

# Immunomodulation as A Treatment to Breast Cancer

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**Abstract:** In recent years, breast cancer has been the leading cause of cancer death among women. Researchers are leading studies related to the breast cancer to help with progress of our understanding of cancer and exploring more efficient and less toxic therapies. Increased public awareness and advances in the preclinical proof of feasibility and clinical confirmation of have led to earlier diagnosis and novel curative therapies. Immunomodulation is an emerging treatment, which enhance the immunity against cancer cells through releasing various cytokines, expanding to gene-based treatments. Therefore, this work reviews the immunomodulation approach and its potential application when combined with other therapies (oncolytic virotherapy, radiotherapy, physical therapy).

**Keywords:** Therapy, Breast cancer, Treatment, Immunomodulation, Immune therapy.

## 1. Introduction

Breast cancer is present as a serious threat to the health and well-being of women in the United States, accounting for 30% of all new cancer diagnosis and almost 41,000 deaths every year [1] despite of the 38% decrease in the death rate thanks to the progresses made in the medical field. Therefore, novel approaches of breast cancer therapy are welcomed that lower the chance of relapse and death for this disease. In recent years, mounting evidence supports a key role for the immune system in determining response to standard therapy and long-term survival in patients with breast cancer. Data and the clinical success of immunomodulation to tumors have reignited interest in immune-based strategies for breast cancer treatment.

This review would focus on immunomodulation, as a branched approach under immune therapy, and divides it into two parts, immunomodulation being used as a stand alone therapy and in combination with other therapies, which altogether can elicit a greater immune response.

## 2. Stand Alone Therapy

### 2.1. Ex Vivo Gene Therapy

Basically, immune therapy relies on the ability of the immune system to identify and destroy tumor cells and to elicit a long lasting memory of this interaction. Under normal circumstances, however, the ability of tumor cells to trigger an effective immune response is limited. The rather poor immuno-genicity of tumor cells results in part from their weak expression of cytokines that could allow T-cell activation. In addition, tumors may also secrete immuno-suppressive molecules, which often fail to express cytokines that activate local immune responses [2]. Generally, a lack of local cytokines accounts for this poor immuno-genicity.

This problem can be addressed by introducing immunomodulatory molecules or genes into the tumor. This immunomodulatory approach of introducing cytokines genes into tumor cells is called Ex vivo gene therapy. It allows a sustained local release of cytokines capable of enhancing the intensity and quality of the immune response to tumor.

Studies in various breast tumor models have proved this sole immunomodulation to be effective. They show that the introduction into hosts of tumor cells secreting cytokines,

such as IL-1, -2, -4, -6, -7, 12, -18, as well as TNF- $\alpha$ , G-CSF, GM-CSF, or IFN- $\gamma$ , can lead to successful tumor rejection by stimulating anti-tumor responses. Rejection depends on a high level of cytokines production by the gene-modified cells and is due in part to stimulation of host anti-tumor effector response [3, 4]. In some circumstances, it allowed the complete rejection of tumor and even protected the host against subsequent challenge with unmodified tumor cells [5].

## 3. Combination

### 3.1. Oncolytic Virotherapy

Oncolytic viruses are attenuated, mutated, or benign viruses that preferentially target cancer cells and do not infect normal, non-transformed cells. Therefore, the key desirable characteristics of oncolytic viruses are the specificity for the targeted cancer cells, their potency to induce cell death and safety to avoid adverse reactions and reversion [6]. It is true that there are numerous naturally occurring oncolytic viruses exist in our body, but recently more researchers are revolving around genetically modified viruses to improve their safety, specificity, immunogenicity, oncolytic potency, and drugability [6]. And this improvement is attained by combining clinical related oncolytic viruses with one or more immunomodulating factors, letting oncolytic viruses be genetically modified.

An example of this combination is the Granulocyte macrophage—colony stimulating factor (GM-CSF) and oncolytic viruses. Using oncolytic viruses engineered to express cytokines to increase the number of antigen presenting cells at the tumor site is proved to be a solid strategy to enhance the anti-tumor effect of oncolytic viruses. T-VEC, an attenuated herpes simplex virus incorporating a GM-CSF trans gene, was granted marketing approval by FDA and EMA in 2015 for IT therapy in patients with stage 3 and 4 melanoma [7]. Similarly, a vaccinia virus engineered to express GM-CSF, JX-594, has been shown to have an enhanced capability in selectively targeting and replicating in tumor cells and has anti-tumor efficacy in both a preclinical and clinical setting [8].

### 3.2. Radiotherapy

Currently, radiotherapy is the frontline therapy for approximately 50% of all patients with newly diagnosed

cancer, alone or in combination with surgery or chemotherapy [9]. Recent advances in radiotherapy technologies and approaches have focused on limiting toxicity and on achieving greater therapeutic effectiveness. The radiation comes principally in X rays that causes the induction of DNA damage, which can result in tumor cell death.

While radiotherapy is extensively used to treat localized cancer, improved understanding of its effects on the immune system has increased interest in its potential systemic effects, particularly in combination with checkpoint inhibitors such as anti-PD1. The majority of patients either do not respond or develop resistance to monotherapy over time. Therefore, the efficacy of OX40 stimulation as an alternative immunomodulating approach in combination with radiotherapy is investigated. The investigators hypothesize that SBRT directed at metastatic breast cancer lesions will result in a systemic anti-tumor immune system response. This amplified and directed immune response could result in anti-tumor responses [10].

### 3.3. Physical Therapy

The basic mechanism of physical therapy is to induce a local acute trauma at the tumor site, thereby inducing the release of antigen presenting cells, aim to initiate an innate immune response targeting both the treated lesion as well as distinct lesions [11]. In the category of physical therapy, electrochemotherapy is most frequently playing a complimentary role with immunomodulatory therapy.

Electrochemotherapy (ECT) is based on the local application of electric pulses to deliver chemotherapeutic drugs at the tumor site. This reversible electroporation enhances the drug uptake by increasing the permeability of the cell membrane. Thereby potentiating the cytotoxicity of non-permeant chemotherapeutic drugs, such as bleomycin and cisplatin [12,13]. The cytotoxicity of ECT acts on the whole micro environment and therefore targets directly the tumor cells as well as the interwoven stromal and endothelial cells lining the tumor microvasculature. The cell death induced in these endothelial cells leads to the abrogation of tumor blood flow thereby impairing the viability of tumor cells surrounding the vessels. This results in a massive release of tumor associated antigens inducing a systemic immune reaction. This immune response can be enhanced when ECT is combined with other immunomodulatory factors, improving the antigen presentation and survival of effector T cells, such as IL-2, IL-12, GM-CSF, and TNF- $\alpha$  [13]. It has been shown that frequent administration of ECT led to an increase in the rate of complete remissions in breast cancer patients [14].

## 4. Conclusions

To sum up, in addition to immunomodulation acting as a mono approach, by combining oncolytic virotherapy, radiotherapy and electrochemotherapy with the local introduction of immunomodulatory factors, both can be achieved in potent immune response.

## References

- [1] Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. *CA Cancer J Clin* 2017; 67: 7–30.
- [2] Leroy, P., et al. 1998. Cancer immunotherapy by direct in vivo transfer of immunomodulatory genes. *Res. Immunol.* 149:681–684.
- [3] Fearon, E.R., et al. 1990. Interleukin-2 production by tumor cells bypasses T helper function in the generation of an antitumor response. *Cell.* 60:397–403.
- [4] Viret, C., and Lindemann, A. 1997. Tumor immunotherapy by vaccination with cytokine gene transfected cells. *Int. Rev. Immunol.* 14:193–212.
- [5] Golumbek, P.T., et al. 1991. Treatment of established renal cancer by tumor cells engineered to secrete interleukin-4. *Science.* 254:713–716.
- [6] Maroun J, Munoz-Alia M, Ammayappan A, Schulze A, Peng KW, Russell S. Designing and building oncolytic viruses. *Future Virol.* (2017) 12:193–213. doi: 10.2217/fvl-2016-0129
- [7] Poh A. First oncolytic viral therapy for melanoma. *Cancer Discov.* (2016) 6:6. doi: 10.1158/2159-8290.CD-NB2015-158
- [8] Parato KA, Breitbach CJ, Le Boeuf F, Wang J, Storbeck C, Ilkow C, et al. The oncolytic poxvirus JX-594 selectively replicates in and destroys cancer cells driven by genetic pathways commonly activated in cancers. *Mol Ther.* (2012) 20:749–58. doi: 10.1038/mt.2011.276
- [9] Jaffray DA. Image-guided radiotherapy: from current concept to future perspectives. *Nat Rev Clin Oncol.* (2012) 9:688–99. doi: 10.1038/nrclinonc.2012.194
- [10] NCT01642290
- [11] Locy H, de Mey S, de Mey W, De Ridder M, Thielemans K, Maenhout SK. Immunomodulation of the Tumor Microenvironment: Turn Foe Into Friend. *Front Immunol.* 2018 Dec 11;9:2909. doi: 10.3389/fimmu.2018.02909. PMID: 30619273; PMCID: PMC6297829.
- [12] Sersa G, Miklavcic D. Electrochemotherapy of tumours. *J Vis Exp.* (2008) 22:1038. doi: 10.3791/1038
- [13] Sersa G, Miklavcic D, Cemazar M, Rudolf Z, Pucihar G, Snoj M. Electrochemotherapy in treatment of tumours. *Eur J Surg.* (2007) 34:232–43. doi: 10.1016/j.ejso.2007.05.016
- [14] Schmidt G, Juhasz-Boss I, Solomayer E-F, Herr D. Electrochemotherapy in breast cancer: a review of references. *Geburtshilfe Frauenheilkd* (2014) 74:557–62. doi: 10.1055/s-0034-1368538