

Controlled Opening of the Blood-Brain Barrier to Achieve Therapeutic Access of Trastuzumab in HER2-Positive Brain Metastases

Background – The Medical Problem: The spread of cancer cells throughout the body represents the greatest threat to the survival of breast cancer (BC) patients, especially when such cells have entered the brain. These brain seeds are particularly difficult to treat. Radiation therapy is commonly used, but the extent of its use is limited by serious risks to normal brain function. Surgery is not always possible. Chemotherapeutics or targeted molecules often are unable to reach the brain lesions at high enough concentrations, because the blood-brain barrier (BBB) prevents their effective passage from the blood vessels into the brain. This problem is exacerbated because BC sometimes spreads to the brain already at early stages of the disease and goes unrecognized, providing the seeds for recurrence with poor prognosis.

The controlled, reversible opening of the BBB could be a means to allow all currently used BC therapeutics to effectively enter the brain and unfold their therapeutic impact as effectively inside the brain as they do within the rest of the body. It would end the protected sanctuary status for brain metastases. However, currently available methods to open the BBB are involved and associated with significant risks, and therefore not available in standard clinical practice.

Our Novel Approach: We are developing a novel method to open the BBB in a controlled, fully reversible fashion that is relatively easy to perform and could be widely used to treat BC patients who present with brain metastases, or are at risk of developing them. We are using NEO100, a highly purified version of perillyl alcohol, a natural compound related to limonene from the oil of citrus fruits. In our preliminary studies in mice, we discovered that arterial injections of NEO100 result in reversible opening of the BBB, without noticeable detrimental effects on the animals. The BBB of these mice remained open for about 2 hours and made the brain accessible to therapeutics coming from the blood circulation. For example, when we injected human antibodies into the tail vein of mice, we were able to detect their presence in mouse brain only after prior arterial injection of NEO100, but not in the absence of NEO100. We hypothesize that equivalent NEO100 injections, via catheter placement into the easily accessible femoral ('groin') artery of BC patients, will result in controlled opening of their BBB that can be employed to effectively deliver BC therapeutics to their brain lesions.

Trastuzumab (Herceptin) is a therapeutic antibody that is used with good success in women with HER2-positive BC, but, like all antibodies, it does not enter the brain very well. In a preliminary experiment, we applied this antibody to a mouse model with HER2-positive BC cells in their brains, and observed that these animals survived longer when trastuzumab was given together with NEO100. In the absence of NEO100, trastuzumab did not result in a survival benefit for these brain-metastatic mice.

Project Goals: (1) In mice, demonstrate that NEO100 reliably opens the BBB to allow entry of trastuzumab in a manner that is well tolerated and safe. (2) In mouse models of HER2-positive BC metastases to the brain, validate and extend our preliminary observation that trastuzumab unfolds superior therapeutic activity when given in combination with NEO100. (3) With the use of a 3-dimensional cell culture (in vitro) model of the human BBB, investigate how NEO100 is able to disrupt its barrier function in a non-toxic, reversible manner.

Completion of this study will provide essential proof of principle and necessary components for the assembly of an investigational new drug (IND) application to the FDA in order to obtain approval to test our novel approach in BC patients with brain lesions. We expect that the IND process can be expedited, because NEO100 has received FDA approval for anticancer clinical trials in the past, and trastuzumab already is well established.

Ultimate Applicability: If successful, our concept of BBB opening via intra-arterial NEO100 will have broad applications in medicine, and due to its relative simplicity we expect it to be widely available and performed on an outpatient basis. Based on the urgent medical need in the case of BC patients with brain involvement, we foresee that this patient group will be the first to benefit from this novel approach. Effective opening of the BBB should make it possible to treat brain metastases as effectively as any systemic disease; it therefore has the potential to substantially reduce morbidity and mortality, and perhaps even result in cures for these patients.