Anti HER-2 Agents in Treatment of Brain Metastases in Breast Cancer. Case Report and Review of Literature

Sawsan Ismail*1
Firas Hussein2
Zubeir Al-Shehabi1
Saleh Ismail3

1Department of Pathology, Faculty of Medicine, Tishreen University, Syria
2Department of Hematology, Internal Medicine, Faculty of Medicine, Tishreen University, Syria
3Department of Histology, Faculty of Medicine, Alandalus University of Medical Sciences, Syria

Abstract
Breast cancer (BC) is the most common solid malignancy in women and the second leading cause of cancer death after lung cancer. The Treatment decision depends on many prognostic factors including, human epidermal growth factor receptor 2 (HER2) overexpression which presents a negative prognostic factor for metastatic breast cancer (MBC). However, the advent of targeted anti-HER2 therapies has revolutionized the management of HER2 positive MBC. In this case, we present a 53-year-old female patient who had a right radical mastectomy with axillary lymphadenectomy according to a diagnosis of an invasive BC grade III. Two years after adjuvant treatment a brain metastases was detected. The patient underwent craniotomy, moreover, FISH technique indicated high positivity of HER2 gene amplification. Thus, the patient was treated with a combination of adjuvant anti-HER2 drug therapy (Lapatinib and Capecitabine), in which easily pass through the blood brain barrier. Since then, no recurrence had been detected.

Introduction
A Breast Cancer (BC) is the most common cancer of women in Europe, USA, Australia, and many Latin American and other countries. It’s also the second most common heterogeneous disease that metastasizes to the brain, with an incidence rate up to 16-30%. Recent studies indicate increasing incidence of brain metastases (BM) in BC patients, due to the development of more sensitive neuroimaging techniques, as well as the invention of more effective systemic treatments, which led to a prolonged patient survival [1]. BC treatment depends on many prognostic factors including age, tumor size, lymph nodes status, metastases, genes expression and breast cancer subtypes. The subtypes classification mainly depends on tumor markers such as, Estrogen Receptor (ER), Progesterone Receptor (PR) and HER2 status. BC is classified into two main subtypes, low grade luminal A type, which is responsive to endocrine therapy with HER2 low expression and ER regulated gene overexpression. Meanwhile, high grade luminal B type is considered more aggressive due to HER2 overexpression [2]. HER2 is a member of the Epidermal Growth Factor Receptor (EGFR) family of tyrosine kinases (TK) play a crucial role in cell growth and proliferation [3]. HER2 gene was first identified in 1984 by Dennis Slamon as an oncogene located on chromosome 17q21.1 [4,5]. HER2 is a...
biomarker associated with rapid tumor growth and poor prognosis in BC patients as well as a well-established risk factor for brain metastases (BM) [4,6]. However, the advent of targeted anti-HER2 monoclonal antibodies starting with trastuzumab in the late 1990s has revolutionized the management of HER2 positive metastatic breast cancer and improved the prognosis of this disease [3].

**Case Report**

A 53-year-old female patient was admitted to the hospital in November 2017 for a HER2 positive brain metastases from a pre-treated breast cancer. The patient’s diagnosis started two years earlier, in August 2015 when she noticed a small lump in her right breast. The lump grew rapidly and developed skin changes and nipple inversion within three months. A core needle biopsy performed on December 7, 2015 indicated an invasive moderately differentiated ductal carcinoma of the breast grade III. The patient underwent radical mastectomy with axillary lymphadenectomy on December 15, 2015. Further specimen hormonal tests using Immunohistochemistry technique (IHC) indicated 100% ER positivity, 100% PR positivity, 70% Ki67 positivity and 80% HER2 positivity score 2. HER2 gene amplification detected using Fluorescent In Situ Hybridization (FISH) technique indicated overexpression of HER2 gene amplification. The patient was treated with chemotherapy of (4×Doxorubicin+Cyclophosphamide) + (4×Docetaxel) from January 19, 2016 to August 16, 2016 followed by adjuvant radiation therapy of 50Gy/25 fractions. After that she was put on adjuvant anti-HER2 drug therapy (Trastuzumab 440 mg) every 3 weeks for a year followed by Hormonal therapy (Tamoxifen). Progression was monitored by image scanning (brain and bone MRI, chest X-ray, abdomen CT). However, brain MRI in November 2017 showed an isolated right spherical frontal parietal mass with a necrotic center more likely to be a metastatic mass (Figure 1 and 2). Full-body CT scan showed no other visceral metastases. She was admitted back to the hospital for a craniotomy to remove the mass on November 13, 2017. Pathological findings indicated a metastatic poorly differentiated invasive ductal breast carcinoma to the brain. Detection of HER2 gene amplification using Fluorescent In Situ Hybridization (FISH) technique on the specimen indicated 3,4 positivity of HER2 gene amplification. The patient was treated with adjuvant radiotherapy with anti-HER2 drug therapy from the second generation tyrosine kinase inhibitors (Lapatinib 1250mg in combination with Capecitabine 2500mg daily). Control brain MRI, chest CT and abdomen CT were used in follow-up.

![Figure 1](brain MRI images on November 11, 2017 before the surgery, showing an isolated right spherical frontal-parietal mass with a necrotic center more likely to be a metastatic mass)

![Figure 2](brain MRI images on November 11, 2017 before the surgery, showing an isolated right spherical frontal-parietal mass with a necrotic center more likely to be a metastatic mass)
(Figure 3, 4 and 5). From December 2017 until her last visit in July 2018, the patient has been disease-free and no recurrence has been noticed.

**Discussion**

Breast Cancer (BC) is the second most common solid malignancy that metastasizes to the brain, with incidence rate 16-30% in BC cases. Brain Metastases (BM) usually develop decades after primary tumor diagnosis. However, in our case, it was detected earlier. The median interval between BC diagnosis and BM development was approximately twenty-two months. Recent studies indicate the importance of the genetic profile in determining the behavior, aggressiveness and treatment methods in primary BC as well as in metastases [7]. Brain Metastases have been historically treated with surgical resection followed by conventional chemotherapy and whole brain radiation therapy. However, an increased incidence of neurocognitive defects has led to increased dependence on alternative systemic targeted therapies [6]. Decision of treatment was based on HER2 gene amplification detection in cancer cells. HER2 is a membrane-spanning protein encoded by the HER2 proto-oncogene which is located on chromosome 17q21.1. HER-2 receptor is composed of three main parts: an intracellular tyrosine kinase (TK) domain, an extracellular ligand-binding domain and a helical transmembrane segment [2]. Two main signaling axes compose the downstream signaling output of the HER2 pathway. The phosphatidyl inositol 3-kinase (PI3K/AKT/mammalian target of rapamycin mTOR), which is important for cell proliferation and protein synthesis, and RAS/RAF/Mitogen Activated Protein Kinase MAPK [2]. Several studies demonstrated alterations in Her2 status during primary tumor progression and metastasizing. They indicated that Her2 positive cells could turn into Her2 negative during metastasizing and less likely vice versa, highlighting the importance of evaluating Her2 status in metastases as well as in primary tumors to optimize treatment decision making [8]. In our case, we evaluated HER2 gene amplification in breast cancer brain metastases cells using Fluorescent In Situ Hybridization (FISH) technique, which is considered –according to many centers- more accurate than IHC in determining HER2 overexpression, and more predictive method in evaluating response to anti-HER2 treatment. However, the debate between IHC and FISH accuracy is still on and further studies are required to settle the argument [5,9]. FISH result revealed 3,4 positivity in brain metastases cells. Examination and counting of signals within 50 tumor cells indicated 316 red signals and 94 green signals [5,9]. Although overexpression of HER-2 has been associated
with poor prognosis in BC patients, the advent of targeted anti-HER2 therapies has revolutionized the management of metastatic BC [3]. Trastuzumab was the first discovered and approved anti-HER2 targeted therapy by Slamon in the late 1990s [10]. It’s a large monoclonal antibody (185kDa) works by binding to HER2 receptor extracellular domain on the cancer cell surface, inhibiting the intracellular signaling pathway by arresting the cell cycle in the G1/S phase [1,6]. The use of chemotherapy in combination with trastuzumab (Herceptin) has been the standard of care for patients with HER2 positive MBC [11]. However, its penetration across the blood-brain barrier (BBB) is limited due to its large size, which makes it unsuitable option for our patient [12,13]. Recently, clinical trials indicated that patients receiving trastuzumab had a higher risk for developing brain metastases (relative risk 1.57, 95% confidence interval CI 1.03-2.37) [11]. Therefore, we utilized a combination of lapatinib and capecitabine for HER2 positive MBC case, as these drugs can easily pass through the BBB. Lapatinib (Tykerb) is an oral small molecule tyrosine kinase inhibitor targeting HER2 receptors. It can cross BBB because it’s a lipophilic highly insoluble molecule (58Da). Lapatinib may limit disease progression according to results from exploratory analysis performed from the pivotal phase III trial [1,6,11]. It has a minor role as a single agent, but according to the LANDSCAPE trial adding capecitabine increased the response rate up to 20% [6]. Pertuzumab is another large HER2 targeted monoclonal antibody with limited access to cross the BBB and limited efficacy in treating BM [6].

Conclusion

In conclusion, a rapid progress in the management of HER2-positive metastatic breast (MBC) cancer has been marked. Thus, HER2 status should be assessed in all primary BC as well as in metastases. Targeted therapy has revolutionized the management of HER2-positive MBC, but the appropriate combination of the newer agents is still not fully defined. Also, there are still many unanswered questions such as how to affect a sanctuary site or impact prior resistance. So the journey has just begun, and there is still a need to work on developing better therapies in order to look at whether we can completely forgo chemotherapy and radiotherapy for most HER2-positive MBC patients.

References