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**Complete Response in HER2+ Leptomeningeal Carcinomatosis From Breast Cancer with Intrathecal Trastuzumab**

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*Summary:*

Trastuzumab, a monoclonal antibody against the HER2 receptor, is a major breakthrough in the treatment of HER2+ breast cancer. However, its high molecular weight precludes it from crossing the intact blood-brain barrier, making the central nervous system a sanctuary to HER2+ breast cancer metastases. We prospectively assessed functional outcome and toxicity of administering trastuzumab directly into the cerebrospinal fluid of a patient with leptomeningeal carcinomatosis and brain metastases from HER2+ breast cancer that had already been treated with other intrathecal chemotherapy, with no benefit. Upon signed informed consent, weekly lumbar puncture with administration of trastuzumab 25mg was begun to a 44 year-old woman with metastatic breast cancer (lymph node, bone, lung and liver involvement) previously treated with tamoxifen, letrozole, anthracyclines, taxanes, capecitabine, intravenous trastuzumab and lapatinib. She received 67 weekly administrations of intrathecal trastuzumab with marked clinical improvement and no adverse events. She survived 27 months after leptomeningeal carcinomatosis diagnosis. A complete leptomeningeal response, with no evidence of leptomeningeal metastasis at necropsy, was achieved. We believe that intrathecal trastuzumab administration should be prospectively evaluated to confirm clinical activity and optimize dose, schedule and duration of treatment.

*Key Words:* Intrathecal trastuzumab, Leptomeningeal carcinomatosis, HER2+ breast cancer

## *Introduction*

Leptomeningeal carcinomatosis (LC) is a rare but rapidly fatal event in the natural history of breast cancer [1]. HER2+ breast cancer has an increased risk of central nervous system (CNS) metastases [2] but there are little data on LC frequency in these tumors [3]. Trastuzumab, a monoclonal antibody against the extracellular domain of the HER2 receptor, is highly effective in systemic control of HER2+ metastatic breast cancer [4] but it is not clear if it can penetrate the intact blood brain barrier (BBB) [5]. We report the case of a patient who received weekly intrathecal (IT) trastuzumab for LC from HER2+ breast cancer for 18 months, with impressive neurological benefit.

## *Case Report*

A 40 year-old woman presented in April 2003 with a left-sided cT4bN1M0 estrogen receptor (ER) positive (70% of cells) invasive ductal carcinoma. She received 6 cycles of neoadjuvant chemotherapy (5-FU 500mg/m<sup>2</sup>, epirubicin 100mg/m<sup>2</sup> and cyclophosphamide 500mg/m<sup>2</sup>) followed by neoadjuvant radiotherapy (50Gy) and tamoxifen. Modified radical mastectomy was performed in July 2004 and pathological complete remission was documented. In April 2006 a fine-needle aspiration confirmed breast cancer recurrence in a cervical enlarged lymph node (ER 20%, HER2 FISH+). Restaging detected bone and lung metastases and docetaxel (75mg/m<sup>2</sup>) was given from May 2006 to February 2007, with a complete response in the lung and lymph nodes and a partial response in bone. Trastuzumab was then started as “maintenance” therapy. In May 2007 she presented with headache, vomiting, gait disturbance and impaired vision. CNS CT-scan showed multiple cerebral and cerebellar cortico-subcortical contrast-enhancing lesions, compatible with CNS metastases. She started letrozole and received whole brain radiotherapy (WBRT, 30Gy/10 fractions) and oral corticosteroids, with neurological improvement. She continued letrozole plus trastuzumab until September 2007, when trastuzumab was stopped because of a drop in left ventricular ejection fraction (LVEF). In February 2008, a CNS CT-scan suggested LC, which was confirmed by a cerebrospinal fluid (CSF) sample (Figure 1a). Liver metastases were detected, so treatment was changed to exemestane and intravenous trastuzumab was resumed, after documenting a normalized LVEF in echocardiogram. IT methotrexate was started, followed by IT AraC, but as CSF malignant cells were persistently detected, IT therapy was stopped for futility. In April 2008, she started capecitabine and lapatinib, for progressive liver and lung metastases, achieving a second complete liver and lung responses and a partial bone response within two months. In October 2008, she presented again with headache, gait disturbance, neck stiffness and reduced flexion of lower limbs. Malignant cells could still be detected in CSF. After discussing the limited available options with the patient and her family, and upon signed informed consent, she was started on weekly IT trastuzumab 25mg plus IT prednisolone 25mg in November 2008. After three doses, she recovered lower limb motion and resumed her daily physical activities. CSF cytology was negative ever since. Figure 2 depicts the timeline of the received IT and systemic therapy, along with the variation in protein and cell counts in CSF. Figure 3a shows her CNS-MRI in the beginning of IT therapy.

In January 2009 she started capecitabine and IV trastuzumab for worsening lung metastases, later changed in July 2009 to cisplatin, etoposide and trastuzumab for progressive CNS parenchymal metastases (Figure 3b, arrow-head). At that time, an increased meningeal gadolinium uptake was also observed (Figure

3b, arrows), but there was neither neurological worsening nor reappearance of malignant cells in CSF. After 3 cycles of the new chemotherapy regimen, a partial CNS response was documented, with a decrease of about 30% in her brain metastases diameter (Figure 3c, arrow head) along with a decreased leptomeningeal uptake (Figure 3c, arrows).

She received 67 administrations of weekly IT trastuzumab with complete resolution of neurological symptoms. She was able to perform manual tasks and walk with no restraints.

Unfortunately, she died from *Listeria meningitis* 27 months after the diagnosis of LC. Autopsy was remarkable for bilateral cerebral and cerebellar metastases from HER2+ BC (Figure 1b and 1c). A complete lung and liver response was documented and surprisingly no macroscopic or microscopic evidence of leptomeningeal dissemination of BC was detected.

### *Discussion*

Trastuzumab, a monoclonal antibody against the extracellular domain of the HER2 receptor [6], has markedly improved the survival of HER2+ BC patients [7]. However, CNS disease remains a challenge, since HER2+ BC patients seem more prone to brain metastases, whether or not previously exposed to trastuzumab [2]. There are few data on the incidence of LC in these patients, but one retrospective study failed to show an increased risk of LC in HER2+ patients compared to the HER2 negative population [3]. Little is known about the pharmacokinetics of trastuzumab in the CNS and its ability to pass the intact BBB [8]. Stemmler and colleagues measured trastuzumab levels in the serum and in CSF of HER2+ MBC patients with brain metastases and systemic trastuzumab treatment, before and after WBRT. They showed a 5.5-fold increase in serum:CSF trastuzumab ratio, reaching 8.5-fold increase in patients with LC, concluding that intravenous trastuzumab should be maintained in these patients [9]. However, CSF trastuzumab concentration is much lower than that reached in serum. If safe for the patient, bypassing the BBB by directly delivering trastuzumab into the CSF, allowing for higher CSF trastuzumab concentrations, seems an attractive and rather simple option.

The first case of IT trastuzumab administration in a patient with LC was published in 2001. No clear clinical benefit could be documented, but there were no side effects other than mild local ventricle inflammation at autopsy [10]. This led others to administer IT trastuzumab [11-17]. Most patients experienced symptoms improvement and no adverse neurological effects.

No consensus exists on the adequate dosing and frequency of IT trastuzumab, ranging from 5mg [10,17] to 100mg [14] dosing in a weekly [10,13-17] to every three weeks [11,13] schedule, with 25mg being the most common. The maximum number of administrations was 50. Reported response duration (assessed by recurrence of positive CSF cytology) ranged from 2 [10] to 24 [13] months and survival after LC diagnosis from 3 [10] to 26 [15] months.

The patient now reported was a heavily pre-treated HER2+ metastatic BC patient who derived benefit from combined IT and systemic anti-cancer therapy for more than two years. To our knowledge, no other patient received IT trastuzumab for so many administrations and for so long (67 over 18.4 months), with a survival of 27 months since LC diagnosis and 36 months since brain metastases developed.

## *Conclusion*

This case report illustrates that the administration of IT trastuzumab is feasible, safe and can lead to a dramatic functional improvement even in a heavily pre-treated patient with LC. Further studies are warranted to confirm clinical activity and optimize trastuzumab delivery into the CNS, including dose, schedule and duration of treatment.

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*Figure Captions*

**Fig. 1** a: Cerebro-spinal fluid sample positive for malignant adenocarcinoma (MGG, 60x). b: Histological section of the brain metastatic disease. The tumor cells are arranged in solid nests or cords with infiltrative growth pattern, with varying size of oval cells showing eosinophilic cytoplasm and prominent nucleoli (H&E 40x). c: Strong membrane positivity for HER2 (3+ score) (IHC 40x).

**Fig. 2** Timeline of therapy and variation of CSF total proteins and cells. Abbreviations: CSF: Cerebro-Spinal Fluid. CNS: Central Nervous System. PD: Progressive Disease. IT: intrathecal. IV: Intravenous. DDP: cisplatin.

**Fig. 3** CNS gadolinium enhanced MRIs over time. a: December 2008, 4 weeks after the beginning of IT trastuzumab; B: July 2009, with progressive CNS disease (arrow head) and increased leptomeningeal gadolinium uptake (arrows). Notably, CSF cytology was negative for tumor cells. C: September 2009, after 3 cycles of cisplatin plus etoposide plus IV trastuzumab, with a partial response in brain lesions (arrow head) and a decrease in leptomeningeal gadolinium uptake (arrows).





