Systemic Treatment for Patients with HER2-Positive Breast Cancer and Brain Metastases

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Abstract
There is no consensus on the treatment of brain metastases in patients with HER2-positive breast cancer. This article reported a patient attained long intracranial control and survival with the use of multiple anti-HER2 agents. Treatment of brain metastases in patients with HER2-positive breast cancer should involve both local therapies and systemic anti-HER2 agents. Radiotherapy and surgery can disrupt the blood-brain barrier. This, in turn, allows the larger molecules like trastuzumab and pertuzumab to penetrate through for better control in the brain metastases. Novel anti-HER2 agents including lapatinib, neratinib, trastuzumab emtansine (T-DM1), trastuzumab deruxtecan (T-DXd) can penetrate the blood-brain barrier and can attain significant improvement in the response of the brain metastases.

Keywords
Breast cancer; Brain metastases; Pertuzumab; Trastuzumab; Neratinib

Introduction
Metastatic Breast Cancer (BC) is the second most common cancer associated with brain metastases (BM). Around 15% of advanced BC patients have BM [1]. Compared to other subtypes; HER2-positive BC has a much higher incidence of BM, as high as 50% [2]. In the past decade, novel anti-HER2 agents were developed and showed promising results in metastatic HER2-positive BC. Nevertheless, recurrent Central Nervous System (CNS) metastases remain a major source of morbidity and mortality for a substantial proportion of patients.

Case
Ms. JW, a 36-year-old, had a right mastectomy for her right breast cancer in 2011. Pathology confirmed invasive ductal carcinoma, T2 (3 cm) N0, estrogen receptor (ER) positive, progesterone receptor (PR) positive and HER2-positive. She received adjuvant chemotherapy using dose-dense anthracycline and cyclophosphamide for four cycles and dose-dense paclitaxel for another 4 cycles with one year of trastuzumab which was all completed in May 2012.

Five months after stopping trastuzumab, she developed multiple brain and bone metastases. Whole-brain radiotherapy (WBRT) 30 Gy in 10 fractions was given. She then received capecitabine and lapatinib from November 2012. MRI brain in July 2014 showed progression in the left parietal BM while PET-CT showed static disease over the bone metastases. Stereotactic radiosurgery to the left parietal BM was done in August 2014. She continued on capecitabine and lapatinib till February 2015, when she had new bone and liver metastases and enlargement of left parietal BM causing recurrent seizure and confusion. Craniotomy with left parietal tumor excision was performed in March 2015. She recovered well and became asymptomatic after surgery. T-DM1 was given from April 2015 to April 2016. PET-CT showed complete remission in all the extracranial disease but the MRI brain showed intracranial progression with multiple BM with diffuse leptomeningeal metastasis. Double anti-HER2 agents with trastuzumab and lapatinib with Aromasin were given from April 2016 to January 2018.

In January 2018, Ms. JW had confused speech, unsteady gait and needed a wheelchair. MRI revealed intracranial progression again but no extracranial progression. Docetaxel, pertuzumab, and trastuzumab (DPH) were started since February 2018. Her condition was much improved after two cycles of DPH. MRI brain after 6 cycles showed near-complete remission of the BM. She could walk without assistance and even joined her friends to Jerusalem for traveling. She continued on maintenance pertuzumab and trastuzumab for a total of one year until March 2019 when BM progressed again. Ms. JW’s condition deteriorated rapidly with confusion and became bedbound. She finally passed away in September 2019 (Figure 1).

Discussion
Treatment of HER2-positive Breast Cancer with Brain Metastases (BCBM) is challenging. BCBM can cause significant morbidities and impair the quality of life of the patients. Despite the development of new anti-HER2 agents, there is no consensus on the best regimen for refractory BCBM. Moreover, most of the studies did not report on their efficacies of intracranial control. A substantial proportion of patients would suffer from intracranial progression while their extracranial diseases are under control, similar to our case. A literature review was performed on the systemic treatment for HER2-positive BCBM.

Monoclonal antibodies (Trastuzumab, pertuzumab)
Pertuzumab and trastuzumab are monoclonal antibodies and have a low penetration into the brain through the BBB. In the phase III CLEOPATRA study, pertuzumab combined with trastuzumab and docetaxel showed a significant improvement in Progression-Free Survival (PFS) and Overall Survival (OS) compared with trastuzumab and docetaxel in the first-line setting in metastatic HER2-positive BC patients. In the post-hoc analysis, the use of pertuzumab delayed the time of onset of CNS metastasis from 11.9 months to 15.0 months, which was likely due to the improved control of the distant metastases with pertuzumab [3]. Since patients with baseline BM were excluded in this study, the efficacy of intracranial control of pertuzumab cannot be evaluated.

Previous studies showed that Cerebrospinal Fluid (CSF)/serum drug concentration ratio can be used to predict the likelihood of drug penetration into CNS and predict the likelihood of efficacy. The ratio

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Received: February 03, 2020 Accepted: February 11, 2020 Published: February 25, 2020
varies with the route of the drug administration, any intracranial disease and any local treatment e.g. surgery or radiotherapy. Stemmler et al. showed the CSF/serum trastuzumab level in patients with BM prior to any local therapy was 1:420 while the ratio increased to 1:79 after radiotherapy [4]. It is unclear whether local therapy like radiotherapy or brain surgery can increase in CSF/serum ratio and enhance the intracranial control of the drugs.

In our case, the patient received WBRT, stereotactic radiotherapy to local BM and surgical resection. These local treatments may change the BBB and allow a higher penetration of pertuzumab and trastuzumab to the CNS for a prolonged intracranial control.

### Antibody-drug conjugates (Trastuzumab emtansine (T-DM1), Trastuzumab deruxtecan (T-DXd))

Trastuzumab emtansine (T-DM1) is an antibody-drug conjugate composed of the cytotoxic agent emtansine (DM1) conjugated to trastuzumab via a stable linker, which facilitates intracellular delivery of DM1 to HER2-overexpressing tumor cells, resulting in inhibition of tubulin polymerization and cell death. Evidence of T-DM1 in treating BM is mainly from retrospective studies.

In the retrospective exploratory analysis of the phase III EMILIA study which included 95 patients with CNS metastases at baseline and randomized to either T-DM1 or lapatinib-capcitabine arm, T-DM1 was associated with improved OS in patients with BCBM at baseline (median OS (mOS) 26.8 versus 12.9 months, HR 0.38, p=0.008) [5]. In a multicentre retrospective study in Italy, which included 87 patients with BCBM on T-DM1, 24.5% had a partial response (PR) and 30.1% had stable disease (SD) [6]. Another French study that included 39 BCBM patients on T-DM1, 44% had PR and 59% achieved SD. T-DM1 appeared to be an effective and well-tolerated option in HER2-positive BCBM [7]. Prospective studies on T-DM1 in controlling BM are warranted.

Trastuzumab deruxtecan (T-DXd, DS-8201) is a novel antibody-drug conjugate composed of an anti-HER2 (human epidermal growth factor receptor 2) antibody, a cleavable tetrapeptide-based linker, and a cytotoxic topoisomerase 1 inhibitor. In the phase II DESTINY-Breast01 study, 184 heavily pretreated HER2-positive BM patients received T-DXd. T-DXd demonstrated impressive efficacy with response rate (RR) 60.9% and median PFS 16.4 months [8]. Among 24 patients with BM at baseline, the objective RR was 58% and the median PFS was 18.1 months (95% CI 6.4-18.1 months). The most common G3 or higher adverse events with T-DXd were neutropenia (20.7%), anemia (8.7%) and nausea (7.6%). 13.6% of the patients had Interstitial Lung Disease (ILD) and 4 deaths were attributed to it. It is recommended to monitor the symptoms of ILD when using T-DXd in future studies or clinical practice.

### Small molecule tyrosine kinase inhibitors (TKI) (lapatinib, neratinib, tucatinib)

Lapatinib is a double-acting TKI that inhibits the phosphorylation and activation of the EGFR/HER1 and HER2/ErbB2 receptors. Lapatinib crosses BBB because of its small molecular structure. In phase III Randomized Controlled Trial (RCT) including women with HER2-positive advanced breast cancer that has progressed after treatment with regimens that included anthracycline, taxane, and trastuzumab, lapatinib-capcitabine improved the median PFS from 4.4 to 8.4 months compared with capcitabine alone [9]. There was a lower percentage of patients in the lapatinib arm having CNS progression as compared with the capcitabine alone arm, though the number was small (2.5% vs. 6.8%, p=0.10).

Moreover, in a meta-analysis, which included 12 studies and 799 patients with HER2-positive BCBM, lapatinib-capcitabine achieved a pooled overall RR 29.2%, median PFS 4.1 months and mOS 11.2 months [10]. In the phase II LANDSCAPE study, 29 out of 44 patients (66%) on lapatinib-capcitabine achieved a partial volumetric response in CNS metastases [11]. A combination of WBRT with lapatinib also showed promising results from phase I and II studies, with CNS RR around 70%-80% and mOS 18-19 months.

Neratinib is an irreversible TKI of EGFR, HER1, HER2, and...
HER4. In phase III NEHER-T study comparing neratinib-paclitaxel and trastuzumab-paclitaxel as a first-line systemic treatment in patients with metastatic HER2-positive BC [12]. Both combinations showed median PFS of 12.9 months but the neratinib-paclitaxel arm demonstrated a lower incidence of CNS recurrence (RR 0.48, 95% CI 0.29-0.79, p=0.002) and delayed time to CNS metastases (HR 0.45, 95% CI 0.26-0.78, p=0.004). In phase II TBCRC 022 trial which included 49 HER2-positive BCBM patients, neratinib-capcitabine attained an impressive CNS objective RR (49% in lapatinib-naïve patients, 33% in lapatinib-treated patients) [13]. The main concern was treatment-related adverse events including grade 3 diarrhea (32%) and treatment discontinuation (16%).

Tucatinib is a new oral TKI that is highly selective of the kinase domain of HER2 with minimal inhibition of EGFR, resulting in fewer diarrheas and fewer skin toxicities. In the recent published HER2CLIMB study, adding tucatinib on top of trastuzumab and capectabine improved both PFS (median PFS: 7.8 vs. 5.6 months, HR 0.54, p<0.001) and OS (mOS: 21.9 vs. 17.4 months, HR 0.66, p=0.005) compared with adding placebo in heavily pretreated patients with HER2-positive metastatic BC [14]. Among patients with BM, PFS was also significantly prolonged (median PFS: 7.6 vs. 5.4 months, HR 0.46). The RR in BM has not been reported. Yet, in an earlier phase IIb study on tucatinib with trastuzumab and capectabine, which included 12 patients with baseline BM, the objective RR in BM was 42% [15].

**Conclusion**

Despite the advances in the development of anti-HER2 therapies, there is still an unmet need in the treatment of HER2-positive BCBM. Future researches on systemic treatment for metastatic HER-2 positive breast cancer should include patients with baseline BM. Studies should also focus on the intracrânial control of these new agents, with or without combinations of local treatment e.g. radiotherapy and surgery which may improve their penetration through the BBB. Studies on quality of life on patients with BCBM are warranted and will guide us on the best treatment for this particular group of patients.

**References**


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