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REVIEW ARTICLE

Recombinant viruses with other anti-cancer therapeutics: a step towards advancement of oncolytic virotherapy

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Abstract

Cancer as a disease is a multifaceted foe which sometimes succumbs to the prescribed treatment and sometimes develops resistance against various therapies. Conventional cancer therapies suffer from many limitations, the least of which is their specificity and systemic side effects. In a majority of cases, acquired mutations render the cancer cells resistant to therapy and lower the prognostic outcome. In the constant effort to devise a therapeutic moiety which can comprehensively eliminate cancer cells, oncolytic viruses provide an attractive avenue as they selectively infect and lyse cancer cells sparing normal cells from their effects. Viruses can be engineered for their host specificity and toxicity as a promising anti-cancer tool. As it is essential to devise a strategy to address all targets involved in cancer development and progression, the idea of using oncolytic viruses with enhanced anti-cancer activity through arming with foreign genes gained merit and is showing promising advent in clinical studies. The use of oncolytic viruses as an agent of combination therapy for cancer treatment also gained much attention in the recent past. This review focuses on the emerging role of oncolytic viruses as vital components of anti-cancer regimen presenting a new dimension in an ever-changing cancer therapy scenario.

Introduction

Current scenario in cancer therapy and lack of comprehensiveness

Cancer therapy is most commonly associated with a combination of surgery, chemotherapy and radiotherapy. The success of surgical removal of tumor relies heavily upon early diagnosis and ease of access but does not guarantee complete removal of primary tumor mass or of metastasized cells. Radiation therapy similarly is bound by inadequate specificity and systemic toxicity. In addition to precincts of efficacy, delivery and penetration of drugs to target site, chemotherapy is mired with various side effects as well as emergence of drug-resistant tumor cells. In addition, drug inactivation, target alteration, DNA mutation and damage repair, cell death inhibition, epigenetics and epithelial–mesenchymal transition [1] lead to cancer relapse unresponsive to established chemotherapeutic drugs.

Advances in molecular biology have led to the emergence of gene therapy as a viable tool for cancer treatment. Contrary to conventional cancer treatment, gene therapy projects a more sustainable therapeutic approach where genetic defects associated with cancer can be substituted or anti-tumor genes can be introduced. This transfer is facilitated by various viral, bacterial and chemical vectors among which viral vectors have garnered interest for their targeted approach. Viral vector-mediated gene therapy had immense success in the treatment of various monogenetic diseases but is unable to replicate it in the majority of cancers where genetic variations among the individuals or within different tumor sites in a patient is substantial [2]. All these approaches are quite effective on their own but their reliance on conjecture for disease progression and the dynamic nature of cancer cells has caused lacunae to develop a therapy which addresses the obstacles of targeted delivery such as efficient internalization at the effector site and efficient expression of anti-tumor genes. At present, there is a need to devise a therapeutic moiety which can be a template with provisions to make it effective towards any cancer type.

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Table 1 Various viruses targeted for oncolysis

Virus backbone	Viral construct	Modifications made	Targeting strategy	Target cells	Ref
Adenovirus	Ad5-Δ24-RGD	Ad type-3 knob incorporated into the Ad type-5 fiber; p16/Rb selective. Contains RGD-4C modification in H1 loop targeting αvβ integrins	Transduction	Lung adenocarcinoma mouse xenograft	[78]
	Ad5- \Δ24-RGD-GM-CSF	Above construct with E3 promoter controlled GM-CSF insertion	Transduction	Various chemotherapy refractory solid tumors	[45]
	$Onco^{Ad}$hTERT-TRAIL	Modified Ad-RGD with E1A under hTERT promoter armed with TNF-related apoptosis inducing ligand	Transduction & Transcription	CAR-negative bladder cancer mouse xenograft	[79]
	AdSur-SYE	E1 under survivin promoter; fiber knob displays pancreatic tumor targeting SYENFSA ligand; AB loop with 4-point mutations for CAR-independent infection	Transduction & Transcription	Pancreatic neuroendocrine tumor and pancreatic adenocarcinoma xenograft models	[80, 81]
	Ad5/3-Cox2L-24	Substitution of Ad5 fiber gene with Ad3 for CAR-independent attachment; E1A under Cox2 promoter	Transduction & Transcription	Various metastatic and refractory tumors	[82, 83]
	Ad5PTD (ASH1-SCG3-EIA)	Protein transduction domain (PTD) of HIV-1 Tat protein in the hypervariable region 5 of adenoviral hexon protein for CAR-independent attachment	Transduction	Drug-resistant neuroblastoma cells in vitro and subcutaneous human neuroblastoma xenograft	[84]
	Ad-hOC-E1	E1A and E1B under vitamin D3 inducible single bidirectional promoter of human osteocalcin. Human bone-marrow derived mesenchymal stem cells used as carrier of virus	Transcription	Orthotopic renal cell carcinoma mouse xenograft	[85]
	AdLCY	E1B-55-kDa deleted Ad under control of CMV mini promoter ligated with Oct-4 response elements and Hypoxia response elements	Transcription	Mice bearing human bladder tumor xenografts and syngeneic bladder tumors	[86]
	ICOVIR-15K-cBiTE	ICOVIR-15K has RGDK sequence in fiber shaft instead of KKTK sequence in H1 loop and was engineered to express a bispecific EGFR-targeting BiTE (cBiTE) antibody under the control of the major late promoter	Transduction & Transcription	Colon colorectal carcinoma and lung carcinoma xenograft mice models	[87]
Measles	DARPin-MV	Bispecific with the insertion of specific DARPins in hemagglutinin (HA) protein	Transduction	Her2/neu-positive human cancer cells in vitro and drug-resistant human ovarian cancer xenograft	[88]
	MV-GFP-H_{AA}-scEGFR	HA mutation at Y481A and R533A to ablate CD46- and SLAM-dependent attachment respectively. Single chain antibody against EGFR inserted at C terminus of HA to target EGFR-positive tumors	Transduction	Patient-derived glioblastoma xenograft	[89]
	MV-Ec4	EpCAM-specific DARPins inserted in HA protein	Transduction	HER2/*neu* or EpCAM overexpressing human cancer cells Orthotopic ovarian carcinoma xenograft	[90]
	rMV-SLAM blind	Mutation of SLAM binding domain to retarget towards nectin-4 receptor	Transduction	Breast cancer, colorectal cancer and lung cancer xenograft	[91–93]
	MV-h-uPA / MV-m-uPA	Insertion of urokinase-type plasminogen activator receptor (uPAR)-specific sequence in HA coding region	Transduction	Colorectal cancer and lung cancer xenograft	[94]
	$MV^{PNP}CDVenv^{antiCEA}$	HA replaced by envelope glycoproteins of canine distemper virus	Transduction	Murine and human colorectal cancer xenograft	[95]
HSV	R-LM249	Single chain antibody against Her2 in gD region allowed it to be specific for Her2-positive carcinomas	Transduction	Murine models of metastatic cancers	[96]
	R-VG803 and R-VG809	R-VG803 has insertion of the scFv to HER2. R-VG809 is a derivative of R-VG803 with additional deletion of the AA 6–38 portion in gD	Transduction	HER2 and nectin1/HVEM-positive cancer cells	[97]

Recombinant viruses provide an attractive avenue towards the development of an all-encompassing cancer therapy

With the prior history of viruses causing spontaneous tumor regression [3, 4], the idea of viruses as an oncolytic agent has become a new reality of multimodal cancer therapy. Viruses as disease-causing pathogens exhibit traits such as host specificity, regulation of host cellular processes for efficient viral replication and the host cell lysis. These features of them can be exploited specifically against cancer cells for the generation of viruses as oncolytic agents.

Oncolytic viruses (OVs) are therapeutically useful anti-cancer agents that selectively infect and damage cancerous tissue without harming normal tissue [5, 6]. An ideal OV should exhibit a high replicative capacity in vivo, ability to infect both dividing and non-dividing cells, inability of chromosomal integration, lack of disease induction and absence of pre-existing antibodies to the virus in the host population. As of now, no single OV has all the desired features but various experimental approaches are being employed to develop a recombinant virus as a vital part of anti-cancer therapy.

Oncolytic virotherapy relies on cancer-specific replication of virus triggering tumor cell death by a number of mechanisms including direct lysis, expression of toxic proteins, autophagy and induction of apoptosis. In addition, OVs can mediate the killing of uninfected cancer cells by indirect mechanisms such as the induction of anti-angiogenic response [7], anti-cancer immune response [8] or through the specific activities of transgene encoded proteins expressed from engineered viruses [5, 6]. There are a number of viruses with natural preference to infect cancer cells such as parvovirus, reovirus, Newcastle Disease Virus (NDV), Mumps virus and Moloney leukemia virus, whereas viruses such as measles, adenovirus, vesicular stomatitis virus (VSV), vaccinia and herpes simplex virus (HSV) can be adapted to infect cancer cells by repeated laboratory cultures [9] or engineered for cancer specificity. However, for a virus to be an oncolytic agent, stringent criteria related to safety of the population from pathogenic reversion or evolution of a novel strain or of person-to-person transmission of the OV have to be followed.

Development of a virus into an oncolytic agent

Virus that may or may not be naturally inclined for oncolysis can be developed into an oncolytic agent by manipulating its genome to enhance its specificity and toxic profile against cancer cells. Viruses can also be engineered to encode additional transcriptional units to modulate virus biology against cancer cells [10]. Following the advent of molecular biology techniques, the early era of OVs was dominated by attenuation of viruses for better safety profile and retargeting viral entry to non-natural hosts. The first-generation OVs were attenuated viruses. Their tumor specificity was natural or was acquired through laboratory passages, but the anti-tumor effect was limited to a small percentage of tumor types. Second-generation OVs were retargeted through genetic modifications for selective internalization or selective replication. Selective internalization was achieved by modifying the viral proteins engaged with specific receptors or their mutants over-expressed in tumor cells. Specificity was also attained for viral gene expression by introducing tumor-specific promoters or generating deletion mutants of viruses where the deletion is substituted in cancer cells. Targeting was also done based on tumor microenvironment and the expression profile of cancer cells towards cell death. Extensive work was done to generate recombinant viruses for oncolytic activity with desirable safety and selectivity. Numerous studies have reported the construction; modification and retargeting of OVs and some examples where tumor specificity and regression was achieved are listed in the Table 1.

Third-generation OVs are not only attenuated and retargeted, but also armed with additional genetic element(s) of viral or non-viral origin to enhance their anti-tumor activity. Generally, OVs are designed to exploit the pathways responsible for induction of apoptosis and to multiply by exploiting the abrogated cell cycle machinery which may induce cell death. The general targets are cancer cells with defective or downregulated p53 tumor-suppressor protein, RAS/PKR, IFN/PKR, p16/Rb pathways or other pro-apoptotic signals [11]. Here we discuss about the armed OVs and their application in cancer therapy in combination with pre-existing cancer regimens.

Arming of OVs to address cancer-specific adaptations

As stated earlier, robust anti-tumor activity can be achieved by inserting cytotoxic elements into OV genome. This ‘arming’ of OV potentiates the therapeutic index of virus-mediated anti-cancer gene therapy by efficient delivery and expression of transgene. Although the use of viral vectors for anti-cancer gene therapy has been quite popular in cases such as Gendicine, an Ad5 vector approved by China’s State Food and Drug Administration for treatment of head and neck cancer in 2004 [12], these were mainly replication-incompetent viruses which served as one-time effector molecule. Thus, the development of replication-competent and conditionally replicating OVs has provided a platform where the viral genome can be equipped with transgenes to generate a stable and sustainable production of both transgene proteins and viral progeny. Transgenes

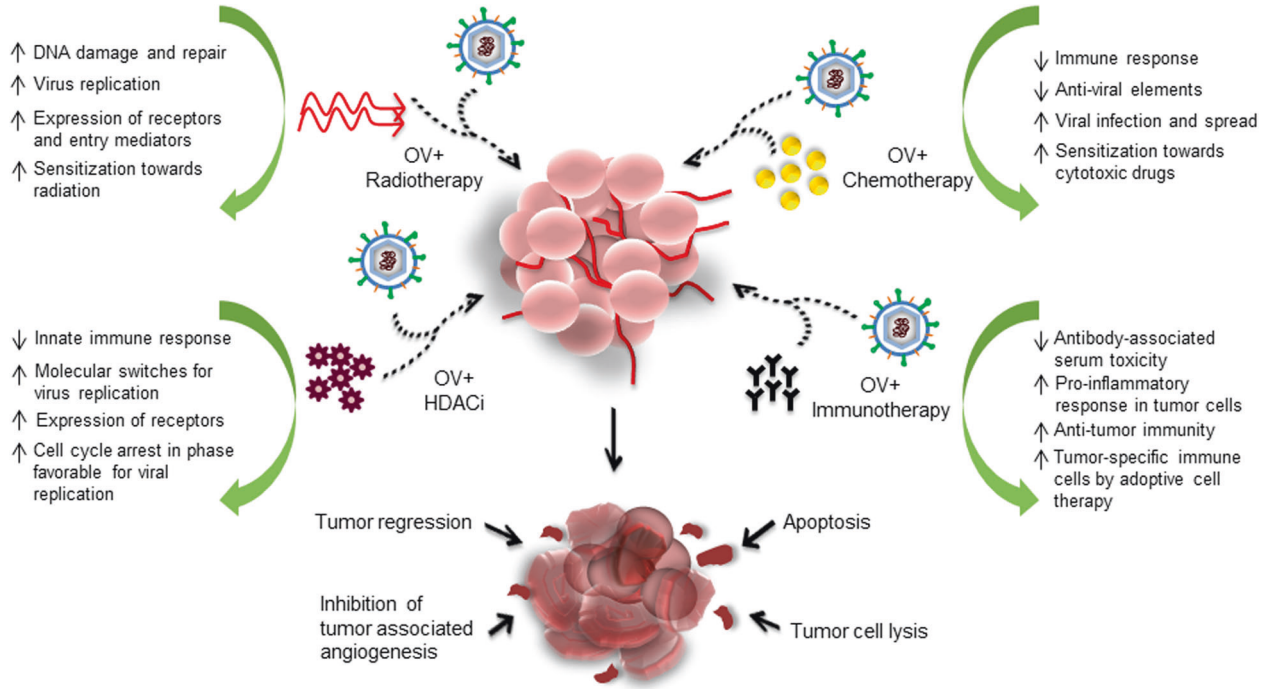

Fig. 1 Effects induced by oncolytic virotherapy combined with other anti-cancer therapeutics. Use of different treatment modalities such as chemotherapy, radiotherapy, immunotherapy and HDACi for antitumor activity in combination with viruses engineered for oncolysis facilitates the replication of recombinant viruses, thus inducing enhanced lysis of cancer cells. Likewise, oncolytic viruses sensitize the tumors to other therapeutics and enable them to exert anti-cancer effects efficiently even at lower doses. By and large, the effects induced by virotherapy and another therapeutic component together lead to tumor reduction and improved treatment outcome

encoding functions of tumor suppression, apoptosis, anti-angiogenesis and immunomodulation [13] are largely chosen for insertion into the OV genome.

Introduction of OVs has opened up new avenues of establishing host immune response against tumor cells. Generally, tumor cells produce immunosuppressive cytokines (e.g., transforming growth factor-β) and recruit cells to inhibit immune response (e.g. regulatory T cells) to halt the host defense mechanism [14]. With OVs, it is now possible to combine debulking of tumor and attack on tumor vasculature due to virus-induced cell lysis with effective activation of adaptive and innate immune response [6, 15]. In fact, the 2015 FDA (The Food and Drug Administration) approved T-Vec, an HSV-based therapy for the treatment of surgically unresectable melanoma, supports this possibility, as in addition to double deletion of γ34.5 and α47genes, it has granulocyte-macrophage colony-stimulating factor (GM-CSF) at the deleted γ34.5 loci [16].

Viruses are also being armed with secretory factors inducing apoptosis, functional p53 gene, prodrug activation gene as well as immune checkpoints which are abrogated in tumor cells. For example, in case of gene directed enzyme prodrug therapy, viral vectors are armed with suicide genes which can convert low cytotoxicity prodrugs into potent cytotoxic agents against cancer cells. The case in point is GLV-1h68, a strain of vaccinia virus carrying β-galactosidase (*lacZ*), that, supplied with prodrug derived from a *seco*-analog of the natural antibiotic duocarmycin SA, caused tumor regression and activation of intrinsic apoptotic pathway in human G1-101A breast cancer xenografts [17] by circumventing the presence of anti-apoptotic viral genes in favor of toxicity of converted prodrug.

Viruses have also been armed to exploit antibody-based cancer therapy, where complement activation and cytotoxic effects of antibody towards tumor vasculature enhanced the therapeutic efficacy. One such example can be seen in case of orthotopic hepatoma-bearing mice treated with velogenic NDV Italien strain armed with chimeric mouse–human antibody targeting CD147 (cHAb18) overexpressed in hepatocellular carcinoma (HCC). The recombinant virus (rNDV-18HL) showed tumor specificity and inhibition of intra-hepatic metastasis of HCC causing prolonged survival [18]. Another study explored the sequential administration of NDV and adenovirus armed with a cytokine, oncostatin M (human), which promotes antigen presentation and co-stimulatory signals triggering anti-tumor immunity. It showed significant anti-tumor activity and immune response leading to increased survival of orthotopic model of pancreatic ductal adenocarcinoma in Syrian hamster. This study elucidated the optimal expression of transgene and low serum concentration of oncostatin M is desirable for maximum effect and low systemic toxicity as well as principle

of prime boost by using two antigenically unrelated OVs to overcome the neutralizing antibody interference [19].

Oncolytic virus in combination therapies

Armed OVs can either be developed as a standalone anti-cancer regimen or as a synergistic component of an established anti-cancer approach. As a standalone therapy, OVs are sometimes restricted by the tumor microenvironment, host-mounted anti-viral response as well as pre-existing neutralizing antibodies decreasing the overall effectivity. In addition, the repertoire of approved candidates constitutes only T-Vec with other OVs still at various stages of clinical trials, resulting in a narrow window of selection and efficiency for treatment of various cancers. Thus, it may be beneficial to combine OVs with conventional anti-cancer therapies to improve the treatment outcome as the multi component regimen can address the shortcomings of each component as a standalone thereby making it more effective (Fig. 1). However, in doing so there is a possibility of either chemotherapy or radiotherapy negatively affecting the viral replication [20, 21]. Thus, it is imperative to analyze the significance of anti-cancer potential of OVs amidst all the established therapies and their role in instituting a comprehensive treatment module.

Radiation therapy

Oncolytic virotherapy and radiotherapy are two different treatment modalities, but pre-clinical studies have indicated their synergistic anti-tumor role. This combination has exhibited a significant enhancement of anti-cancer activity with various OVs. Variants of recombinant HSV have shown increased viral load [22] and appreciable toxicity against various carcinomas when combined with radiation therapy. For example, mutated HSV (G207) with ICP6/γ34.5 deletions combined with radiation exhibited multifold increased toxicity and reduction of carcinoma in cervical cancer mouse models [23]. Similar effects were reported in the case of colorectal cancer mouse xenograft where the combination of G207 and low-dose radiation resulted in upregulation of ribonucleotide reductase causing increased anti-cancer toxicity [24]. Another HSV variant NV1066, with ICP0/ICP4/γ34.5 deletions administered in combination with radiation, resulted in the reduction of tumor mass in xenogenic mice tumor flank model of non-small-cell lung carcinoma [25] and mesothelioma [26]. This synergism can be attributed to upregulation of GADD34 in response to radiation-induced DNA damage, as carboxy terminus of mammalian GADD34 shares structural homology with deleted viral neurovirulence gene ICP34.5 and substitutes its action in cells to favor viral replication leading to enhanced oncolysis [25]. Temporal sequestration of radiation with respect to viral gene expression has been reported to cause regression in high-grade glioma mouse models as irradiation is known to enhance the late promoter genes of HSV-1 [27]. Similarly, measles virus encoding for human carcinoembryonic antigen (MV-CEA) in combination with radiation therapy has shown a significant regression of tumors in subcutaneous model of human gliomas [28].

Combination of oncolytic adenovirus and radiation has also shown significantly greater toxicity as compared to single-agent treatment modalities [29, 30]. ONYX-015, a mutant adenovirus with E1B-55k gene deletion, has been reported to enhance radiation-induced cytotoxicity in vitro and in vivo in mice xenograft model of anaplastic thyroid cancer [31] as well as in mice xenograft model derived from primary human malignant glioma [32]. Two prostate-specific adenoviral vectors CV706 [33] and CV787 [34] in combination with radiation resulted in reduction of tumor mass and serum prostate-specific antigens in xenograft mouse models for prostate cancer. Gendicine (E1/E3 deletions expressing p53 under RSV promoter) in combination with radiation [35] and chemotherapy [12] has been approved as intra-tumoral therapy against head and neck squamous cell carcinoma in China. AdΔ24 (24-bp deletion in C2 domain of E1A region) and AdΔ24-p53 (p53 gene in deleted E3 region) have shown increased anti-tumor efficacy in combination with radiation in mice xenograft model of therapy-resistant glioma [29].

VSV expressing tumor-associated antigens (TAAs) has shown significant reduction in locally established and metastasized mouse model of oligometastatic melanoma in combination with stereotactic ablative radiation therapy. The tumor regression was associated with priming of substantial tumor-infiltrative CD8+T-cell response [36].

Reovirus in combination with radiation in murine-human colorectal carcinoma model has shown synergistic oncolytic effect as compared to individual therapy even at low input of virus. This combination resulted in a statistically significant death of cell lines relatively resistant to reovirus-mediated oncolysis, suggesting that this synergism is not simply additive but is causative due to increased apoptosis and bystander effect [37]. The combination of T3D, a non-pathogenic reovirus with radiation, showed increased viral replication due to CUG2 upregulation causing down-regulation of PKR and eIF2-α. It activates mitochondrial apoptotic signaling in wild type (WT) and in both mutant BRAF-Ras cell line and BRAF mutant xenograft mouse model of malignant melanoma which is generally chemotherapy and radiation resistant [38]. GLV-1h68, a construct of oncolytic vaccinia virus, showed induction of intrinsic apoptotic pathway by downregulation of anti-apoptotic Bcl-2 proteins when combined with external beam radiation leading to decreased tumor mass and

increased survival in a rat–human orthotopic model of advanced extremity sarcoma [39].

Chemotherapy

The road to develop OVs as an efficient standalone therapy is still not completely paved, and thus all major studies and trials focus towards using viruses with chemotherapeutic modalities. Chemotherapeutic drugs generally inhibit DNA replication or disrupt the microtubule structures. As the mechanism of action of OV varies from that of cytotoxic drugs used, the effects exerted by combination therapy depend on the nature of the virus used and the synergism created between two therapeutic components. It is thought that the expression of viral genes and their interaction with cellular factors determine the sensitivity of the tumor to chemotherapy [40]. For example, Gendicine, approved for the treatment of head and neck squamous cell carcinoma, in combination with chemotherapy is also being used in clinical studies involving both the agents against other cancers such as HCC. In many cases the use of Gendicine in combination with doxorubicin, camptothecin or 5-flurouracil resulted in better quality of life and increased patient survival [41]. Oncorine (H101), a derivative of ONYX-015, showed promising anti-cancer effects in various pre-clinical studies involving tumor cells having either mutated or normal p53 gene. It also showed enhanced anti-tumor effects in nasopharyngeal and squamous cell carcinoma patients in phase III clinical trials especially in combination with cisplatin and 5-fluorouracil [35, 42] and was approved as therapy for head and neck squamous cell carcinoma in China. Similarly, Advexin (adenovirus with E1/E3 deletions expressing p53 under CMV promoter) in combination with methotrexate showed enhanced toxicity as compared to both the therapies given independent of each other in phase III clinical trials against advanced recurrent head and neck squamous cell carcinoma [43]. Silica implants bearing Ad5-Δ24-RGD and Ad-Δ24-RGD-GM-CSF in combination with gemcitabine have shown marked increase in survival of mouse and hamster xenograft model of peritoneal disseminated pancreatic cancer [44]. In addition, both the viral constructs showed decrease in tumor marker expression and conversion of progressive state of different cancers to stable disease in almost 50% of patient population tested [45].

Oncolytic WT reovirus has shown significant synergistic anti-tumor toxicity with low dose of docetaxel in murine flank model of hormone refractory metastatic prostate cancer as compared to modest or negligible affects respectively as a single therapeutic agent. This effect was partially due to microtubular stabilization of cells by docetaxel promoting mitotic arrest resulting in apoptotic induction [46]. The combination of chemotherapy and virotherapy has also been exploited to overcome the constraints imposed by neutralizing antibodies in the patients by using chemotherapeutic agent as an immuno-modulator. For example, administration of cyclophosphamide prior to the use of reovirus for the treatment of refractory or metastatic solid tumors in phase I clinical trials resulted in no rise of neutralizing antibody baseline level [47]. Similar effects were seen during co-administration of gemcitabine and Reolysin [48]. Combination of cisplatin, paclitaxel and Reolysin also showed significant rise in overall survival of refractory or metastatic head and neck cancer patients in phase II clinical trials [49]. Cisplatin in combination with NV1066, an oncolytic HSV-1 with γ34.5 deletion, showed increase in viral replication and cytotoxicity due to upregulation of DNA damage-inducible protein GADD34 in human malignant mesothelioma cell lines [50]. A study involving paclitaxel in combination with oncolytic rhabdovirus, Maraba-MG1, showed prolonged survival in various murine breast cancer models [51]. Pre-clinical studies with doxorubicin and rituximab in combination with NDV have shown enhanced toxicity against hematological malignancies such as plasmacytoma and non-Hodgkin lymphoma in vitro [52].

Recombinant vaccinia virus, GLV-1h68 with cyclophosphamide in mice model of human lung adenocarcinoma has shown complete loss of characteristic hemorrhagic phenotype of the disease in addition to reduction in tumor growth, angiogenesis further leading to epidermal growth factor (EGF) downregulation. It also increased the viral distribution within the tumor and elevation of pro-inflammatory cytokines such as M-CSF-1, monocyte chemoattractant protein-1 (MCP-1), MCP-5 and chemokine eotaxin [53]. In a larger context the oncolytic potential of vaccinia virus has been observed in pre-clinical studies with various cancers such as breast cancer including breast cancer stem-like cells [54], squamous cell carcinoma [55], salivary gland carcinoma [56], human sarcomas [57], etc. Cyclophosphamide has been used as a chemotherapeutic agent for the treatment of various carcinomas, and thus it can arguably be said that this combination, if successful in clinical settings, can emerge as a viable therapeutic model.

Histone deacetylase inhibitors (HDACis)

HDACis are a class of chemotherapeutic agents which have already been approved for lymphoma therapy [58]. In many instances carcinogenesis and tumor progression have been attributed to deregulation of HDACs. There has been a growing interest in the use of HDACis with OVs to enhance the oncolysis as they have been shown to hyperacetylate nucleosome core proteins to drive expression of anti-tumor genes and also acetylate non-histone proteins such as chaperones, regulators of DNA damage repair and transcription factors including p53 [59]. Many molecules are being

investigated at clinical levels for the treatment of various malignancies out of which vorinostat (cutaneous T-cell lymphoma), romidepsin (cutaneous and peripheral T cell lymphoma) and belinostat (refractory peripheral T cell lymphoma) have been approved by the FDA [60].

VSV variant VSVΔ51 in combination with vorinostat has been found to increase viral replication, apoptosis, decrease interferon-mediated anti-viral response in xenograft models of refractory prostate, melanoma, colon, breast and ovarian tumors [61]. Replication-deficient adenoviral vector Ad.CMV-GFP administered in combination with romidepsin increased the expression of viral entry receptor CAR (Coxsackievirus and adenovirus receptor) in xenograft mouse model of melanoma causing increased infectivity with respect to virus internalization into tumor cells [62]. Patient-derived xenograft model of glioblastoma showed differential activation of multiple cell death pathways upon synergistic use of LBH589 and Scriptaid with Ad-Δ24-RGD vector [63]. HSV-1 variant G47Δ and trichostatin A decreased vascular endothelial growth factor secretion and angiogenesis in xenograft model of glioma and colorectal cancer [64]. Alternatively, this combination of OV and HDACi is not limited to a two-component therapy.

Pre-clinical testing of adenoviral vector bearing p73 gene and a small hairpin RNA against HDAC1 (OV.shHDAC1.p73) to target mice xenograft model of malignant melanoma exhibited increased apoptosis, induction of autophagy, complete regression of tumor and extended survival with no resurgence within 16 weeks of observation [65].

Immune checkpoint inhibitors

Emerging studies suggest that immunogenic cell death is a major component of OV-induced cell death. It establishes anti-tumor immunity by either secretion/release or exposure of DAMPs (danger-associated molecular patterns) and PAMPs (pathogen-associated molecular patterns) causing maturation of antigen-presenting cells leading to activation of antigen-specific CD4+ and CD8+ T cells [66, 67]. Antibodies such as Ipilimumab (CTLA-4), Nivolumab (PD1) and Penbrolizumab (PD1) have been approved by the FDA for treatment of advanced metastatic melanoma [68] due to observed reversal of tumor cell-mediated repression of T-cell response by blocking immune checkpoint proteins [60]. Examples can be found in pre-clinical studies with VSV and CTLA-4 inhibitor in Her2/neu-positive D2F2/E2 murine mammary tumor model showing complete remission and immunity towards tumor antigens [69]. Intra-tumoral NDV and anti-CTLA-4 antibody therapy caused tumor regression with increased survival rate in bilateral B16-F10 melanoma mouse model and a prostate adenocarcinoma transgenic mouse model, TRAMP C2 [70]. Similarly, phase I clinical trials with T-Vec and Ipilimumab or Penbrolizumab for metastatic melanoma therapy have shown encouraging results [71].

In many instances, the use of immune checkpoint blocking antibodies lead to systemic immune-related adverse effects and restriction of viral replication [60]. Insertion of checkpoint inhibitors into the viral genome ensures the safety of this therapy and localization of antibodies to tumor site. Recently, Western Reserve oncolytic vaccinia virus harboring hamster monoclonal IgG (J43) recognizing murine programmed cell death protein (mPD-1) was successfully generated by the insertion of three different forms of mPD-1 binders: the whole antibody (monoclonal antibody (mAb)), fragment antigen-binding (Fab) and single-chain variable fragment (scFv). Testing of this construct on B16-F10 melanoma model and MCA 205 fibrosarcoma model showed significantly enhanced localization of J43 antibody at the tumor site with reduced tumor growth and increased survival in case of the MCA 205 model [72]. Earlier studies also support the feasibility of OVs armed with antibodies against checkpoint inhibitors such as adenoviral vector Ad5/3-Δ24aCTLA4 expressing complete human mAb specific for CTLA-4 causing increased oncolysis in mouse xenograft models of prostate and lung cancer [73]. Similarly, measles virus coding for anti CTLA-4 (MV-aCTLA-4) and PD-L1 (MV-aPD-L1) antibodies also showed enhanced therapeutic benefits with antibody localization in B16-CD20 melanoma model with no immune-mediated toxicity [74].

A recent study involving Ad-Δ24-RGD armed with immune co-stimulator mouse OX40 ligand (OX40L) administered in combination with anti-PD-L1 antibody showed an effective example of potent in situ autologous cancer vaccination in immunocompetent mouse glioma models by enhancing the tumor-specific activation of lymphocytes and proliferation of TAA-specific CD8+T cells resulting in long-lasting immune memory and therapeutic efficacy [75].

Other modalities which can also be combined with OVs are radionucleotides, nucleotide analogs [76] and another OV. For example, intra-tumoral administration of reovirus and systemic delivery of VSV encoding complementary DNA library of melanoma antigens (VSV-ASMEL) in a B16-melanoma mice model showed significantly increased survival [77].

Conclusion

OVs as a tool of cancer therapy can be the missing link in the development of a comprehensive anti-cancer regimen. Earlier representative of anti-cancer virotherapy despite being mildly cancer-selective had limitations related to morbidity and low activity, making them unsuitable for the

development of a viable therapeutic model. On the contrary, genetic alteration of viral genome has allowed researchers to generate candidate OVs to fill the lacunae of a specific and targeted anti-cancer therapeutic moiety with desirable safety, tumor toxicity and margin for alterations to target wide variety of cancers. The most successful example can be found in T-Vec, an HSV-1-based OV armed with GM-CSF [66] which has been approved for the treatment of melanoma. In addition, ongoing clinical trials with various candidate OVs has further augmented the hope for a viable anti-cancer therapy. However, there are many challenges still posed by the ever-changing nature of cancer and its microenvironment. Despite the promising results in pre-clinical settings, there have been host-dependant reactions with respect to anti-cancer, anti-viral immune response and the accessibility to all malignant cells, which have proven to be major limiting factors for OV-based anti-cancer therapy. In many instances, this interplay of tumor and host responsiveness towards the presence and activity of OVs pose a hindrance in the effectivity of OV-based mono-therapy. However, many limiting host responses can be curbed by administering OV with pre-existing anti-cancer therapeutics. For effective translation of pre-clinical success of OVs to clinical settings, validation of OV is needed to be carried out in animal models considering the accessibility of OV to tumors and host immune response as selection criteria. Until the development of OVs as a single anti-cancer therapeutic, not bound by the above-mentioned short-comings, virotherapy can be incorporated as an arm of anti-cancer regimen along with various pre-existing therapeutics such as chemotherapy, immunotherapy and radiation which supplement the viral activity and heighten the anti-tumor response.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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