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REVIEW ARTICLE

A Novel Approach to Cervical Cancer Therapy: A Short Review

Amir Sasan Mozaffari Nejad[1], Farideh Kamarehei[2], Amir Khodavirdipour[3], Parvaneh Mehrbod[4] and Mohammad Yousef Alikhani[2,*]

[1]*Universal Scientific Education and Research Network (USERN) Office, Jiroft University of Medical Sciences, Jiroft, Iran*
[2]*Infectious Disease Research Center, Hamadan University of Medical Sciences, Hamadan, Iran*
[3]*Department of Molecular Genetics, Faculty of Natural sciences, University of Tabriz, Tabriz, Iran*
[4]*Department of Influenza and Other Respiratory Viruses, Pasteur Institute of Iran, Tehran, Iran*

Abstract:

Cervical cancer is one of the most common cancers affecting women worldwide, and it occurs following persistent infection. Cervical cancer incidence is tightly linked to HPV infection (human papillomavirus), and particularly, type 16 and type 18 viruses cause the majority of cases. The common therapies for cervical cancer include surgery, chemotherapy, and radiation therapy, which are often invasive or unbearable treatment methods with many side effects. They just probably slow down the disease progression or alleviate any comorbid conditions, including vaginal bleeding and pain, which is called palliative care, while novel treatment approaches, especially virus-like particles and viral oncolysate, could eliminate these complications. In this review study, we have proposed a novel approach to cervical cancer therapy focused on utilizing Newcastle disease virus as viral oncolysate with a high potential of immunity induction and low side effects. Furthermore, we have attempted to shed some light on the perspectives of novel virus-based cervical cancer immunotherapy. Finally, we review the recent findings from basic and clinical studies and also discuss the usefulness and limitations of this approach, as well as the reasons why it is believed that viral oncolysate immunotherapy may be of relevance in the treatment of human cervical cancer.

Keywords: Human papillomavirus, Newcastle disease virus, Papillomaviridae, Viral oncolysate, Cervical cancer, Chemotherapy.

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1. INTRODUCTION

Cervical cancer ranks fourth in terms of prevalence and mortality in females worldwide after breast, colorectal, and lung cancer, and is one of the tumor-forming malignancies [1]. Cervical cancer could occur following persistent infection and its incidence is tightly linked to human papillomavirus (HPV) infection, particularly virus types 16 and 18 that cause the majority of cases [2 - 4]. E6 and E7 viral oncoproteins are part of the molecular cascade and their associations with tumor-specific genes, such as p53 and pRB (tumor suppressor genes), have been ascertained [1, 4, 5]. Screening programs have been successful in the prediction of cervical neoplasia by cytology (Pap-test) and high-risk (hr) HPV DNA (Molecular) testing for years, although the hr HPV DNA is preferred as primary screening because it is cost-effective, efficient, and sensitive than cytology [6, 7].

The common cervical cancer therapy includes surgery, chemotherapy, and radiation therapy, which are often invasive or unbearable treatment methods with many side effects, while novel treatment approaches, such as oncolytic virotherapy, virus-like particles (VLPs), and viral oncolysate, could reduce the side effects of these current cancer treatments [2, 3, 8, 9]. The old therapies just probably slow down the disease progression and alleviate any comorbid conditions, including vaginal bleeding and pain, which is called palliative care, but the new approaches could prove to be beneficial in eliminating the disease with little side effects [10].

2. VIRUS-BASED CANCER VACCINES: A SUMMARY

In recent years, recombinant antigens, DNAs, nanoparticles, virus-like particles, and viral oncolysate have been introduced as cancer vaccines. However, the concerns related to anticancer vaccines in patients are the induction of B cell responses to produce antibodies and T cell immunity in less progressed or advanced-stage cancer patients, but cancer vaccines should have multilateral effects to overcome disease progression in end-stage cancer patients. Overall, tumor-specific vaccinations are safe [2, 11].

In a systematic and meta-analysis review, the clinical and immunologic responses of colorectal cancer patients who

* Addresss correspondence to this author at Infectious Disease Research Center, Hamadan University of Medical Sciences, Hamadan, Iran;
Tel: 09125443147; E-mail: alikhani43@yahoo.com, alikhani@umsha.ac.ir

underwent active specific immunotherapy were analyzed. Immune response induction of specific immunization with different agents (*e.g.*, peptide vaccine, autologous tumor cells, idiotypic antibody, dendritic cells, and the virus-based vaccine) was described in approximately half the patients. However, a very weak clinical response with pooled results of <1% of the clinical trials rate in human colorectal cancer was revealed but it might have different results in diverse tissue cancers [12].

The potential advantages of virus-based cancer vaccines over traditional and miscellaneous new approaches are the stimulation of both B- and T-cell responses, antigen presentation by both MHC class I and class II molecules, and T-cell response toward type 1 or type 2. Virus-based cancer vaccines have strong antigens that provide cells with antigen-presenting properties, including macrophages, DCs (dendritic cells), and B cells. Subsequent antigen presentation, T cell stimulation, and proliferation occur; furthermore, IFN-γ has been secreting from CD4 and CD8 T cells, after that T-helper cells could induce the antibody responses. On the other hand, the virus antigens promote the formation of germinal centers of B cells; moreover, the plasma cells increase secretion of antibodies and elevate antibody titers. The viruses, as therapeutic agents, are oncolytic, but they must be engineered to improve efficacy and safety. The engineering process might be due to stimulating immune genes or pro-apoptotic cytokines; therefore, T-cells could be enhanced by the mediation of cross-priming DC cells to recognize tumor antigens and neo-antigens that lead to accelerating tumor cell apoptosis [13 - 16].

Anti-PD-1 therapy is a type of modern immunotherapy that has shown promise in treating advanced cervical cancer in patients who need to be treated. T cells express the protein PD-1, which regulates immune response on their surfaces. Some cancer cells can use the protein PD-1 to evade recognition and destruction by the immune system. Anti-PD-1 therapy works by blocking the interaction between PD-1 and its ligands, slowing down the immune system functioning and allowing it to fight cancer cells better. Several clinical trials have evaluated the efficacy of anti-PD-1 therapy in patients with advanced cervical cancer. Results have shown that anti-PD-1 therapy can result in durable responses in a subset of patients with advanced or recurrent cervical cancer, including those previously treated with chemotherapy. In some cases, anti-PD-1 therapy has resulted in tumor regression and prolonged survival. However, the response rate to anti-PD-1 therapy in cervical cancer is relatively low compared to some other cancers [17 - 19].

The viral oncolysates as a cancer treatment strategy provide great immunotherapy compared to traditional vaccine agents. In this review, firstly, we outline the latest knowledge of viral vaccines, which may be used against viral oncolysates and cancers associated with interactions of host-virus for further improvement of future therapeutic administrations. Later, we talk about recent advances from basic to the latest trials implementing the NDV (Newcastle disease virus) as viral oncolysate in cervical cancer therapies.

3. TYPES OF VIRAL VACCINE AGAINST CANCER

In recent years, the virus-based cancer vaccine is a very fascinating research topic for medical researchers. There are different experimental viral vaccines as therapeutic agents specifically targeted for cancer therapy; some of them are listed as follows:

3.1. Virus-like Particles

These are molecules that are closely similar to viruses, without infectious potential because of no viral genetic material. They can be naturally occurring or synthesized through the individual expression of viral structural proteins, which can then self-assemble into the virus-like structure. They involve a tiny size (ranging from 20 to 200 nm) to be drained into lymph nodes [20].

3.2. Nucleic Acid Vaccines (NAVs)

Nucleic acid vaccines have lately been employed as a potential option in cancer therapies. mRNA and DNA vaccines carry out genetic information that encodes for hosts tumor antigens, which later stimulate the immune responses against malignancies that involve tumor antigens. NAVs are simple, safe, and easy in terms of production, but still, they have not been recognized as a viable substitute for peptide vaccines. Right tumor antigens selection, the immunosuppressive nature of cancer, and insufficient immunogenicity are a couple of challenges in this field. Few viewpoints can be considered to ameliorate the NAV's efficacy [21].

3.3. STING Activation

The other unique approach in cancer vaccines is STING activation to subsequently trigger anti-tumor immunity in Batf3-dependant DC *via* the utilization of replication-attenuated viral vectors. Cyclic dinucleotides promote STING signaling [22].

3.4. Polymeric Multilayer Capsules (PMLC)

Murine models of melanoma and influenza were used to validate induced immune responses and their functional relevance. The ability of PMLC to initiate the NALP3 inflammasome and set off the potent pro-inflammatory cytokine IL-1β releases was observed in a mechanical stage. DC-depleted mouse model might recognize DCs as the main properties of immunogenic mediators of PMLC [23].

3.5. Viral Oncolysate

Viral oncolysates are being studied as cancer vaccines. They are specific and can be considered as active immunotherapy for cancer. It seems that oncolysate viral usage is worth going after in early melanoma cases. The ideal point of application would be presumed to be while the tumor burden is minimal (stage I) and there is a critical need for the host to search out and destroy malignant cells. When an extract from cancer cells is infected by a special strain of the virus, it is then called viral oncolysate that breaks down and overcomes cancer cells. This extract accommodates both viral proteins and cancer cell proteins [2, 16, 24].

4. VIRAL ONCOLYSATE-BASED VACCINES

Viral lysate of Vaccinia virus was found efficient for cancer patients as it showed improvement in GMMSVl cell line *in vitro* and male Balb/c mice *in vivo*. These findings show that this vaccine is a precise and specific functional immune system stimulator, and may prove to be a potential therapeutic agent in the treatment of human cancers [25]. Viral lysate of Vaccinia virus used against tumor tissue removed cancerous cell line *in vitro* and also in the patients with advanced Dukes' C and Dukes' D carcinoma of the colon and rectum. This shows that live Vaccinia virus-augmented (vaccinia oncolysate) tumor cell vaccine is safe and may be worthwhile in the surgical adjuvant treatment of colorectal cancer [16].

Viral oncolysates of fowl plague-infected allogenous leukemic myeloblasts were surveyed on the myeloblasts cell line and also in acute myelogenous leukemia (AML) patients. Fowl plague virus has been utilized for immunization by viral oncolysate that can be proposed in the course of remission of acute myelogenous leukemia patients and for detecting patients whose treatment has been insufficient. In this study, there were an association observed between antiviral antibodies in the serum and the percentage of myeloblasts in the bone marrow [26].

Sindbis virus infection was reported to have cytopathic and apoptosis effects in two cervical cancer cell lines (HeLaS3 and C33A) and three ovarian cancer cells (HOC-1, HAC-2, and OMC-3) but not in normal human keratinocytes *in vitro*. In the metastasis model of ovarian cancer, suppression of ascites formation was observed in nude mice with Sindbis virus treatment. Systemic treatment with Sindbis virus targeted tumors specifically was shown by using a green fluorescent protein imaging system *in vivo* [27].

The concentrated lysate of Newcastle disease virus prepared by sonication could control human malignant melanoma on BMCL and M40 cell lines, and its action was proved in the metastatic disease (stage 111) *in vivo* model. In this study, antitumor immunologic responses in metastatic melanoma patients with the benefit of cellular changes but a low level of humoral antibody were observed [28].

4.1. Virus-based Vaccines against HPV

Preventive vaccines in case of infections, such as HPV, are promising as they are cheap and lower cervical cancer risks. The preventive HPV L1 capsid protein vaccine uses a virus-like particle method that has been utilized to avert widely reported HPV 16 and 18. Since vaccines like L1-VLP may be effective only in particular subtypes of HPV used to develop the vaccine. Ultimately, there are serious challenges that still need to be overcome in response to next-generation virus vectors as a future therapeutic option in cancer treatment [29].

Recombinant vesicular stomatitis virus (VSV) vectors were developed as prophylactic vaccines to induce strong humoral and cellular immune responses in rabbit papillomavirus model infected by high-risk HPV. These preclinical results, obtained in a physiologically relevant animal model of HPV infection, demonstrate that VSV vectors have to be considered as therapeutic antitumor vaccines [30]. Furthermore, the latest finding elucidates the immunogenicity and safety of a recombinant virus vaccine expressing E7, HPV 16, and 18 genes, in patients with progressive cervical cancer [31].

4.2. A Clinical Trial of Virus-based Vaccines against HPV

Prominent research has elucidated recombinant vaccines in all individuals to have mild-to-moderate but no severe side effects or toxicity, so they can be considered as a well-tolerated vaccine. After the first dose of the HPV vaccine, all 4 patients of the study demonstrated CTLs (3 patients: HLA A24 and A1; and 1 patient: HLA A1, A3), and the other 8 individuals showed a serological-specific response to the HPV. The above project asserted the immunogenicity and safety of the said vaccine in the study population [31].

4.3. Viral Oncolysate of NDV

NDV (Newcastle disease virus), an avian RNA virus as a cancer vaccine is a biological response modifier that stimulates the body's natural immune system. This may be utilized to destroy the cancerous cells straight forward, as it replicates faster than human cancer cells compared to almost all regular and normal body cells. NDV was primarily utilized as a Newcastle disease vaccine in avians, but for the first time, it was reported in 1964. NDV can cause minor side effects in human beings; thus, mild illnesses triggered by NDV and its capability for quicker replication by 10,000 times in human cancer cells haveinspired scientists to have a closer look at NDV as potential cancer prevention and treatment option. NDV's clinical trial results show a new horizon of hope, but FDA (USA) so far has not approved cancer therapy options involving NDV [32].

NDV has a wide variety of strains, and they are capable of lysing by covering its non-lytic and outer membrane *via* suppressing the basic actions for a cell to demolish the infected cell. Both non-lytic and lytic strains have been utilized to produce a vaccine for humans as they may combat cancer cells directly, but it depends on the form of the virus and how it is used *versus* human cancer cells. On the other hand, NDV can be used to infect the individual directly or to develop vaccines for cancer [33]. Primarily, NDV can be administered into a tumor, vein (IV injection), or muscle, or directly to the colon. This virus can be taken by inhalation. Consequently, NDV can infect the cells and later start to replicate to generate more copy numbers of the virus that may then stimulate the immune response. This process could kill cancer cells by damaging their outer membranes. A miscellaneous way is the use of oncolysate vaccines that contain some part of cancer cell membranes infected with NDV, which can be delivered by cutaneous or subcutaneous injection. In another way, the vaccines that contain the whole tumor-based cells stimulated by NDV can be engineered in the laboratory to eliminate the multiplication and infection potential of this agent. However, just the intradermal route can be used for whole-cell vaccine administration [28].

NDV is a prophylactic vaccine against HPV cervical cancer. The two surveyed mechanisms of NDV on cancer cells include acting as an apoptotic stimulator and migration inhibitor of human oral cancer cells. The inhibition of migration occurs by a reduction in matrix metalloproteinase-7 (MMP-7) levels, the primary main target gene of Wnt/β-

catenin and β-catenin, which are the vital pathways for the growth of the cell, metastasis, and differentiation. However, the high level of MMP-7 could reduce the inhibitory effect of NDV, but the Wnt/β-catenin pathway involvement has never been observed in NDV infection. On the whole, NDV can deregulate the Wnt/β-catenin pathway by downregulation of p-GSK3β and p-Akt chiefly, thereby downregulating β-catenin. Also, infection by NDV leads to a decrease in nuclear and cytoplasmic levels of β-catenin [34].

The disadvantages of viral oncolysates are the risk of integrating into the host genome and leading to other diseases; also, previous exposure to the virus and the presence of immunity against the vector as well as the production of antibodies that can neutralize it, can reduce the vaccine's efficacy. Some of the studies have used oncolysate vaccines of NDV for the treatment of patients with metastatic melanoma in phase I and phase II trials. Three of them had shown some positive points and one demonstrated no benefit in the clinical trial. Some patients in these studies had shown a longer disease-free survival when similar patients were treated with surgery alone. However, the above strain has been used to develop said vaccines, but other techniques were utilized to produce them. The above trials were not control-based studies as patients were administered different types of treatments, and it is not well defined that the result is because of NDV oncolysate or other agents. The above studies' results need to be re-evaluated by controlled and randomized trials including more patients [24, 35]. Research involving NDV whole-cell vaccine has been conducted on patients with breast cancer, colorectal cancer, kidney (renal) cancer, malignant glioma, and ovarian cancer. The same NDV variant has been used in all later studies. Some individuals have been reported to improve significantly and survive the disease administered with the whole-cell vaccine. However, due to the lack of control-based studies and weak design, it is uncertain and debatable that the observed improvements are because of the vaccine or any other external or internal factors. All these findings demonstrate that whole-cell vaccines may kill more cancerous cells with the help of the immune system in the course of the vaccination process but may not offer permanent immunity against cancer [36].

Oncolytic virus (OV) treatment according to infection with the MTH-68 strain of NDV has been found to be useful in most of the patients treated for high-grade gliomas. A weakened MTH-68/H strain of NDV may result in apoptosis in the pheochromocytoma cells of the rat. Cytotoxicity of MTH-68/H was evaluated with tumor cell (human) and specific biochemical properties with oncolytic effects were analyzed. MTH-68/H has shown the ability to kill and destroy different types of transformed cells by apoptosis. While caspases 8 and 9 did not play a role in apoptosis induction of MTH-68/H, the activation of caspases 3 and 12 was discovered in virus-infected PC12 cells. A human glioblastoma cell line with the repressible expression of the p53 protein did not show any difference in MTH-68/H sensitivity in its p53-expressing and p53-depleted states, indicating that the apoptotic process induced by MTH-68/H does not depend on p53. Virus replication associated with apoptosis was tested in 2 different cell lines, including HeLa and PC12, and endoplasmic reticulum stress signs were observed and identified in transformed cells. On the other side, treatment by MTH-68/H did not affect non-transformed human primary fibroblast rat and mouse fibroblasts' proliferation. MTH-68/H, thus, selectively kills tumor cell cultures by inducing endoplasmic reticulum stress, leading to p53-independent apoptotic cell death [37, 38]. PV701 type of NDV was also tried on advanced cancer patients when the condition of individuals did not improve by conventional therapies. Few patients showed a positive reaction to the PV701, while the rest did not respond to it [39]. Side effects of exposure to the NDV were reported to be mild to moderate. As stated above, NDV in humans may cause mild conjunctivitis, flu-like symptoms, and laryngitis. Other reported adverse effects depend on the type of administration through which the virus has been given. The most common side effects reported after the fever include itching, headache, skin redness, and swelling at the injection site. In some cases, swelling and inflammation are seen near the tumors. The inflammation at the injection site is the sole downside of NDV oncolysate treatment. Trials, in which whole-cell vaccines or NDV oncolysates have been used in combination with conventional therapies and substances, such as cytokines, have reported swelling, flu-like symptoms, and fever as side effects, which may be because of cytokines [40].

4.4. Newcastle Disease Virus Oncolytic for Immunotherapy against Cervical Cancer of Papillomavirus

The NDV's LaSota strain's oncolytic effectiveness on the TC-1 tumor cell line was evaluated *in vitro* by destroying the tumor cells. Murine TC-1 cells of HPV-related (human papillomavirus) carcinoma were chosen as a model to demonstrate human HPV-16 E6 and E7 (human papillomavirus) oncoproteins. For this purpose, LaSota strain was used to infect the TC-1 cell line, and LDH release assay and MTT tests were used to evaluate and assess the cellular integrity and metabolic activity. These findings demonstrate that the LaSota strain of NDV induced an effectual oncolytic activity against TC-cells. LDH and MTT assay showed considerable NDV cytotoxicity in the TC-1 cell line. Apoptosis may be induced by OVs and the result of MOI-dependent death can be assessed by annexin V/PI double staining. Additionally, the findings express that the LaSota strain of NDV's capacity to treat TC-1 tumor leads to the build-up of ROS in comparison to the control cell lines. Elevated ROS levels end up in apoptosis, especially in cancer cell lines dedicated to NDV oncolysis output [8]. To scrutinize whether the association of HA2 (influenza hemagglutinin 2) with FMG can alleviate the NDV oncolytic characteristics in cervical cancer, the mice model was injected with iNDV, NDV-HA2, HA2, and iNDV-HA2. Furthermore, anti-PD1 mAB was also added to evaluate the immune checkpoint blockade's complementary role in the progression of tumor size. The efficacy of treatment was assessed by immunohistochemical and immunological analysis. The output of combinational therapy (NDV+HA2 genes) expressed that this combination induces antitumor immune responses to HPV-associated carcinoma with synergistic effect by elevating E7-specific lymphocytes proliferation, triggering the cytotoxicity responses of CD8+ T-cells and granzyme B, and rising splenic cytokine levels, while inducing a drop in E6 oncogenic and immunosuppressive cytokines expression, and thus upregulating the expression of apoptotic proteins. Furthermore, PD-1 blockade inclusion reduced the size of tumor and induced a rise in cytokine responses [41]. The NDV

Hitchner B1 (HB1) strain role vs. cell proliferation of cervical cancer *via* cytochrome-C expression assessment, apoptotic pathway and autophagy analysis, was surveyed. In addition, the relationship between the development of ROS, activation of the intrinsic apoptotic pathway, autophagy, and cytolysis of NDV mediated in the cervical cancer model was investigated by HPV. An LDH assay was performed to estimate cell viability. The cells were inoculated by HB1 NDV MOIs (MOI: 5, 10, and 15), and for apoptosis, ROS development and autophagy were determined by flow cytometry. Also, cytochrome-C level proteins were evaluated by ELISA. Through the development of caspase-3, infection of HB1 NDV could significantly elevate the apoptotic pathway rate within the TC-1 cell lines. Additionally, the LC3-II and caspase 3 upregulation in the TC-1 cell line affirmed autophagy and apoptosis induction in a dose-dependent manner. Besides, the capability of NDA to induce the development of ROS, which may involve TC-1 apoptosis, was observed. Infection with HB1 NDV may potentially raise the level of cytochrome-C and decrease the level of surviving protein in TC-1 cell lines, which are associated with apoptosis. After NDV therapy, multiple cell death pathways are activated, which induce the apoptosis mechanism and promote unique potential as anti-tumor agents [3]. MSCs (mesenchymal stem cells) are utilized as a porter in oncolytic delivery for NDV in tumors associated with HPV. These mesenchymal cells are harvested to find cell surface markers from the C57BL rat bone marrow, and then cultured and analyzed by flow cytometry. The impacts of oncolytic NDV packed with MSCs on cytokine immune responses, T cells, myeloid and MDSCs (myeloid suppressor cell), and caspases 3 and 9 expressions by TME (tumor microenvironment) were analyzed by immunohistochemical and histological assays. The findings furnished that the peri-tumoral MSCs administration holds both tumor tropism and migratory capability against transplanted tumor tissue. The tumor therapy studies show that oncolytic NDV MSCs-engineered delivered system considerably suppresses the growth tumor associated with intensified proliferation of E7-specific lymphocyte, splenic IFN-γ, IL-4 and 12 and CD+ T cell cytolysis responses rather than the control group. Also, the treatment causes apoptosis protein upregulation (caspase 3 and caspase 9) and elevates TME infiltration with Gr1+MDSCs and CD11b+myeloid [41].

CONCLUSION

In accordance with all the previous studies, NDV oncolysate is secure and possible to be used as a remedial agent. Also, the safety of strains of NDV as an antitumor agent has been found to be normally high with low toxicity. Therefore, more systemic researches are essential to raising the quality and efficacy of the NDV vaccine. In brief, NDV oncolysate can be used as a potential intermittent vaccine in cancer therapy, especially against cervical cancer.

CONSENT FOR PUBLICATION

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LIST OF ABBREVIATIONS

NDV	=	Newcastle Disease Virus
HB1	=	Hitchner B1
LDH	=	Lactate Dehydrogenase
ROS	=	Reactive Oxygen Species
OV	=	Oncolytic Virus
ELISA	=	Enzyme-linked Immunosorbent Assay
MSCs	=	Mesenchymal Stem Cells
DC	=	Dendritic Cells
HPV	=	Human Papillomavirus
MOI	=	Multiplicity of Infection

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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