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Oncolytic Virotherapy in Breast Cancer

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Abstract:

Breast cancer has a high incidence and fatality rate, making it a major worldwide health problem. Traditional treatment methods, treatments including chemotherapy, radiation therapy, and surgery, are partially effective in treating advanced breast cancer. Oncolytic viruses are a class of viruses with potential antitumor activity, demonstrating significant promise in cancer therapy through targeted invasion and elimination of tumor cells. In recent years, oncolytic virus therapy and its combination treatments have shown promise in the treatment of breast cancer. This review explores the potential applications of oncolytic viruses, including adenovirus, herpes simplex virus, and vaccinia virus, in breast cancer treatment. The effectiveness, safety, and methods of action of various viruses are covered in the article, as well as the achievements and progress in current research. The objective of this article is to elucidate the advantages of existing oncolytic therapies and inspire the development of novel strategies for treating breast cancer by enhancing understanding and utilization of oncolytic virus therapy. It seeks to harness the potential of new technologies to benefit patients.

Keywords: Oncolytic virotherapy; breast cancer; cancer therapy.

1. Introduction

According to the latest data from the World Health Organisation (WHO) for 2022, out of all cancer forms, breast cancer has the highest incidence rate worldwide (age-adjusted rate) of about 47.1 cases per 100,000 people for both sexes. Among women, breast cancer, which caused about 666,103 deaths in 2022, has become the cancer with the highest mortality rate. Tragically, this figure will persistently increase. These substantial statistics can impose both a physical and psychological hardship on patients, as well as a burden on their families and community.

The primary conventional therapies for breast cancer include surgical intervention, radiation, and chemotherapy. Surgery has undergone many enhancements, progressing from extreme techniques to breast-conserving methods. However, surgery still has several drawbacks, including its inability to effectively treat metastasis and the potential for negative impacts on the patient's physical appearance, which can have a detrimental influence on their emotional well-being. Post-operatively, the efficacy of radiation has been substantiated [1]. Nevertheless, there is also a study that fails to demonstrate the increase in survival rate following radiotherapy [2]. Radiotherapy might potentially harm healthy body cells, resulting in severe effects, even with local therapy. Regarding chemotherapy, while it is undeniably beneficial, it can also develop resistance and lead to lasting systemic damage. Furthermore, all the treatments above have documented evidence of their capacity to induce tumor development [3]. Hence, there is a requirement for innovative therapeutic approaches to address the constraints of conventional cancer treatment. Oncolytic viral therapy is gaining prominence due to its distinct advantages.

The use of oncolytic viruses in cancer therapy has advanced significantly throughout the past 20 years. Oncolytic viruses (OVs), whether they are genetically engineered or naturally existing, possess the capacity to infiltrate and eliminate cancer cells without endangering healthy cells. The types of oncolytic viruses (OVs) commonly employed in cancer therapy include herpesviruses, adenoviruses, vaccine viruses, measles viruses, and reoviruses. Oncolytic viruses naturally target specific types of infected tissue due to the presence of certain surface receptors, abnormal signal transduction pathways, and the hypoxic tumor microenvironment. Oncolytic viruses exploit host cell proteins and pathways that are employed by tumor cells for processes such as replication, invasion, immune evasion, and metastasis. They exert their effects through various methods. Oncolytic viruses specifically target cancer cells, leading to their destruction through lysis or immunogenic cell death. Furthermore, they initiate systematic immune responses against tumors and disturb the environment in which tumors grow, so preventing tumor cells from avoiding suppression, invading other tissues, spreading to other parts of the body, resisting

programmed cell death, and stimulating the formation of new blood vessels [4]. Compared to traditional medicines, oncolytic virotherapy has a number of advantages, one of which is the lack of reported deaths to date. Furthermore, while there have been instances where oncolytic virotherapy has been unsuccessful, it has not resulted in any notable deleterious consequences in clinical settings. Remarkably, a significant number of patients choose to engage in clinical trials after they have reached the point where they can no longer tolerate conventional treatment [5]. This demonstrates that oncolytic viruses provide far greater safety while demanding considerably less stringent physical conditions from patients. Furthermore, oncolytic viruses possess notable benefits in terms of their targeting capabilities and their capacity to reproduce within the bodies of patients.

The goal of this study is to provide a thorough investigation of the potential use of oncolytic viruses in the treatment of breast cancer. Specifically, it focuses on three categories of DNA viruses: adenovirus, herpesvirus, and vaccine virus. The present progress can be summarized by examining the ongoing research and clinical application of these viruses, as well as analyzing their qualities, modes of action, and significance in breast cancer therapy. This review will assess the safety and effectiveness of these viruses by examining the existing literature.

2. Oncolytic Virotherapy

2.1 Adenovirus

Adenoviruses are icosahedral, non-enveloped viruses that are now divided into seven subgroups according to the linear double-stranded DNA genome that they possess. The subtypes under subgroup C are often utilized in the creation of oncolytic viruses. Adenoviruses possess the capacity to infect cells at any point in the cell cycle. The reason for this is that adenovirus is not a retrovirus and has minimal ability to affect the genetic machinery of the host cell. Adenovirus possesses notable safety benefits. The initiation and sustenance of tumor cell infection relies on the attachment of viral fibers to receptors located on the surface of tumor cells. Various viruses possess the capacity to identify certain receptors, and some receptors can be reduced in tumor cells. Using type 5 as an illustration, the particular receptor for it, CXADR, has the potential to be reduced in advanced tumor cells. Recombinant oncolytic viruses that incorporate CRA can reproduce within cancer cells and specifically eliminate them. The E1A gene, which is the initial gene activated after viral infection, serves as the foundation for the creation of CRA. Changes in the expression of the E1 gene in adenovirus DNA are necessary to give it the ability to replicate specifically in cancer cells.

The China Food and Drug Administration (CFDA) granted a license for oncorine, the first recombinant oncolytic adenovirus, to treat nasopharyngeal cancer in late 2005. It is created by the H101 with E1B deletion and partial E3 deletion and is used in conjunction with chemotherapy. Success was obtained in a Phase III clinical study, which included patients with esophageal squamous cell carcinoma (ESCC) and head and neck squamous cell carcinoma (HNSCC). The China Food and Drug Administration (CFDA) has approved the use of H101 as a combination therapy for the treatment of cancer as a result of this accomplishment[6]. Chinese clinical trials were carried out after the marketing period to evaluate the effectiveness of H101 in treating different kinds of cancers. The trials revealed that patients with malignant, recurrent pleural effusion achieved a remarkable 38% rate of complete recovery, which was the highest recorded success rate. Simultaneously, the adenovirus Onyx-015, characterized by the absence of the E1B gene, also surfaced. Even in individuals with pre-existing neutralizing antibodies, clinical trials employing Onyx-015 have shown promising results in a variety of cancer patients.

The safety of mixing Onyx-015 with gemcitabine has been confirmed by researchers Among individuals with pancreatic cancer undergoing Phase I studies [7]. Presently, research has shown that certain adenoviruses, such as ONYX-015, have proven to be successful in treating breast cancer [8]. In 2012, Ad3-hTERT-E1A was especially used in studies by Hemminki et al. to target cancers that are resistant to chemotherapy. They also provided a report on the safety and possible effectiveness of this approach. Each of the five breast cancer patients exhibited indications of potential anticancer effects, and two patients who were administered trastuzumab at the same time had a prolonged survival period [9]. A study conducted in 2016 explored the possibility of using oncolytic adenoviruses to produce antibodies locally for the treatment of HER2-positive cancer. The study revealed the significant potential of recombinant adenoviruses. HER2, a receptor for human epidermal growth factor, is frequently overexpressed in prevalent malignancies affecting women, such as breast cancer [10]. Trastuzumab is a monoclonal antibody that has been humanized to have a strong affinity for the extracellular domain of HER2. The research team developed a modified adenovirus, called Ad5/3-Δ24-tras, which was intended to specifically target and eliminate cancer cells[11]. This modified virus was engineered to produce and release trastuzumab, an antibody used in cancer treatment, in a manner that was dependent on its ability to kill cancer cells[11]. Ad5/3-Δ24-tras treatment yielded favorable outcomes in HER2-positive N87 gastric cancer xenograft mouse models [11]. The therapy effectively suppressed the growth of the tumor and enhanced the levels

of antibodies in the immediate vicinity [11]. The results indicate that Ad5/3-Δ24-tras, by combining the localized presence of trastuzumab with the virus's capacity to kill cancer cells, improves the effectiveness of treatment in living organisms and stimulates the immune system to fight against HER2-positive cancer. This technique shows great potential as a treatment option [11]. The information clearly demonstrates the enormous potential of adenoviruses in the treatment of breast cancer.

2.2 Herpesvirus

The virus known as Herpes simplex virus (HSV) possesses an outer envelope and a genome made up of two connected components of DNA, one long and one short, that are arranged in a double-stranded structure. Within the nucleus of infected cells, replication takes place. HSV can act as a carrier for delivering cancer-killing properties and can produce several offspring particles when cells are destroyed. The method by which HSV enters cells is complex and includes a variety of interrelated systems. The cell membrane contains distinct regions of heparan sulfate produced by 3-O-sulfotransferases, which can bind to viral glycoproteins such as gB, gC, and gD of HSV. Once the viral gB and gC glycoproteins link to the glycosaminoglycan (GAG) chains on the cell surface, they specifically bind to heparin sulfate. This interaction allows the virus to localize and attach to the cell surface. The gD glycoprotein then attaches itself to certain receptors, such as nectin-1 and nectin-2, on the cell's outer membrane. These receptors are members of the cell adhesion protein family. They are capable of causing the viral nucleocapsid to enter the cytoplasm by fusing the viral envelope with the cell membrane. However, the nectin-1 receptor can also engage in other routes on separate cells, enabling endocytosis as a means of viral entry rather than membrane fusion [12]. This indicates that HSV has the potential to redirect its activity toward other receptors.

For more than a decade, oncolytic herpes simplex virus type 1 (HSV-1) has been a primary focus of oncolytic virotherapy research. This virus was generated utilizing homologous recombination by taking infectious DNA from wild-type HSV-1 KOS/Dluc/oriL that expresses luciferase. This genetically modified virus has an increased ability to infect cells. It can evade antibodies that target the herpes simplex virus (HSV), making it a significant tool in the field of research.

In human studies, talimogene laherparepvec (T-VEC) has paved the road for the research of oncolytic viruses (OVs). Because T-VEC has demonstrated efficacy in Phase I, II, and III clinical studies, regulatory agencies, including the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA), have approved it for the treatment of cancer, including melanoma. [13,14]. T-VEC is produced through the genetic modification of HSV-1, where two GM-CSF genes are introduced, and the ICP34.5 and ICP47 genes are deleted. The objective of this modification technique is to restrict viral replication within the tumor by suppressing the ICP34.5 gene, enhance the presentation of antigens by eliminating the ICP49 gene, and stimulate the recruitment and development of the immune system through the GM-CSF gene. These changes increase the virus's ability to trigger an immune response that targets the malignant cells.

A Phase I study of T-VEC was conducted in 2006 on a cohort of thirty patients with various cancer types, including fourteen cases of treatment-resistant breast cancer [15]. The individuals were categorized into two distinct categories. Within the group that received a single dose, one patient with breast cancer showed no progression of the disease. In contrast, a different breast cancer patient, despite having other tumors, saw the complete removal of widespread infiltration of breast cancer in the skin two weeks after the injection [15]. This improvement continued until the completion of the trial. Within the group receiving multiple doses, two patients with melanoma exhibited stable disease. In comparison, two patients with breast cancer experienced stable disease specifically at the treated site but experienced disease progression at other sites [15]. The clinical examination revealed a reduction in the size and shape of the injected lesions and the surrounding areas [19]. In summary, the trial unequivocally demonstrated T-VEC's safety and efficacy in the treatment of breast cancer.

Herpes simplex virus type 1 (HSV-1) is a weaker kind of HF-10, which is a naturally occurring variant caused by several gene deletions, most notably UL43. Similar to T-VEC, HF-10 has demonstrated exceptional oncolytic capabilities against malignant tumors. HF-10 was given to animal models with disseminated or subcutaneous melanoma either through intraperitoneal or intratumoral administration in a laboratory environment. The results indicated that the HF-10 oncolytic virus effectively treated melanoma in mice models. Additionally, injecting HF-10 directly into the tumor also triggered a widespread antitumor response throughout the body [16].

A pilot study using HF-10 was carried out in 2006 by Hideto Kimata et al. on six patients who had metastatic breast cancer that had spread to the skin or subcutaneous tissue. Each patient received an injection of HF-10 suspension with varying virus dosages or sterile saline into their separate nodules for three consecutive days [17]. The findings demonstrated that all patients exhibited a favorable response to intratumoral injections of HF-10, with cancer cell mortality rates surpassing 30% [17]. This initial investigation determined that HF-10 demonstrated both safety and efficacy in treating metastatic breast cancer. Six patients with recurrent breast cancer were includ-

ed in a different clinical study that found an increase in CD8+ T cells [18]. Herpes simplex virus type 1 (HSV-1) serves as the origin of G47Δ, an oncolytic virus. According to recent research, G47Δ may effectively eradicate several types of breast cancer cells and selectively target cancer cells that are resistant to paclitaxel [19]. Additionally, it can be utilized in conjunction with paclitaxel [20].

2.3 Vaccinia Virus

The vaccine virus, or VV, is the first virus used to deliver vaccinations and has undergone much research and development in the biomedical area to function as an oncolytic virus. Like the two previously reported oncolytic viruses, this virus is similarly enclosed and has a linear double-stranded DNA. As previously noted, the specific cell type involved in the herpes simplex virus infection determines the viral entry method. Likewise, the manner in which VV enters host cells is similar to that of the herpes simplex virus. It can take place at the plasma membrane or trigger endocytosis when exposed to low pH circumstances. The distinction resides in its ability to utilize two distinct pathways within the same cell type. Upon entering the cell, VV undergoes the process of DNA replication in the cytoplasm. The organism depends on its own encoded proteins as well as proteins from the host cell to carry out various functions over the entire lifecycle of the host cell. This facilitates the organism's ability to generate progeny within the cytoplasm of the host cell. The construction of VV commences approximately 5-6 hours following infection. Currently, two contagious types are being produced. The virus comes in two flavors: extracellular enveloped virus (EEV) and intracellular mature virus (IMV). The EEV form has a unique outer membrane that encapsulates the IMV. The latter is more effective in spreading, and its membrane appears to have developed a "silencer" that inhibits the activation of signal transduction when it enters cells. Vesicular stomatitis virus (VV) is highly suitable for oncolytic virotherapy because of its excellent safety record, potent infectivity, and ability to accommodate large foreign DNA segments. The properties above render it a compelling candidate for oncolytic viral therapy.

Within the field of breast cancer research, VV has demonstrated noteworthy accomplishments as an oncolytic virus when tested on several types of cells. The VV Western Reserve strain (VVWR) is widely recognized as the most powerful in treating different types of malignancies [21]. Researchers have identified a mutant form called VVDD, which has been double-deleted (VGF/TK) and has been found to have a high level of safety according to VVWR. While they can be replaced in tumor cells, the VGF and TK proteins are necessary for viral replication in normal cells. Preclinical investigations have shown that VVDD has exceptional tumor-specific replication in both rodent and primate models, suggesting its potential for advancement in clinical settings [22]. VVDD (JX-929) is a mutant strain of the WR virus that has been used as the first VV vector in a phase I clinical experiment. Seventeen individuals with various cancer diagnoses, including four cases of breast cancer, were included in this experiment. The breast cancer patients underwent intratumorally injections of VVDD at a dosage of 3x107 PFU and showed good tolerance to the treatment [23]. There was only one patient who had severe discomfort at level 3, but it went away within 48 hours [23]. While no notable therapeutic advantages were detected in these individuals, there was a considerable observation of tumor-specific replication of VVDD, suggesting its potential for targeting malignancies [23]. GLV-1h153, which originates from the LIVP strain, is potentially the initial oncolytic vaccinia virus that has been demonstrated to include the hNIS gene [24]. It has demonstrated notable accomplishments when used in conjunction with other therapeutic approaches. Previous studies in both laboratory and live creature settings have demonstrated that GLV-1h153 increases the presence of hNIS in triple-negative breast cancer (TNBC) cells. This, in turn, heightens the responsiveness of tumor cells to radioactive iodine treatment [25]. As GLV-1h153 and 131I were used together, the rate of tumor regression increased significantly—six times—as compared to when GLV-1h153 was used alone [25]. The Wyeth strain was used to create the first oncolytic poxvirus product, which is referred to as Pexa-Vec or JX-594. This novel virus contains transgenes that encode both lacZ and granulocyte-macrophage colony-stimulating factor (GM-CSF). The virus can stimulate the host immune system to produce a tumor-fighting response thanks to GM-CSF. Studies have shown that administering low doses of JX-594 (less than 1 PFU/cell) can effectively destroy many types of tumor cells, including those found in breast cancer [26]. JX-594 with cyclophosphamide is now being tested in phase I/II clinical research (NCT02630368) to determine its efficacy and safety in patients with advanced soft tissue sarcoma and advanced breast cancer. Furthermore, scientists have developed many strains, including VG9-IL-24, VV-GMCSF-LacZ, and PANVAC-VF, among others, and evaluated their safety and effectiveness in breast cancer [27-29]. Patients treated with the PANVAC vaccination in conjunction with docetaxel had a median progression-free survival (PFS) of 7.9 months, according to the results of a phase II clinical study. This notable outcome marks a twofold increase compared to the control group treated solely with docetaxel, who had a PFS of 3.9 months [29]. Such a substantial improvement in PFS underscores the promising potential of the extensive poxvirus family as an oncolytic virus.

2.4 Other Oncolytic Viruses

In addition to DNA oncolytic viruses, certain RNA viruses

have also played substantial roles in oncolytic virotherapy for breast cancer, including reoviruses and the measles virus.

In a laboratory study, reovirus was utilized to infect six different established breast cancer cell lines, which showed reduced sensitivity to infection compared to normal breast cell lines used as controls [30]. On the seventh day of infection, more than half of the cancer cells were destroyed through lysis [30]. Researchers subsequently used core biopsy samples from breast cancer patients with primary invasive ductal carcinoma to induce the growth of detectable tumors in the mammary fat pad of NOD/SCID mice with compromised immune systems. Subsequently, the mice were subjected to reovirus treatment. Notably, the number of cancer stem cells (CSCs) within the tumors decreased in tandem with a significant decline in the proliferation of tumor cells [31]. This discovery implies that reovirus can specifically target and invade these cancer stem cells (CSCs). This represents a significant milestone in medical research as it is the first time that tumors derived from solid human cancer samples have been effectively treated in a mouse model utilizing reovirus. This achievement holds great importance in the field of clinical medicine. According to a 2019 study, triple-negative breast cancer (TNBC) cells showed greater DNA damage and higher levels of type III interferon (IFN) when a DNA topoisomerase inhibitor and reovirus were combined [32]. The combined therapy demonstrated a synergistic impact, leading to increased killing of TNBC cells. This indicates that combination therapy has the potential to be a successful treatment method for TNBC.

In a separate study, researchers noticed that within two days of administering MV-GFP (a genetically modified measles virus that produces green fluorescent protein), all MDA-MB-231 cells (a specific type of human breast cancer cell) in a single-layer culture were infected. Following the measles virus infection, cell death occurred within 72-96 hours [33]. Through in vivo investigations, it was observed that administering MV-GFP through repeated intravenous injections in mice with late-stage breast cancer resulted in a significant 45.5% increase in survival time. This led to a prolongation of survival from 22 days to 32 days. Furthermore, there was a noticeable postponement in the occurrence of malignant pleural effusion [33]. This study presented preliminary evidence that the use of measles virus-based therapy could improve survival rates and reduce pleural effusion in a model of invasive breast cancer xenograft. Moreover, a current phase I clinical research (NCT04521764) is examining the safety profile and ideal dosage of MV-s-NAP, a modified measles virus, in patients with invasive breast cancer that has spread to other regions of the body. In a separate investigation, scientists discovered that MV-GFP, a measles virus that can produce green fluorescent protein, resulted in complete infection of MDA-MB-231 cells, a human breast cancer cell line, within two days of vaccination in a single layer culture. The infected cells experienced cell death between 72 and 96 hours after the measles virus infection.

3. Summary

To summarize, oncolytic viral therapy offers a revolutionary method for combating breast cancer. Oncolytic viruses, such as ONYX-015, have been proven effective in treating several types of cancer, including breast cancer. These viruses show promise in improving the overall well-being of cancer patients. Their low occurrence of adverse effects and capacity to target issues like pleural effusion have demonstrated encouraging results in both clinical trials and preclinical models, highlighting the significance of investigating new approaches to relieve patient distress. The current research, demonstrated by phase I clinical trials using oHSV-1 expressing HER2, showcases the adaptability and effectiveness of these viral vectors in selectively targeting cancer markers. Oncolytic viruses, in conjunction with prospective combination medicines, are driving us towards a new age of tailored and efficacious treatment for breast cancer. Collaboration between academics, doctors, and pharmaceutical corporations is crucial for effectively converting these promising research discoveries into medicines that have a significant influence on clinical practice. As we further understand the intricacies of oncolytic viral therapy, inventive solutions provide the potential to provide hope and enhance treatment outcomes for individuals with breast cancer.

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