Improving Oncolytic Herpes Simplex Virus for Metastatic Breast Cancer

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A steady decline in the overall number of deaths due to breast cancer since 1990 represents remarkable progress in early detection [1]. Survival rates are near 100% when the disease is localized; however, breast cancer patients that have distant metastases have a 5-year survival rate that is below 25% - a rate that has not changed over the years. There are few effective treatment options for patients with metastatic disease indicating that improved therapies are clearly needed. Emerging strategies utilizing a variety of oncolytic viral therapies have been described in the literature and clinical trials have been ongoing for many cancer types with mixed results [2]. The intent of an oncolytic virus is to complete multiple cycles of cell lysis and infection of adjacent cancer cells to eradicate a tumor while sparing normal cells. A particularly attractive oncolytic virus that has received recent attention is the attenuated oncolytic herpes simplex virus type 1 (oHSV) [3].

HSV-1 has a number of advantages as an oncolytic virus. It is widely prevalent and does not cause serious disease in most individuals. Specific anti-herpetic drugs exist if safety intervention becomes necessary. The genome has been well characterized and is amenable to genetic modifications and additions. Finally, HSV-1 infects an array of cell types, thus making oHSV a potential therapy for a variety of cancers including breast cancer. The classical method to render HSV oncolytic is the deletion of the diploid γ 34.5 gene, which encodes the primary neurovirulence factor [4]. This deletion precludes the ability of the virus to overcome cellular protein kinase R (PKR)-mediated block of viral protein synthesis, thereby rendering the virus non-replicative in quiescent cells. Tumor cells with defective PKR pathways or activated MAP/ERK kinase (MEK) remain permissive for viral replication. Several well-known oHSV including G207 [3], HSV1716 [6], and OncoVexGM-CSF [7] are based upon γ 34.5-deleted platforms. Other viral genes, including those for infected cell protein (ICP) 6 or ICP47 are often deleted or mutated in the generation of an oHSV, either in combination with or in lieu of γ 34.5 deletion [3,8]. Much of the early interest in oHSV has been directed towards their use against brain tumors and this remains an active area of investigation. However, an increasing number of preclinical studies have also shown that oHSV can be effective against breast cancer. In some cases, the complete eradication of breast cancer tumors [9] or the inhibition of metastases has been reported [10,11].

Clinical trials conducted thus far have included at least six different oHSV [3,8]. These trials have generally relied on the γ 34.5-deleted oHSV and have focused predominantly on brain tumors, although trials involving melanoma and oral squamous cell carcinoma, as well as colorectal, head and neck, pancreatic and liver cancers have also been completed or are underway. A breast cancer-specific trial has not yet been conducted; however, trials involving solid tumors have included breast cancer patients. A team of investigators at Nagoya University in Japan has performed a pilot study involving intratumoral injection of oHSV into six breast cancer patients [12]. Overall, these trials have repeatedly demonstrated that oHSV is safe to administer to patients. Temporary tumor responses and evidence of in situ viral replication have been confirmed. It has become increasingly apparent, though, that antitumor activity of oHSV must be made more robust before the full potential of this strategy can be realized.

Three main approaches have been utilized to enhance the efficacy of oHSV. In the first, an anticancer transgene is incorporated into the virus. As an example, the expression of 15-prostaglandin dehydrogenase enhanced antitumor properties of an oHSV in an immunocompetent mammary carcinoma model [13]. Other transgenes have included prodrug-converting enzymes or anti-angiogenic factors [14]. In particular, the delivery of immune-stimulating cytokines such as interleukin 12 [15,16] or granulocyte macrophage colony stimulating factor [7] drastically improve tumor responses by promoting antitumor immune activity. The second general strategy for improving oncolytic HSV is to enhance viral delivery and intratumoral spread. Examples of this approach that are intrinsic to the virus are the mutation of glycoprotein D to include a single chain antibody targeted against HER2/neu [17] and the inclusion of fusogenic mutations to enhance cell-to-cell spread [18,19]. Other examples, extrinsic to the virus, include the use of mannitol to disrupt the blood-brain barrier [20] and the use of the hypertension drug losartan to inhibit collagen I synthesis and improve the intratumoral distribution of oHSV [21]. The third major approach to enhance oHSV effectiveness includes combination of the virus with other treatment modalities. Combination of oHSV with chemotherapy can yield synergistic tumor cell killing and enhance viral replication, although a maximum benefit is achieved only when the agent selected complements the mutational background of the oHSV [22]. Small molecule inhibitors such as histone deacetylase inhibitors have been reported to enhance oHSV efficacy [22]. Viral replication has also been improved by radiation to yield synergistic antitumor effects [23,24]. It is important to note that the above approaches are not mutually exclusive and the successful implementation of oHSV will likely involve a combination of these strategies.

Combination therapies involving oHSV hold great promise for future clinical successes against metastatic breast cancer. As we learn more about the interactions between a replicating virus with the heterogeneous tumor that includes a complex microenvironment and immune system, modifications may be designed for clinical benefit with few side effects. As personalized medicine becomes a reality, it may become possible to identify those individuals with particular molecular subtypes of breast cancer that are most likely to benefit from specific oHSV combination therapies.

References


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