Theme: Pre-clinical Research and Mechanisms of Disease

Targeted radionuclide therapy with [177Lu]Lu-DOTA-trastuzumab for HER2-positive breast cancer brain metastases

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Abstract:
Background: Breast cancer (BC) is the most prevalent malignancy in women, with HER2 amplification occurring in 25–30% of metastatic cases. While HER2-targeted therapies such as trastuzumab have significantly improved patient outcomes, their efficacy in HER2+ brain metastases (BrM) is hindered by the emergence of resistance mechanisms. To address this, we investigated the therapeutic potential of trastuzumab radiolabeled with the β^--emitting radionuclide ^{177}Lu.
Methods: HER2+ BC cell lines and their brain-tropic derivatives were assessed for HER2 expression and sensitivity to trastuzumab and [177Lu]Lu-DOTA-Trastuzumab. In vivo models were established by injecting HER2+ BC cells intracardially for BrM formation or orthotopically into the mammary fat pad for primary tumor establishment. Tumor progression was monitored by magnetic resonance imaging (MRI). Non-invasive imaging of HER2 expression was performed using positron emission tomography (PET) with [^{89}Zr]Zr-DFO-Trastuzumab. Blood-brain barrier (BBB) permeability was evaluated by dynamic contrast-enhanced (DCE)-MRI. Mice with established tumors received either trastuzumab or [^{177}Lu]Lu-DOTA-Trastuzumab, and therapeutic efficacy was evaluated.
Results: Brain-tropic HER2+ cells exhibited trastuzumab resistance despite maintaining HER2 expression. In contrast, [177Lu]Lu-DOTA-trastuzumab induced significant DNA damage and potent cytotoxicity. PET imaging confirmed specific radiotracer uptake in HER2+ primary tumors and BrM. A single dose of [177Lu]Lu-DOTA-trastuzumab effectively suppressed primary tumor growth and achieved complete BrM remission in 40% of treated animals. Heterogeneous BBB permeability across brain lesions influenced radiotracer uptake and therapeutic efficacy.
Conclusion: Our findings underscore [^{177}Lu]Lu-DOTA-trastuzumab as a novel therapeutic strategy to overcome trastuzumab resistance in HER2+ BrM, offering a promising approach to improve outcomes in metastatic BC.

Keywords: HER2+ breast cancer, brain metastasis, trastuzumab resistance, targeted radionuclide therapy, lutetium-177