if such infection is not endemic (that means the infection does not persist forever) and could potentially aid to control tumor growth (Ribacka and Hemminki, 2008).

Measels virus (MV) enters cells through interaction of its H-protein and cellular CD46 (membrane cofactor protein) and signaling lymphocyte activating molecule (Tatsuo *et al.,* 2000). CD46 is overexpressed on tumor cells (Fishelson et al., 2003), MV vaccine affects only cells with a high density of CD46, and therefore, does not affect normal cells (Anderson *et al.,* 2004). MV kills tumor cells by inducing cell-to-cell fusion through F-protein, formation of syncytia and subsequent apoptotic death (Anderson *et al.,* 2004). Several preclinical studies in animal models, including both solid tumors and hematologic malignancies, have evaluated MV through different routes (ITu, IV, IP or intrapleural) and administration schedules (Blechacz *et al.,* 2006).

The enzymes thymidine kinase and ribonucleotide reductase in cells are responsible for DNA synthesis and are only expressed in cells which are actively replicating (Gentry, 1992). These enzymes also exist in the genomes of certain viruses like HSV, vaccinia and allow viral replication inquiescent (non-replicating) cells (Singh *et al.,* 2012), so if they are inactivated by mutation the virus will only be able to replicate in proliferating cells, such as cancer cells. All these models were used to investigate adenoviral targeting on cancer stem-like cells. Resistant cancer stem-like cells constitute a major hurdle in cancer therapy, especially when combating glioblastomas. As such, reovirus, measles vaccine virus, and parvovirus have been successfully targeted to glioblastoma stem-like cells in spheroid models (van den Hengel *et al.,* 2013, Josupeit *et al.,* 2016). Treated animal tumors demonstrate cytopathic effect with syncytia formation followed by apopt- otic cell death of MV-infected tumor cells (Zhang *et al.,* 2012). Canine p53 family proteins have biological activities similar to their human counterparts (Zhang *et al.,* 2009), mutations in conserved domains of p53 appear to play a significant role in mammary carcinogenesis in both humans and dogs (Queiroga *et al.,* 2011).

Oncolytic viruses are distinguished by their property to either inherently or after genetic modifi -cation replicates selectively in cancer cells. These viruses have multiple mechanisms to harm the host cells including direct lysis, induction of apoptosis and autophagy, expression of toxic prot- eins and shutdown of proteinsynthesis. At the end of the replication cycle, cells are destroyed and infective viral progeny is released into remaining tumor tissue. In addition to local amplifying antitumor effect, infective viral particles are able to enter the systemic circulation and infect distant metastasis (Roberts *et al.,* 2006).

2.1.2 Induction of antitumor immune responses

To enhance viral distribution and tumor cell killing, irradiation has been successfully combined with an oncolytic adenovirus in glioblastoma spheroids (Lamfers *et al.,* 2007). Lower myxoma-virus-mediated cell killing in spheroids than in adherent cells, because of downregulated Akt kinase in non-adherent cells (Correa *et al.,* 2012). An oncolytic virus destroys tumors either by direct viral lysis of tumor cells(Atherton andLichty, 2013; Gentschev *et al.,* 2012), by the destruction of the tumor vasculature (Gentschev *et al.,* 2012), by induction of host antitumoral immune responses(Gentschev *et al.,* 2013; Fridlender *et al.,* 2009) or most likely, a combination of these mechanisms(Moehler *et al.,* 2005)(Figure 1). An increased infiltration of neutrophils, macrophages and natural killer cells to the tumor site might be involved in the vaccinia virus mediated immune response in different canine cancer xenograft models (Breitbach *et al.,* 2007; Winkler *et al.,* 2004).

The presence of such activated inflammatory cells in the tumor tissue may enhance the antitumoral effect by increasing the phagocytic or cytotoxic activities of these cells (Ferrara *et al.,* 2003; Millanta *et al.,* 2002). In addition, an increase in proinflammatory interferon gamma (IFN-gamma), interleukin-2 (IL-2), interleukin-6 (IL-6), tumor necrosis factoralpha (TNF-alpha), interferon gamma-induced protein 10 (IP-10), macrophage inflammatory protein-1 alpha (MIP-1 alpha), macrophage inflammatory protein-1 beta (MIP-1 beta), monocyte chemotactic protein-1 (MCP-1), and monocyte chemotactic protein-3 (MCP-3) was observed in vaccinia virusinfected canine xenografted mice(Patil *et al.,* 2012).

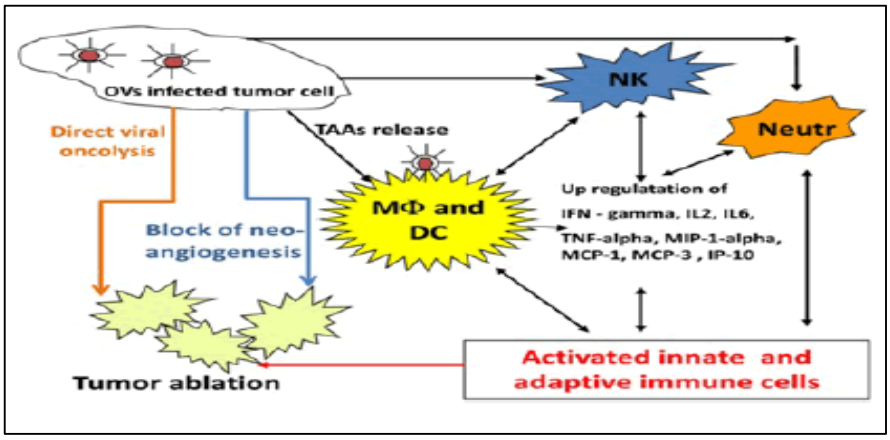

Figure 1: Possible mechanisms of oncolytic virus-mediated tumor ablation.

Many of these proteins stimulate innate immunity mediated by dendritic cells, neutrophils, macrophages and NK cells. OVs naturally prevent neoangiogenesis either by direct infection and destruction of tumor vasculature (Adelfinger *et al.,* 2014) or "vascular normalization" in tumor tissue, as described by Winker and colleagues (Breitbach *et al.,* 2016). IFNs are a group of secreted cytokines; exert pleiotropic effects on important cell functions, including cell prolifera tion and modulation of the immune system (Dunn *et al.,* 2006; Stetson and Medzhitov, 2006).

2.2 Use of Oncolytic Virotherapy of Cancer in Animals

2.2.1 Toxicity of Oncolytic Viruses to Pet Cancer Patients

Some NDV strains have been developed to elicit potent oncolytic capacity.The MTH-68/H strain showed beneficial effects in patients with advanced cancer (Csatary *et al.,* 2004).This strain exerts direct cytotoxicity in vitro against various tumor cell lines, suggesting that direct cytotoxicity and oncolysis are key factors in the antitumor activity. NDV-induced apoptosis of infected tumor cells is the dominant mode of cytotoxicity, but activation of either the intrinsic or extrinsic apoptotic pathways is cell type dependent (Elankumaran *et al.,* 2006). Overall, onco lytic virus therapy has been well tolerated, with largely minor and expected toxicity, and no evidence of uncontrolled or latent infection, household transmission, or malignant transfor mation (Russell *et al.,* 2012; Cattaneo *et al.,* 2008).

Table 1: Oncolytic viruses tested for cancer therapy.

Virus strain	Virus family/Virus type	Study/Tumor type/Animal model	Ref.
Canine adenovirus type 2 (CAV2)	Adenoviridae (double stranded DNA viruses)	Infection of canine osteosarcoma cells and osteosarcoma xenografted mice	(Hemminki *et al.,* 2003)
Human adenovirus type 5 (Ad5)	Adenoviridae	Infection of canine osteosarcoma, melanoma and mammary carcinoma cells	(Ternovoi *et al.,*2005)
Ad5, CAV2	Adenoviridae	Infection of canine cells and osteosarcoma xenografted mice	(Le *et al.,* 2006)
CAV2	Adenoviridae	Infection of canine osteosarcoma cells and healthy dogs	(Smith *et al.,* 2006)
CAV2	Adenoviridae	Treatment of canine osteosarcoma xenografts using tumor cells as a carrier for CAV2	(Alcayaga-Miranda *et al.,* 2010)
Ad5-based vector with CD40 ligand (AdCD40L)	Adenoviridae	Treatment of canine malignant melanoma patients	(Westberg *et al.,* 2013; Suter *et al.,* 2005)
Ad5-based vector encoding IL-12 (Ad hsp feline IL-12)	Adenoviridae	Treatment of cats with soft tissue sarcoma	(Siddiqui *et al.,* 2007)
Ad5-vector-mediated p53 gene transfer	Adenoviridae	Treatment of canine osteosarcoma xenografts	(Kanaya *et al.,* 2011)
Canine Distemper Virus	Paramyxoviridae	Infection of canine lymphoid,	(Suter *et al.,* 2005)

Virus strain	Virus family/Virus type	Study/Tumor type/Animal model	Ref.
(CDV)	(single stranded RNA viruses)	osteosarcoma and melanoma cells	
Reovirus	Reoviridae (double stranded RNA viruses)	Infection of canine mast cell tumor cells (MCT) and treatment of MCT xenograft mice	(Hwang *et al.,* 2013)
Vaccinia virus (Lister) strain (GLV-1h68)	Poxviridae (double stranded DNA viruses)	Treatment of canine mammary adenoma and carcinoma and soft tissue sarcoma xenograft mice	(Gentschev *et al.,* 2009; 2010; 2012)
Vaccinia virus (Lister) strain expressing anti-VEGF antibody (GLV-1h109)	Poxviridae	Treatment of canine soft tissue sarcoma and prostate xenograft mice	(Patil *et al.,* 2012)
Vaccinia virus (Lister) strain (LIVP 6.1.1)	Poxviridae	Treatment of canine soft tissue sarcoma and prostate xenografted mice	(Gentschev *et al.,* 2013)
Vaccinia virus (Lister) strain expressing anti-VEGF antibody (GLV-5b451)	Poxviridae	Treatment of feline mammary carcinoma xenograft mice	(Adelfinger *et al.,* 2014)
Myxoma virus (MYXV)	Poxviridae	Infection of different canine tumor cells	(Urbasic*et al.,* 2012)
Myxoma virus (MYXV)	Poxviridae	Infection of feline carcinoma cells	(MacNeill *et al.,* 2012)
Canary pox virus expressing IL2 (ALVAC-fIL2)	Poxviridae	Therapy of cats with feline fibrosarcomas	(Jourdier *et al.,* 2003)
Vaccinia virus (Copenhagen) strain expressing IL2 (NYVAC-fIL2)	Poxviridae	Therapy of feline fibrosarcoma patients	(Jourdier *et al.,* 2003)

2.2.2 Optimization of Onclytic virotheraphy delivery to the Tumor tissue and metastases

As a result, oncolytic virotherapy may result in incomplete eradication of the primary tumor mass or possibly even promote metastasis of the tumor cells and eventually leading to recurrence of disease. Similar to what is observed in chemotherapy and radiotherapy regimens, malignant cells are also prone to become resistant to oncolytic virotherapy over time. This is presumably linked to the intrinsic nature of cancers to exhibit genomic instability and the propensity for accumulating mutations (Alain *et al.,* 2006; Vitale *et al.,* 2011).

Viral replication was demonstrated via transgene expression of GFP or luciferase. Moreover, they quantified viral DNA in the supernatant. In conclusion, the authors showed replication of the wild-type adenovirus in liver slices, whereas replication of the tumor targeted virus was almost fully restricted to tumor slices and attenuated in liver slices. Mixed slices are containing tumor and healthy liver tissue (Zimmermann *et al.,* 2009). Genetic engineering of oncolytic viruses is supported by the safety data from genetically engineered products like DNA vaccine in dogs and non-human primates (Peruzzi *et al., 2010;* Pluhar *et al., 2010).*

Multiple ambiguities exist regarding the optimization of combination strategies. It is unclear when the OV should be administered in regards to other novel agents. For example, administration of checkpoint inhibitors with OV on the same day or subsequent days in clinical trials or preclinical models has been performed but not been compared in a single study. Real-time evidence of enhanced antitumor immune response generation as well as dynamic imaging for tumor perfusion may be methods that predict the benefit from oncolytic virotherapy. For example, in patients treated with T-VEC who develop minimal increase in CD^{8+} T cells from baseline after 6 weeks of therapy, the risk of subsequent disease progression is high (Puzanov *et al.,* 2016).

Canine osteosarcoma cells treated with replication selective canine adenovirus (OCCAV) were used as virus carriers for evading pre-existing neutralizing antibodies against adenovirus. When administered systemically, even in the presence of adenovirus neutralizing antibodies, OCCAV carrier cells showed superior infection of tumors and tumor regression in a xenograft mouse model compared to OCCAV (osteosarcoma cell canine adenovirus) alone (Alcayaga-Miranda *et al.,* 2010). Moreover, the enhanced oncolytic effects were attributed to an increase in the effective local viral dose in the tumor as a con- sequence of the tumor specific delivery of the virus by the cells and the escape of the pre-exist- ing antiviral immunity (Power *et al.,* 2007; Fujiwara *et al.,* 2011).

2.2.3 Enhancing anti-tumor immunity and/or anti-tumor effects of OVs by virus-integrated genes

Oncolytic viruses (OVs) have a number of advantages over conventional antitumor agent, because they have their own cancer specificity and better safety margin. They selectively target and replicate in cancer cells, as a host cell;

thus, OVs survive by lysing cancer cells (Guo *et al.,* 2008). OVs-mediated oncolysis not only leads to tumor regression but also provides important immune responses. Key signals provided by oncolysis to dendritic cells and other antigen-presenting cells (APCs) can then initiate additional potent antitumor immune response (Kaufman *et al.,* 2015). OVs have been recently recognized as an effective treatment for cancer in preclinical models and promising clinical responses in human cancer patients (Russell *et al.,* 2012).

In addition to its oncolytic characteristics, OV can be engineered to express some functional genes. For instance, granulocyte macrophage colony-stimulating factor (GM-CSF) expression in OVs increases tumor cell lysis. GM-CSF is an immune modulator, acts as a paracrine manner on various cells, and recruits circulating neutrophils, monocytes, and lymphocytes to enhance their functions in host defense (Kanerva *et al.,* 2013). As for HCC treatment in clinical trials, adeno- virus and vaccinia virus are mostly used (Downs-Canner *et al.,* 2016; Samson *et al.,* 2016). Oncolytic viruses form a diverse biological group whose members belong to at least 10 different virus families, contain either an RNA or a DNA genome, and vary considerably as regards geno me size, particle complexity, and natural host preferences (Russel *et al.,* 2012).

OVs naturally possess or are engineered to acquire the capacity to selectively infect, replicate in, and destroy tumor cells (oncolysis) while sparing their normal counterparts (Russel *et al.,* 2012; Kelly and Russel, 2007). Multiple factors explain this onco-selectivity altered expression by tumor cells of virus entry receptors and/or intracellular permissiveness factors, rapid tumor cell division and high metabolic activity, deficient antiviral type I interferon responses in tumor cells (Lawler *et al.,* 2016). Furthermore, there is mounting evidence that OV infection of tumor cells induces an immunogenic process, with neo-antigen recognition and establishment of specific antitumor immune responses (Lichty *et al.,* 2014).

Enhanced glioma cell killing has been observed when the virus was applied shortly after tumor cell irradiation, suggesting that this protocol might be translated to cases of non-resectable recurrent glioblastoma (Geletneky *et al.,* 2010). In animal models, local, systemic, or intranasal administration of H-1PV has been found to cause regression of advanced tumors, virus replication being restricted to tumor tissues (Geletneky *et al.,* 2010; Kiprianova *et al.,* 2011). In addition, administration of this modified canine adenovirus to normal dogs showed only moderate virus-associated toxicity and showed therapeutic benefits in the xenograft model in killed canine osteosarcoma cells in cell culture (Carter *et al.,* 2005).

In addition, armed oncolytic viruses can also prevent neoangiogenesis, leading to cancer cell necrosis. Vascular endothelial growth factor (VEGF) is a protein that plays a key role in tumor angiogenesis (Hicklin and Ellis, 2005). Another approach that has been used to enhance viral potency has been to arm a conditionally replicative adenovirus with transgenes that promote anti tumor activity through other mechanisms, including use of antiangiogenesis and immuno stim ulatory genes (Jin *et al.,* 2005; Seth *et al.,* 2006). Evasion of the immune system has been accom plished by the use of chemical polymers or poly-ethylene glycol to coat conditionally replicative adeno viruses, which in turn increased local virus delivery to tumor sites (Doronin *et al.,* 2009).

Other approaches have tried to enhance the intrinsic cytolytic properties of NDV via increased expression of native viral proapoptotic proteins (example, F-protein), inhibition of innate immune responses for enhancement of viral replication and cell-to-cell spread, tumor-associated antigens, and immunostimulatory cytokines (example, GM-CSF, IL-2, and tumor necrosis factor-α) (Zamarin *et al.,* 2012).The importance of the immune response with oncolytic NDV vectors has been highlighted in murine tumor models (Fournier *et al.,* 2012). Therapeutic activity can be seen with only a small dose of injected NDV, suggesting that therapeutic responses are not comp letely dependent on the oncolytic activity of the virus (Bian *et al.,* 2006).

2.2.4 Successful combination therapy is context-dependent

Recently, the combination of oncolytic virotherapy with chemotherapy has shown that use of these two therapies with very distinct antitumor mechanisms may also lead to synergistic interactions (Wennier *et al.,* 2011). Oncolytic viruses as a standalone therapeutic intervention have rarely been shown to induce complete, long-term regression of established tumors *in vivo* (Vaha-Koskela *et al.,* 2007). The use of recombinant OVs as clinical biotherapies, it is important to determine whether viremia could be induced that could result in shedding of the OV. The use of Ad 5 - prime/MG1-booster vaccination as a promising, novel therapy for testing in the context of veterinary clinical trials (Doronin *et al.,* 2009; Thorne *et al.,* 2007).

The efficiency of OV replication in tumor bearing immunocompetent dogs may be enhanced by various means such as combination of viro- with chemo-(MacTavish *et al.,* 2010) or radiation therapy (Advani *et al.,* 2011) or the conjunctive use of different oncolytic viruses (Le Boeuf *et al.,* 2010). Recombinant vaccinia vectors encoding tumor associated antigens have demonstrated antitumor activity in murine tumor models (Kirn and Thorne, 2009; Thorne *et al.,* 2005). A new generation of oncolytic vaccinia viruses co-expressing tumor antigens and a variety of proinflam matory cytokines has shown improved therapeutic responses and induction of tumor specific immunity in animal models and early-phase clinical studies (Liu *et al.,* 2008; Park *et al.,* 2008).

Induction of antitumor immunity is likely aided by oncolytic-mediated cell death and release of tumor antigens and danger signals, such as ATP and high mobility group box-1, into the extracellular microenvironment (Guo *et al.,* 2005). Viral-mediated oncolysis that induces release of these and other immunogenic signature mole

cules (example, calreticulin) during cell death can promote an antitumor immune response and be further enhanced by viral expression of immunomodulatory transgenes (eg, GM-CSF). The potential benefit of this approach was initially reported for a recombinant vaccinia virus encoding GM-CSF that abrogated formation of B16 melanoma tumors in mouse models (Thorne *et al.,* 2007). A number of clinical trials have combined oncolytic viruses with a second form of therapy. These trials include widely used chemotherapeutics, such as cisplatin or radiation, and these trials have shown a high frequency of clinical responses (Russell *et al,* 2012).

The effect of the combination of an oncolytic measle virus with the novel oral HDACi resminostat (Res) was checked in HCC cell panels. The combination effect showed a boosted cytotoxic effect as an enhanced induction of apoptosis with improved rate of primary infections (Ruf *et al.,* 2015).The generation of an antitumor immune response is an indirect mechanism of malignant cell death for both OV infected and non-infected cells vasicular stomatitis virus (Pecora *et al.,* 2002). Cyclophosphamide has been shown in preclinical animal models to improve reovirus access to the tumor and preserve neutralizing antibody levels sufficient for prevention of severe toxicity (Qiano *et al.,* 2008). But, they did not appear to affect antibody levels and duration of viremia (Kolb *et al.,* 2015).

Gemcitabine appears to negatively impact late phases of reovirus replication; however, the net effect is synergistic as it accelerates antitumor immunity generation most likely by decreasing immune suppressive cells within the tumor microenvironment (Gujar *et al.,* 2014). Antibody response to Reolysin also appears to be attenuated with this combination strategy (Lolkema *et al.,* 2011). Activation of the programmed death-1/programmed death-ligand 1 (PD-1/PD-L1) axis in tumor cells can be induced by oncolytic virotherapy (Mahalingam *et al.,* 2015; Ranki *et al.,* 2016), a finding likely related to natural stimulation of checkpoint molecules in the setting of chronic viral infections in order to minimize tissue damage (Keir *et al.,* 2008).

There are preclinical data for synergy between OVs and immune checkpoint inhibition. In melanoma xenografts, the combination of Reolysin and anti-PD1 antibody significantly prolonged mice survival compared to either agent alone (Rajani *et al.,* 2016).There was evidence of enhanced antitumor cytotoxic T cell and natural killer (NK) cell activity with the combination therapy. Suppression of antitumor immunity by regulatory T cells (Treg) in Reolysin alone treated mice was ameliorated by anti-PD1 therapy. In an immunotherapy resistant lung adenocarcinoma animal model, treatment with oncolytic adenovirus plus anti-PD-1 antibody significantly increased antitumor immune responses to multiple neoantigens and decreased tumor growth, suggesting reversal of anti-PD-1 resistance with oncolytic virotherapy (Woller *et al.,* 2015).

NDV combined with immune checkpoint inhibition in immunogenic and non-immunogenic tumor animal models led to increased antitumor immunity and efficacy compared to either agent alone (Zamarin *et al.,* 2014). Synergy of oncolytic VSV with anti-PD1 antibody therapy has been also demonstrated in glioma models (Cockle *et al.,* 2016). Synergy of ITu vaccinia virus with ITu immune checkpoint blockade and radiation had been established in a lymphoma xenograft model, with tumor shrinkage in both treated and untreated tumors (Minev *et al.,* 2014). The results of oncolytic virotherapy and immune checkpoint inhibition in a Phase I clinical trial are promising (Puzanov *et al.,* 2015).

2.2.5 Biosafety of Treatment

The tumor normal immune viral dynamics 1–4 days in the presence of immune response triggered by the escalated viral infection of normal cells. This is very important because the induction of activated $CD8^+$ T cells into the tumor site may limit subsequent oncolytic virus spread and intratumoral infection. It is important to note that the innate immune response against the virally infected cells is often active in about 2–7 days post-infection (Carolan *et al.,* 2016).

Non-replicating or replicating viruses can be used as a gene transfer vector to introduce for example a therapeutic gene, co-stimulatory molecule or cytokine into cancer cells or to prime lymphocytes with tumor antigens in cancer vaccine approaches (Roberts *et al.,* 2006). There are two important aspects to oncolytic virotherapy; there is a direct treatment of tumors with replica ting oncolytic viral vectors alone or in combination with therapeutic transgene delivery, chemo therapy, or radiation therapy. On the other hand, there is indirect increase of antitumor immunity through a modulation of the immune response, as with viral oncolysate vaccine, and tumor protective monoclonal antibodies (Mathias *et al.,* 1994).

Treatment with JX-594 induced antitumor immunity, as evidenced by regression of distant uninjected lesions, and appearance of tumor infiltrating eosinophils, T cells, B cells, and macrophages in injected lesions. Further studies have suggested that the oncolytic activity and transgene expression of JX-594 are highly selective and mediated via several mechanisms, including activation of replication by epidermal growth factor receptor and Ras signaling, cellular thymidine kinase levels, and an abnormal interferon response in tumor cells (Parato *et al.,* 2012).

2.3 Limitations and Prospects of Cancer Gene Therapy

The induction of activated $CD8^+$ T cells into the tumor site may limit subsequent oncolytic virus spread and intratumoral infection. Even though they do not model the innate immune responses, it is important to note that the innate immune response against the virally infected cells is often active in about 2–7 days post-infection (Carolan *et al.,* 2016). The role of GM-CSF in promoting proliferation of monocyte-derived suppressor cells

suggests that caution may be needed when using GM-CSF to enhance the immunostimulatory properties of vaccinia and other viruses (Filipazzi *et al.,* 2007). Tumors can develop multiple barriers to various anticancer therapies, including oncolytic virotherapy. Several mechanisms that may hinder the therapeutic efficacy of OVs and the challenges they pose to the development of improved cancer virotherapies.

2.3.1 Immunological barriers

Immune responses against viruses presumably limit ongoing viral replication in immuno competent dogs. In this context, a high level of pre-existing immunity to parental viruses in canine populations might limit the use of oncolytic viruses for cancer therapy. The role of virus neutralizing antibodies following intravenous administration remains to be determined. Use of unrelated viruses from different hosts, such as vaccinia for dog cancers, may solve the problem of pre-existing immunity. However, carrier cell based therapy also provided promising results to escape pre-existing immunity (Fujiwara *et al.,* 2011).

Specific delivery to tumors and escape of the pre-existing antiviral immunity increased the effective local viral dose in the tumor tissue and thus enhanced the oncolytic effects (Hamada *et al.,* 2007; Iankov *et al.,* 2007). In order for an OV to establish a niche within the tumor after systemic administration, the OV has to by pass the liver that may actively sequester a percentage of the administered dose (Alemany *et al.,* 2000). Administering the virus directly within the tumor overcomes this limitation, mainly in the minority of tumors with easily accessible skin and subcutaneous lesions such as melanoma, with an abscopal effect and dissemination in distant sites (Andtbacka *et al.,* 2015; Senzer *et al.,* 2009 and Zamarin *et al.,* 2014).

The adaptive immune system may be a double edge sword, playing a role in both tumor killing and early elimination of viral infection through humoral (example, antibody and complement binding) and cellular mechanisms (Wakimoto *et al.,* 2003). Exogenous factors include cellular stress resulting from chemo- and/or radiotherapy and reovirus modulation of interferon signaling (Prestwich *et al.,* 2008). The presence of "infected" tumor cells and the release of viral- and tumor associated antigens after tumor cell lysis, induce robust innate and adaptive antitumor immune responses (Adair *et al.,* 2013; Gujar and Lee, 2014; Hall *et al.,* 2012).

Combination therapy can overcome pre-existing immunity to reovirus without affecting metastatic tumor regression. Reovirus has been shown to preferentially infect, induce ER stress and kill Ras-activated pancreatic cancer cells (Carew *et al.,* 2013). Furthermore, IP admin istration of RV inhibits the peritoneal dissemination of pancreatic cancer cells in a syngeneic immunocompetent animal model (Hirano *et al.,* 2009). Intraportal administration of reovirus has decreased the number and size of treated tumors in the same model (Himeno *et al.,* 2005).

This therapeutic approach faces a major challenge consisting of the immune system's response to the virus, which hinders oncolytic virotherapy. To date, complex dynamics of oncolytic viral tumor infection and the consequences of OV-induced immune response are poorly understood (Workenhe *et al.,* 2015; Woller *et al.,* 2014 and Alvarez-Breckenridge *et al.,* 2015). Denderitic cells and NK cells produce a range of cytokines that promotes T helper 1 cell activity and potent cytotoxic T lymphocyte responses that are necessary for clearing virus-infected cells (Romagn ani *et al.,* 2005).

Additionally, humoral immune responses, namely the production of neutralizing antibodies by B cells and plasma cells, provide several lines of antiviral defense (Dorner and Radbruch, 2007). Plasma cells derived from B1 cells imparts early defense against viral infection by producing polyspecific antibodies. $CD4^+$ T helper cells then stimulate naive B cells at later stages, in order to generate memory B cells and long-lived plasma cells that produce high amounts of specific neutralizing IgG antibodies. Finally, the complement system, composed of soluble factors and cell surface receptors, blocks viral infection by acting on both the innate and adaptive immune responses. These mechanisms include, enhancing humoral immunity, regulating antibody effector mechanisms, and modulating T cell function (Stoermer and Morrison, 2010).

The infectious potential of recognized OVs (example, Ad, HSV) becomes limited by high levels of neutralizing antibodies (Massari *et al.,* 2002). These circulating antibodies can limit viruses from ever reaching the tumor site, especially since some viral particles, including HSV-1- and murine leukemia virus-derived viruses, are particularly prone to inactive action by the comple ment system (Ikeda *et al.,* 2000). Poxviruses elicit a strong cell mediated immune response and are ultimately cleared from the body by the humoral immune system, preventing poxviruses from causing latent or recurrent infection (Chaudhri *et al.,* 2004).

2.3.2 Tumor environment

The immune system has often being perceived as a major impediment to successful oncolytic virus therapy by facilitating viral clearance (Prestwich *et al.,* 2009 and Bridle *et al.,* 2010). Even though intratumoral viral injections offer direct tumor infection, they are of limited use in regions (such as the brain) where the tumor cannot be reached directly (Crittenden *et al.,* 2005). Intrinsic barriers within the tumor microenvironment, such as dense intratumoral connective tissue and induction of antiviral immunity, can impair these processes. Alteration of the microenvironment by administering exogenous enzymes directly to the tumor or by equipping viruses to encode recombinant enzymes can facilitate viral spread (Guedan *et al.,* 2010).

Tumor-infiltrating leukocytes can negatively regulate immune responses within the tumor, which include

regulatory T cells (Tregs), myeloid derived suppressor cells, and type 2 macrophages. Their immunosuppressive functions can be exerted by secretion of cytokines (e.g., IL-10 and TGF-β), through inhibitory receptors (e.g. CTLA-4 and PD-L1) via cell contact, and secretion of amino-acid depleting enzymes (arginase and IDO) in the tumor microenvironment. Tumor cells themselves also have mechanisms to suppress antitumor immunity, such as the shedding of NKG2D ligands, MICA/B that blocks NK cell and T cell function (Groh *et al.,* 2002) and facilitates the expansion of immunosuppressive $CD4^+$ T cells (Groh *et al.,* 2006).

Oncolytic virotherapy has the potential benefit of altering the tumor microenvironment enough to break existing tumor immunotolerance. Failure of the immune system to recognize tumor cells may be due to a paucity of stimulated immune cells infiltrating the tumor and/or masking of tumor or antigens. Aberrant cytokine patterns in the tumor microenvironment may severely limit an antitumor immune response (Zou, 2005).

2.3.3 Challenges of combination theraphy

Although seropositivity for herpes simplex virus is common and could prevent booster inject- ions, preclinical and clinical data suggest that pre-existing antiherpes antibody titers do not appreciably impact therapeutic responses, which may relate to the intratumoral route of admin isteration. Because local antiviral immunity may limit therapeutic efficacy, strategies to limit local immune response have been used to enhance the oncolytic activity of herpes simplex virus vectors. For example, cyclophosphamide has been used to block bone marrow-derived generation of inflammatory cells prior to administration of herpes simplex virus (Currier *et al.,* 2008; Fulci *et al.,* 2006).

Another approach is the use of agents either exogenously administered (eg. cilengitide, bevacizumab) or re engineered into the virus (eg. vasculostatin) to inhibit vascular permeability or formation of neovasculature in the tumor to limit the extravasation of inflammatory cells into the tumor, and permit enhanced virus production in tumor cells (Kaur *et al.,* 2005; Kurozumi *et al.,* 2008). Introducing genes that are make cancer cells more sensitive to standard chemotherapy or for radiation treatments. Drug convertases ("suicide genes") which can turn an inactive prodrug into an active drug which can be introduced to tumor cells to cause cell-specific toxicity. For example, the herpesvirus thymidine kinase can phosphorylate and convert nontoxic drug ganciclovir into toxic metabolites (Mullen and Tanabe, 2003).

Serum from individuals who were sero-positive for CVA21 failed to show cross-neutralization to other group A coxsackie viruses, that is, A13, A15, or A18. Thus, prime boost strategies utilizing alternate strains of coxsackie A virus might be one approach to increase antitumor immunity and therapeutic responses with oncolytic coxsackie viruses (Au *et al.,* 2011). However, as far as veterinary medicine is concerned, development of oncolytic virotherapy for cancer to heal canine patients is of prime importance. Many of the treatment options used in veterinary medicine rese- mble protocols used to treat human cancer patients. In addition, public release of nearly 99% canine genome sequences provided a window of opportunity to expand the scope of comparative oncology (MacTavish *et al.,* 2010).

The most common immunosuppressant drug used in the context of oncolytic virotherapy is cyclophosphamide; a chemotherapeutic alkylating agent that also induces apoptotic cell death. CPA has complex immune-modulating effects, affecting humoral and cellular mediators of both the innate and acquired immune responses. These immunosuppressive functions have been shown to enhance viral oncolysis and improve antitumor efficacy of HSV (Ikeda *et al.,* 2003; Kambara *et al.,* 2005). Some OVs can actually stimulate angiogenesis to increase vascular perm eability in tumors (Aghi *et al.,* 2007).

Thus, anti-angiogenic therapy may thus adversely affect the localization of OVs to the tumor microenvironment. Finally, modulation of the host immune response through chemotherapy may conflict with the therapeutic function of the oncolytic virus. For instance, low dose CPA may remove immunosuppressive cells such as Tregs to improve vaccine induced adaptive antitumor immune responses; however, it also promotes the antiviral immune response, leading to early viral clearance (Bartlett *et al.,* 2013). Conversely, high dose CPA may enhance viral oncolysis through wide spread immunosuppression of the innate and adaptive antiviral immune response, but also completely abrogate the antitumor immune response (Prestwich *et al.,* 2008).

3. CONCLUSION

Oncolytic virotherapy constitutes an alternative treatment option for a broad spectrum of cancer entities and quickly moving toward the forefront of modern medicines. By direct and indirect mechanisms of tumor killing, virotherapy provide rationale for investigation of clinical trials using engineered OVs in support of conventionl cancer therapy as well as in combination with immune checkpoint inhibitors. In general the tumor selective property of oncolytic viruses method is based on the capability of OVs to preferentially infect and lyses cancer cells and to initiate specific antitumor immune response. After genetic engineering, The other advantage of oncolytic virotherapy is that, OVs selectively replicate in cancer cells leads to tumor cell destruction and oncolysis. On top of this, a better understanding of the functional roles of various viral genes has aided the modification of oncolytic viruses to alter tumor selectivity, pathogenicity, and immunogenicity, and to optimize the clinical potential of these vectors. Concomint to the current encouragement of more study on oncolytic virus enter human

clinical trials, more oncolytic therapeutics may become available for use in companion animals in near future. Hence, further investigation is needed to give attention on type of cancers and stages of disease, viral dose and mode of immune cells enforced. Further research on the optimization of the OV-drug combination strategies for both the oncolytic and antitumor immune effects of OVs is requires. On top of this, the clinical impact of oncolytic viruses and the potential promise of this approach for the treatment of animal cancers need to be investigated.

Competing Interests

The authors declare that they have no competing interests.

Acknowledgments

The authors are thankful to library and ICT office of Hawassa University for providing the facilities to prepare this review paper.

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