REVIEW

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CURRENT DEVELOPMENT OF VIROTHERAPY IN BREAST CANCER: A BRIEF REVIEW

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Abstract. *Breast cancer is the cancer with the greatest incidence in the world by 2020. This cancer has a high mortality rate, has the capability of metastasizing, and causes damage to important organs of the human body. Therefore, a lot of studies have been done to find the best therapy to overcome this problem. However, cancer has various special abilities that make it survive and continue to invade its host body, for example, the ability to evade its host immune system by several mechanisms. One of the potential cancer therapies is virotherapy. Virotherapy is a therapeutic method using viruses to destroy cancer cells. Several mechanisms can be provided by viruses, such as stimulating the host immune system and inducing apoptosis of cancer cells. Especially for breast cancer, there are 4 groups of viruses based on their genome that have oncolytic capability, such as the dsDNA, dsRNA, + ssRNA, and -ssRNA groups. Currently, there are several therapeutic virotherapy-based modalities for breast cancer that are in clinical trial phases. Each trial has shown positive results in developing virotherapy for breast cancer.*

Key words: *breast cancer, virotherapy, potential therapy, immunotherapy, viruses*

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INTRODUCTION

Cancer is a disease characterized by massive and uncontrolled cell development [1]. One classification of cancer is solid cancer, which is cancer that develops in solid organs. One common example of solid cancer is breast cancer [2]. Breast cancer is a malignant condition of the breast and the disease has become a major problem worldwide [3]. This cancer can affect both men and women [4, 5]. In 2020, breast cancer accounted for the newest cases in the world among other cancers, at 11.7% with an estimated more than 2 million people diagnosed. Breast cancer also caused 6.9% of all cancer deaths in 2020 [3].

Breast cancer is influenced by various factors in its occurrence and progressiveness [6]. Risk factors that affect breast cancer include family history, hormonal activity, lifestyle, aging, gender, and other factors that cause genetic mutations [7]. Breast cancer is also capable of metastasizing and can cause wider problems in several organs, such as the bones, lungs, liver, brain, and other organs [8]. According to National Cancer Institute (NCI) data taken from women diagnosed with breast cancer in 2010-2016 based on SEER (Surveillance, Epidemiology and End Results) stage, the 5-year relative survival rate for localized cancer is 99%, for regional stage is 86%, and for distant stage is 28% [9]. This also shows that breast

cancer is a dangerous and increasingly threatening disease [10].

Because of this condition, various parties are currently trying to develop the main mechanism to overcome this problem. However, the progress to find an effective therapy for cancer, especially breast cancer, is difficult. This is due to many things, the most important of which is due to the special ability of cancer itself, one of which is the ability to evade the immune system and cause resistance to many therapies [14, 15]. One therapy that is currently being developed is virotherapy, which utilizes viruses to treat cancer, including breast cancer. Viruses are used to stimulate the body's system to form antitumoral immune responses [13]. Research into using viruses to treat various cancers has been conducted over the past 40 years, but complicated genetic and molecular customization has been a bottleneck in some of the processes. There are many advantages of this therapy which is also a promising therapy for cancer patients including breast cancer [16, 17]. This review article aims to evaluate briefly the current development of virotherapy in breast cancer.

VIROTHERAPY IN BREAST CANCER

Pathogenesis and Signaling Pathways Associated with Breast Cancer

The emergence and progression of breast cancer is influenced by several signaling pathways. In normal cells, cell proliferation and differentiation are tightly controlled and regulated by specific signaling pathways [16]. However, in cancer cells, there are mutations in some genetic molecules that cause cells to enter other signaling pathways and develop into abnormal cells [17]. In cancer in general, 4 classes of regulatory genes are targets of genetic damage, namely proto-oncogenes, tumor suppressor genes, cell death regulatory genes, and DNA repair genes [5, 18].

Some several pathways and mutations lead to breast cancer. In virotherapy, one of the most frequently utilized tumorigenesis pathways is the Human Epidermal Growth Factor Receptor 2 (HER2) signaling pathway. HER2/NEU is a type of epidermal growth factor receptor which is a receptor tyrosine kinase. This receptor consists of extracellular parts such as ligand-binding domain, transmembrane domain, and intracellular domain. It is a receptor that is expressed in normal tissues and some cancer cells. When a suitable ligand is present, this receptor will be activated by forming dimers and affecting other signaling pathways. Pathways that will then be activated include the mitogen-activated protein kinase (MAPK) pathway and also the phosphatidylinositol 4,5-bisphosphate 3 kinase (PI3K) pathway. Activation of these pathways will lead to cell growth [19-22].

In breast cancer, due to exposure to various carcinogenic agents, there are changes in genes encoding the formation of HER2, one of which is at the TFAP2C locus. In addition, changes in HER2 expression are also caused by epigenetic influences, namely DNA methylation and histone modification. This causes HER2 amplification resulting in overexpression and excessive proliferation of breast cells that develop into cancer [20, 23].

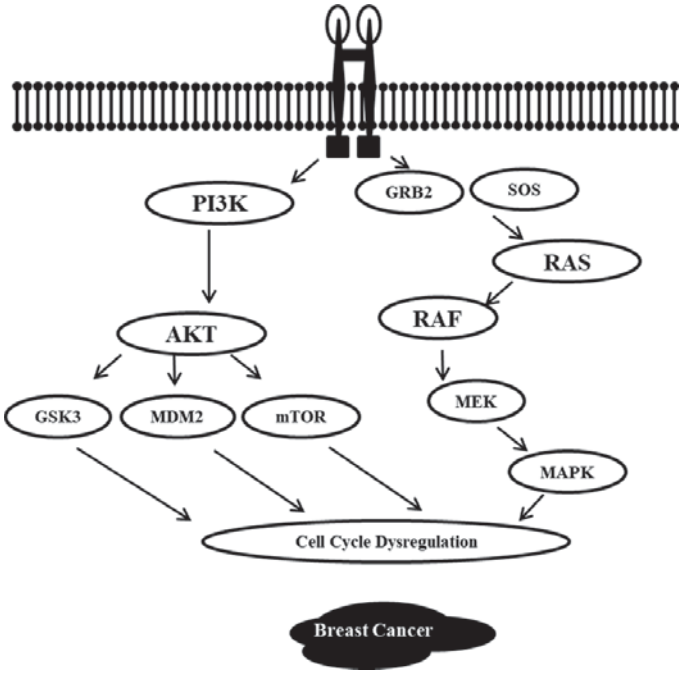

Fig. 1. Human epidermal growth factor receptor 2 (HER2) signaling pathway in breast cancer [19-22]

Characteristics of Cancer Cells

In general, the 10 hallmarks of cancer comprise biological capabilities acquired during the multistep development of human tumors, namely: evading the growth suppression system, unlimited replication, causing inflammation, invasion, and metastasis, genomic instability and mutation, being able to induce angiogenesis, evading apoptosis, re-regulating the body's energy utilization, maintaining pro-cancer signals, and evading the immune system. Of these ten markers, virotherapy is most often used to overcome cancer's ability to evade the host immune system.

Under normal conditions, the body already has several antitumor-effector mechanisms. These mechanisms involve several immune cells, 3 of which are cytotoxic T lymphocytes, natural killer (NK) cells, and macrophages. Cytotoxic T lymphocytes in humans may be able to act as antitumors caused by viruses, such as tumors caused by human papilloma virus (HPV). However, to be able to recognize and function against certain antigens, an antigen must be able to express MHC class I (Major Histocompatibility Complex) molecules which will then be recognized by these CD8+ T cells. NK cells are the cells that are at the forefront of defense in destroying tumors. NK cells are differentiated cells from lymphocyte cells that have two types of receptors, namely inhibitory receptors and activation receptors. Foreign cells that successfully express MHC class I will be recognized by inhibitory receptors. Meanwhile, if there is DNA damage, the cell has an infection or the cell is under stress, it will be detected by NK cell activation receptors. Thus, if tumor cells do not express MHC class I, they can still be recognized by NK cells. Macrophages can provide cytotoxic effects to help other immune cells fight tumor cells. However, these cytotoxic M1-type macrophages need to be activated through the classical pathway. To be activated, an antigen must be able to express IFN-γ then M1 will release molecules that support it to eliminate the foreign agent [5, 24].

However, cancer cells have several characteristics that allow them to evade destruction by the immune system. These characteristics include:

Selective growth of antigen-negative variant

In the development of tumor cells, some immunogenic molecules will be eliminated which also causes the immune system to be unable to recognize them.

Loss or reduced expression of MHC

Tumor cells have the ability to not express normal amounts of MHC class 1 molecules so cytotoxic T lymphocytes are unable to recognize them. However, this condition also leads to the activation of NK cells through their activating receptors.

Immunosuppression

Tumors may also express molecules that lead to decreased immunity. One of these is TGF-β, a potent immunosuppressant molecule secreted by tumor cells in large amounts [25].

Antigen masking

Failure of tumor cell antigen recognition can be caused by the closure of the antigen. One of the things that can block access to antigen recognition is the external glycocalyx layer produced by tumor cells.

Reducing T cell-stimulating molecules

To be activated, T cells require stimulation from various molecules, mainly immunoglobulin superfamily (IgSF) and tumor necrosis factor receptor superfamily (TNFRSF) molecules. Unfortunately, cancer can reduce the expression of these molecules [5, 26, 28].

Overview of virotherapy

Research into using viruses as anticancer agents has started a long time ago. Viruses can reproduce well in living cells. However, some viruses have a special ability to show attraction to tumor cells or what is known as oncotropic viruses. These viruses include reoviruses, parvovirus H-1, Vesicular Stomatitis Virus (VSV), Newcastle Disease Virus (NVD), and others [15]. These viruses generally do not have severe clinical symptoms when infecting

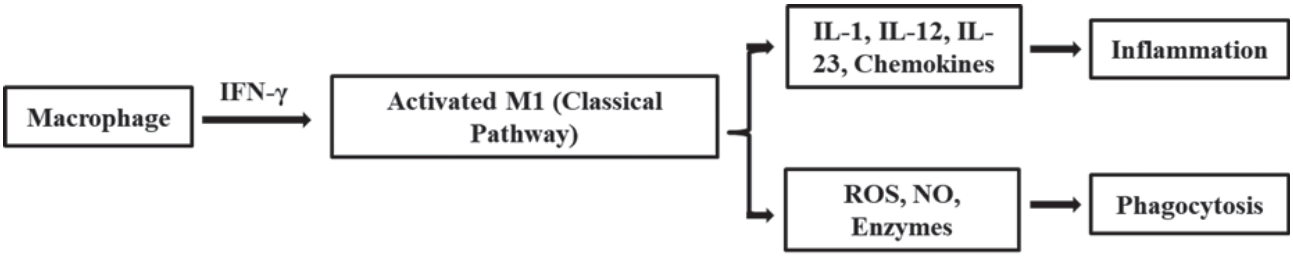

Fig. 2. Macrophage (M1) activation via the classical pathway [5]

humans. The special virus will then be engineered by targeting transcription and transduction so that it can specifically infect and kill cancer cells so that normal body cells are not destroyed as well [28]. In its development, it is explained that there have been 3 generations of using oncolytic viruses as cancer therapy based on how it works.

Cancer cells can evade the immune system in various ways as they evolve and mutate. However, in a review written by Russell SJ. et al, in the stage of preparing to evade the body's immune system, cancer cells will disable their antiviral mechanisms, for example, the interferon pathway which makes the cells vulnerable to viruses [27]. This gap is then used as an opportunity to enter the virus into tumor cells so that it can specifically attack and replicate in tumor cells without damaging normal cells. This is how first-generation oncogenic viruses work. Examples of viruses used include reovirus, vesicular stomatitis virus (VSV), and Newcastle Disease Virus (NDV) [28]. Second-generation oncogenic viruses utilize genetic engineering so that they can specifically recognize certain cancer cells. Examples of viruses in this generation such as Herpes Simplex Virus (HSV), measles virus, poliovirus, etc. have been genetically altered to be selective against cancer [29]. It is known that there are many obstacles for viruses to be able to specifically activate the immune system to respond to cancer, so the second-generation oncolytic virus is armed (external virulence factor) in the form of transgenes to activate antitumor immunity and is known as the third generation oncolytic virus [30, 31]. When the virus has entered and infected cancer cells, it will form a microenvironment consisting of infected cancer cells. The viral antigens, Pathogen-Associated Molecular Patterns (PAMPs) will be recognized by Intracellular Host Pattern Recognition Receptors (PRRs) which will cause activation of the type I IFN signaling pathway. This leads to the activation and recruitment of inflammatory cells such as macrophages, neutrophils, NK cells, and others that cause an inflammatory response in the virus-infected area. In addition to eliminating the virus, inflammation will destroy the microenvironment created by the viral infection. This will lead to the elimination of cancer cells [32, 33]. In addition, the viral microenvironment will also cause the activation of adaptive immune responses from B cells and T cells that will form an antitumoral system so virotherapy is a promising method for immunotherapy [34, 35].

Virotherapy in Breast Cancer

Currently, many virotherapy-based modalities are being developed for breast cancer. Some of these modalities are undergoing clinical trials before they can be used generally. Here is a list of such therapies.

Based on the Baltimore classification, viruses are grouped into 7 groups based on their genomes. Various studies have been conducted on all of these groups to see the oncolytic effects of viruses that can be used as candidates to treat breast cancer. Of the 7 groups, the viruses that have been studied to have opportunities for breast cancer therapy are viruses from group I (double-stranded DNA viruses), group III (double-stranded RNA viruses), group IV (single-stranded RNA viruses – positive-sense), and group V (single-stranded RNA viruses – negative-sense).

Group I viruses (double-stranded DNA viruses)

Herpes Simplex Virus Type 1 (HSV-1)

HSV-1 has long been investigated and is a strong candidate for virotherapy in a wide variety of tumors. The most well-known modification of this variant is Talimogene laherparepvec (T-Vec HSV-1), a viral product that has been approved by the Food and Drug Administration (FDA) as a therapy for melanoma [36]. HSV-1 variants for breast cancer are currently undergoing various stages of clinical trials. Based on previous research, there are several mechanisms for modifying HSV-1 to treat breast cancer.

Talimogene laherparepvec itself is currently undergoing phase 1 clinical trials for breast cancer. One of the reviews explained that T-Vec has a deletion of 2 genes, namely ICP34.5 and ICP47. Deletion of ICP34.5 results in a virus that is selective against breast cancer

T**able 1.** Clinical Trials of Virotherapy-Based Breast Cancer Therapy.

Virus	Disease	Phase	Status	ID
Ad3-hTERT-EI A (Adenovirus)	Solid tumors	I	Completed	PMID 22871667 [37]
HF10 (HSV)	Breast cancer, squamous cell carcinoma of the skin, melanoma	I	Completed	NCT01017185
Reolysin (Reovirus)	Breast cancer metastasis	II	Finished	NCT01656538
MG1MA3 (Maraba virus)	Solid tumor metastasis	I	Recruitment	NCT02285816
Talimogene Laherparepvec (HSV)	Breast cancer	I	Recruitment	NCT02779855
PVSRIPO (polio virus)	Stage II-IV Triple Negative Breast Cancer	I	Not yet recruiting	NCT03564782

cells and prevents infection of the nervous system. The ICP34.5 gene is deleted and then replaced with a gene encoding Granulocyte-Macrophage.

Colony-stimulating factor (GM-CSF). GM-CSF is one of the cytokines for the hematopoietic growth factor. It can induce proliferation, differentiation, and activation of dendritic cells and macrophages as well as cytotoxic T cells [37]. In addition, GM-CSF can recruit neutrophils and other proinflammatory modulators. In addition, deletion of the ICP47 gene can result in the presentation of antigens that can be recognized by the immune system [38, 39]. This will lead to an inflammatory response and elimination of the virus as well as destruction of the viral microenvironment [33].

Some HSV-1s are modified to retarget receptors that are overexpressed in breast cancer, such as human epidermal growth factor receptor 2 (HER-2). Modifications were made by forming oHSV R-LM249 through the insertion of a mediator glycoprotein (gD) containing the anti-HER-2 single-chain antibody trastuzumab in the viral envelope. This variant can affect and retarget HER-2 [40]. Several vectors of HSV-1 have been combined with various proteins, enzymes, or other anticancer drugs to increase their effectiveness. One of them is the insertion of the 15-hydroxyprostaglandin dehydrogenase (15-PGDH) gene which encodes an enzyme capable of breaking down tumors by promoting prostaglandin E2 (PGE2). The presence of PGED will cause an immune response triggered by viral infection in primary tumor cells [41].

Adenovirus

The human adenovirus (Ad) is the most studied virus in breast cancer research. There are several pathways affected by Ad that lead to impaired cancer cell function. The virus targets cancer cells, attaches to their receptors, enters the cancer cell, and replicates to disrupt processes within it. Ad type 5 (Ad5) targets cells through attachment to the Adenovirus receptor (hCAR) found on the cell surface. However, research shows that breast cancer cells have a low amount of hCAR, so the influence of the virus is less strong against breast cancer cells and the destruction caused by adenovirus is also not as great. Due to these conditions, adenoviruses with the concept of third-generation oncolytic viruses are applied where the virus is armed with many other molecules to increase its effectiveness in affecting the destruction of cancer cells. In addition to the local development of cancer, these additional molecules are also used to prevent some breast cancer metastasis so that the influence of cancer on the body can be suppressed.

Group III (double-stranded RNA viruses)

Double-stranded RNA (dsRNA) viruses are a group of pathogenic viruses that have an icosahedral structure and contain many different RNA molecules encoding one or more viral proteins. Infection of the dsRNA genome will be transcribed by the cell into mRNA that is translated and replicated. The protein formed is the infecting agent. In breast cancer therapy, reoviruses are the most frequently studied group of viral dsRNAs. In general, these viruses are not pathogenic to humans. However, the type 3 strain of reovirus was found to have oncolytic properties on breast cancer cells. The selective and potent oncolytic properties of type 3 reoviruses are attributed to aberrations in cancer cells, most notably the activation of the Ras oncogene signaling pathway. These aberrations lead to increased expression of Ras which can then be recognized and infected by this virus. Unfortunately, the mechanism and life cycle of this virus is not fully understood [29, 52].

Table 2. Adenovirus modification for breast cancer therapy

Modified	Target	Reference
Ad5 fiber modification with Ad3 and D24-GM-CSF insertion	● Enhancing viral affinity to breast cancer cells by damage to the p16/Rb pathway ● Specific immunotherapy	[43]
Granulocyte Macrophages Colony Stimulating Factor (GM-CSF) gene insertion	Forms a microenvironment in cancer cells Recruits lymphocytes to the area	[48, 49]
KISS01 molecule insertion	Activating GPR54 receptor in breast cancer causes: a. Effects of tumor suppression b. Prevents breast cancer metastasis c. Breast cancer apoptosis	[46, 47]
Addition of IL-24 to CNHK600-IL 24	● Reduces metastasis ● Causes apoptosis induced by IL-24	[48]

Group IV (single-stranded RNA viruses – positive-sense)

One of the viruses from group IV that is under intensive research as a cancer therapy is the polio virus. One study showed its effectiveness in the destruction of cancer cells. This therapy is similar to the polio vaccine, using a virus that is unable to invade normal tissue [48]. The effect is obtained by combining the polio virus and recombinant rhinovirus into a polio-rhinovirus chimera (PVSRIPO). Interestingly, PVSRIPO can enter cancer cells through the polio virus receptor, CD155, which is overexpressed in solid cancers including breast cancer. In one study, it was found that this virus causes cytotoxic effects on cancer cells and also found neutrophil invasive activity in tumor cells in response to PVSRIPO so this virus is an agent being developed for cancer immunotherapy [50].

Group V (single-stranded RNA viruses – negative-sense)

Various studies have been conducted on these group V (-ssRNA) viruses and several potential virus types with high oncolytic ability have been found, one of the most famous being the maraba virus. Currently, a Maraba virus-based breast cancer virotherapy is undergoing clinical trials, MG1MA3. Maraba is a virus from the Rhabdoviridae family that rarely gives significant clinical manifestations in humans. From a screening of 20 rhabdovirus strains, Maraba showed the most extensive oncolytic ability and has been tested on human cells and mouse cells with various types of cancer, including breast cancer [48].

To be able to increase its specificity by attacking only malignant cells, some genetic engineering was carried out on the Maraba virus. Two mutations were L123W and Q242R substitutions in the M and G protein sequences, which became known as MG1. MG1 cannot invade healthy cells due to its inability to block the Interferon type 1 signaling pathway, but this pathway is abnormal in cancer cells which allows the virus to infect them. This mutant virus shows the ability to replicate faster with higher cancer cell-killing ability. After 5 days of MG1 infection, there will be a huge increase in NK cell effectors that will secrete IFN-γ which will cause the activation of humoral and adaptive immune responses. Recent studies have shown surprising results that MG1 can create a long-term immune response making it a potential candidate as a future cancer therapy [48, 51].

Current and Future Perspective of Oncolitic Virotherapy Combination

The combination of virotherapy with standard cancer therapy has been shown to be effective in improving clinical outcomes in subjects receiving therapy, both in breast cancer and other types of cancer. Breast cancer can become a highly invasive disease that frequently metastasizes. In an *in vivo* study on breast cancer by Deng et al. (2022), it was observed that the number of metastatic tumors in the lungs significantly decreased after treatment with mVG161 in combination with PTX. VG161 is a genetically modified herpes simplex virus (HSV) that includes IL-12, IL-15, IL-15RA, and a fusion protein (TF-Fc), capable of inhibiting PD-1/PD-L1 interactions. This study demonstrated that VG161 enhanced tumor infiltration by CD4+, CD8+ T cells, and NK cells, as well as promoting the production of proinflammatory cytokines TNF-α and IFN-γ, contributing to an altered tumor microenvironment (TME) that favors immune-mediated tumor clearance. TNF-α and IFN-γ are crucial proinflammatory cytokines with strong antitumor properties that further amplify CD4+ T cell activation [52]. These findings are consistent with results from Zhang et al. (2024), who explored oncolytic therapy using OH2 in combination with anti-PD-L1 for colorectal cancer. This combination led to increased infiltration of CD4+, CD8+ T cells, and B cells, and an improved inflammatory response, transforming the TME from an immunologically “cold” to a “hot” state, likely due to the release of tumor-associated antigens and damage-associated molecular patterns (DAMPs) that enhanced immune activation [53]. The summary of virotherapy combination with standard therapy in several types of cancer can be seen in Table 3. below.

Zhang et al. also identified a significant reduction in genomic gene mutations, such as the loss of TP53mut, missense mutations, frameshift deletions, nonsense mutations, in-frame deletions, and splice site mutations after oncolytic virus OH2 and anti-PD-L1 therapy. Patients with TP53 mutations typically have a poor prognosis. However, patients with non-small cell lung cancer harboring co-mutations of TP53 and KRAS showed a favorable response to PD-L1 inhibition, while those with KRAS mutations alone did not benefit similarly. In triple-negative breast cancer models with TP53 mutations, restoring TP53 activity can sensitize the PD-L1/PD1 axis, promoting a more favorable TME for immune attack. Nonsense mutations in p53 mainly cause premature translation termination and result in the production of truncated, unstable, and non-functional p53 proteins, whereas missense mutations generally lead to single amino acid changes and partial dysfunction. By week 6 of therapy, there was a notable reduction in missense mutations and frameshift deletions, which persisted through week 12. Furthermore, nonsense mutations,

Table 3. Current and Future Perspective of Oncolitic Virotherapy Combination

Study	Population	Intervention	Control	Outcome
Deng, 2023 [53]	Breast cancer xenograft mouse model	Oncolytic herpesvirus (VG161) with paclitaxel (PTX) (n = 8)	Vehicle, VG161, PTX monotherapy (n = 8 each group)	VG161 infection with PTX cotreatment reduce metastatic pulmonary lesion ($p < 0.05$), reduce tumor size ($p < 0.05$) compare to control and other treatment, improve the anti-tumor activity in tumor microenvironment through increasing the expression of CD8+ T cells, natural killer cells (NKs), IFN-γ, TNF-α, and CD107a on the tumor cell
Monge et L, 2023 [55]	Clinical Trial Phase I / II (Colorectal Cancer Patient)	PexaVec/ tremelimumab/ durvalumab (N=18)	PexaVec/ durvalumab (N=16)	The median progression-free survival (PFS) was 2.3 months in the PexaVec / durvalumab / tremelimumab cohort and 2.1 months in the PexaVec/durvalumab cohort. Flow cytometry showed an increase in Ki67+ CD8+ T cells during treatment.
Zhang et al, 2024 [56]	Clinical Trial Phase I (Colorectal Cancer Patient)	Oncolytic virus OH2 and anti-PD-L1 antibody LP002 (n = 4)	Before therapy "immunologically cold"	A gradual shift was observed in the patient's immune environment before and after the combination therapy of OH2 with anti-PD-L1 in CRC patients, from a "cold" to a "hot" state, characterized by increased infiltration of CD4+ T cells, CD8+ T cells, and B cells, along with an inflammatory response.
Bernstein, 2017 [57]	Clinical Trials Phase II (Breast Cancer)	Arm A Paclitaxel combined with Pelareorep (n = 36)	Arm B Paclitaxel Alone (n = 38)	The combination therapy have longer PFS (3.78 months in Arm A vs. 3.38 months in Arm B) and showed a longer median overall survival (17.4 months vs. 10.4 months in Arm B)
Chesney, 2017 [58]	Clinical Trials Phase II (Melanoma)	Talimogene Laherparepvec Plus Ipilimumab (n = 98)	Ipilimumab (n = 100)	The combination of T-VEC and Ipilimumab significantly improved the ORR, with 39% of patients in the combination arm showing tumor shrinkage or disappearance, compared to 18% in the Ipilimumab-only group.
Ye, 2014 [59]	Clinical Trials Phase II (Head and Neck Carcinoma)	Recombinant human endostatin adenovirus (E10A) + (paclitaxel and cisplatin) (n = 68)	only the standard chemotherapy regimen (paclitaxel and cisplatin) without the E10A (n = 67)	The addition of E10A improve the primary outcome of objective response rate (39.7% in the E10A group vs. 29.9% in the control group and extend the progression-free survival (7.03 months vs. 3.60 months, $p = 0.006$) with a higher disease control rate (92.6% vs. 80.6%, $p = 0.034$)

in-frame deletions, and splice site mutations were no longer detected by week 6 [52, 53].

Disadvantages and Limitations of Virotherapy

Currently, the development of virotherapy has entered the third generation, where the virus is equipped with several specialized vectors to help its effectiveness. However, many of the added vectors have not been able to penetrate solid cancers including breast cancer due to the thick physical barrier of the endothelium and extracellular matrix around the solid cancer [60]. In addition, in the immunological aspect, the virus will cause the recruitment of immune cells. However, it is very difficult to predict whether the immune cells will sufficiently reach the cancer site and whether the immune cells will successfully kill the cancer. Therefore, more research is needed to improve the effectiveness of virotherapy [60, 61].

CONCLUSION

This review shows that virotherapy can be a potential treatment approach for breast cancer. The general mechanism developed with this method is to utilize viruses as immunotherapy by entering into cancer cells and causing cell destruction. Groups of viruses based on their genomes that have been proven to be able to fight breast cancer are dsDNA, dsRNA, +ssRNA, and -ssRNA viruses. In addition to the advantages provided, there are still many limitations and weaknesses of this method so future development is highly expected.

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