

## Can Cancer Brain Metastases be Treated Using Humanized Monoclonal Antibodies?

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### Editorial

Brain metastases occur in 15% of patients with metastatic breast cancer [1], challenging daily practice in medical oncology. Their prognosis is poor with a median survival of about one year [1]. Brain metastases are more frequent in women with metastatic HER2-over-expressing breast cancer, up to 53% of them [1]. This can be explained by the fact that anti-HER2 targeted therapies, highly efficient on extra-central nervous system (CNS) metastases [2], are not able to cross the blood-brain barrier.

Trastuzumab is a humanized anti-HER2 monoclonal antibody currently used for the treatment of HER2-over-expressing breast cancers [3,4]. Following intravenous administration of trastuzumab, concentrations in the cerebrospinal fluid are 300 times lower than in the serum [5], and this could explain why brain metastases occur even when other metastases are controlled by the treatment. Histological and clinical studies have shown the persistence of HER2 over-expression in tumor cells of CNS metastases [6,7].

These clinical and pathological data led us to hypothesize that intra-theal administration of trastuzumab could circumvent the lack of passage of trastuzumab from blood to brain across the blood-brain barrier, thus leading to pharmacologically efficient concentrations of the drug in the brain parenchyma.

We performed a sequential pharmacokinetic pilot study in a 36-year-old woman with metastatic breast cancer who developed HER2-overexpressing brain metastases resistant to standard treatments [8]. Under trastuzumab-based therapy, she had a 3-year durable complete response of liver metastases, but she developed brain metastases unresponsive to radiation therapy and to a new line of oral chemotherapy with capecitabine and lapatinib. With her informed consent, lumbar and ventricular reservoirs were implanted for repeated intra-theal injections of trastuzumab. We then performed a detailed pharmacological study enabling us to compare the Area Under the Curve concentration (AUC) of trastuzumab in the ventricular and lumbar cerebrospinal fluids, and in the peripheral blood. Over the first 6 weeks, a set of results confirmed that trastuzumab did not efficiently cross the blood-brain barrier from the serum to the ventricular cerebrospinal fluid. In contrast, and this was an unexpected result, the clearance of trastuzumab from the cerebrospinal fluid was very high. On the basis of reported pharmacokinetic studies of trastuzumab in the serum after intra-

venous injection [9], we maintained a residual concentration of at least 10 ng/mL in the cerebrospinal fluid to obtain sufficient tissue penetration of the drug and an anti-tumor effect on brain metastases. Close monitoring of trastuzumab trough concentrations in the cerebrospinal fluid over 8 months enabled us to determine the intra-theal drug administration schedule required to stabilize the brain metastases on resonance magnetic imaging. The patient died from an infectious complication 3 years after the diagnosis of brain metastases, while median survival is one year in this clinical situation.

Because of the high clearance from the cerebrospinal fluid, repeated injections of trastuzumab 3 times a week were required. This innovative scheme, guided by individual pharmacology and mimicking a continuous perfusion, can be used for other patients with HER2 over-expressing brain metastases.

Apart from this therapeutic effect in our patient, the pharmacological study we performed provided an important physiological finding on the rapid efflux of trastuzumab from the cerebrospinal fluid to the blood compartment. This phenomenon has not hitherto been described. The FcRn transmembrane receptor of the immunoglobulin Fc fragment is expressed by the capillary endothelium of the blood-brain barrier, and experimental data show that it contributes to this efflux phenomenon by reverse transcytosis of therapeutic monoclonal antibodies from the cerebrospinal fluid [10]. Thus, the engineering of a F(ab')<sub>2</sub> fragment of a humanized monoclonal antibody against HER2 could prevent the binding of immunoglobulin to FcRn, and the mechanism of efflux. Engineered Fab fragment antibodies of this sort have been developed for the treatment of neovascular macular degeneration, by chemical modification of bevacizumab, a humanized monoclonal anti-vascular endothelial growth factor antibody [11]. Strong pharmacologic similarities have been established between the epithelial outer blood-retina barrier and the blood-brain barrier, and the efflux systems are similar [12].

This pilot study also opens the way for industrial developments of F(ab')<sub>2</sub> fragments of other monoclonal antibodies for the treatment of primary or metastatic brain tumors.

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