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# Brain Metastases of Her2-Positive Breast Cancer: A Case of 34 Months' Remission with Lapatinib plus Capecitabine

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## Key Words

Breast cancer · Brain metastases · Her2-positive tumors · Lapatinib · Capecitabine

## Abstract

Breast tumors overexpressing Her2 (15% of breast cancers) are particularly at risk for central nervous system parenchymal metastases. Whole-brain irradiation (WBI) is the standard of care of brain metastases (BM), and secondarily, systemic treatment is used in case of progression. We report the case of a patient with Her2-positive breast tumor with BM developed 10 months after the initial diagnosis of cancer. The BM were initially treated with WBI then trastuzumab before a recurrence occurred, which was controlled during 34 months with lapatinib and capecitabine. The treatment was regularly adjusted according to the tolerance and the efficacy in order to obtain the control of systemic and neurological disease and to maintain the patient's quality of life. Studies on new targeted agents and/or new combinations with chemotherapy are ongoing. This suggests a better efficacy of treatment and an increased survival of patients. However, these patients are sometimes in a very poor general condition. In this case, we show that a good evaluation of efficacy and toxicities may allow an adaptation of the sequence and dose of treatment in order to preserve the response to treatment and the quality of life. Indeed, systemic treatments are available in addition to WBI. Therefore, the objective of the management of BM is twofold: survival and quality of life.

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## Introduction

Central nervous system (CNS) metastases have a major impact on patient survival but also on their quality of life. The incidence of CNS metastases is currently increasing due to the improved patient survival obtained thanks to new drugs or new combinations with limited CNS penetration [1].

Breast tumors overexpressing Her2 (15% of breast cancers) are particularly at risk for CNS parenchymal metastases [2]. The introduction of trastuzumab increased significantly the prognostic and survival [3]. Currently, about 20–45% of patients with Her2-positive metastatic breast cancer will develop parenchymal brain metastases (BM) [4]. This incidence is particularly high and remains the same in patients having received trastuzumab or not [2]. The median survival after BM is longer in Her2-positive patients receiving trastuzumab compared to Her2-positive patients without trastuzumab and Her2-negative patients (11.9 vs. 3 vs. 3.6 months) [5]. Moreover, we can note that in the case of Her2-positive cancers the extracerebral disease is controlled in 50% of cases at the diagnosis of BM. Death is related to BM in about 50% of cases [6, 7]. A correlation between Her2 expression in primary tumors and BM was found in 97% of cases [8]. This result suggests that trastuzumab (148 kDa) has difficulties in crossing the blood-brain barrier (BBB) in the absence of CNS metastasis. The hypothesis of a particular affinity for Her2-positive cells of the CNS is also mentioned [4]. BM occur most frequently in patients with advanced and active systemic involvement. They may, however, remain the main location in some patients. The parenchymal locations are multiple in 78% of cases [9]. Whole-brain irradiation (WBI) is considered by far as the standard treatment of multiple parenchymal metastases. Currently, systemic treatment is mainly used in case of progression after radiotherapy.

Here, we report the case of a patient with Her2-positive breast tumor with BM developed 10 months after the initial diagnosis of cancer. BM were initially treated with WBI then trastuzumab before a recurrence occurred, which was controlled during 34 months with lapatinib and capecitabine.

A 40-year-old woman consulted the Oscar Lambret Center (Lille, France) in September 2006 due to a recent occurrence of a right breast mass. The clinical examination revealed no inflammatory sign, but the tumor involved the entire right breast and there was a nipple-area retraction and rigidity of the muscles. A breast biopsy was performed and highlighted a poorly differentiated ductal adenocarcinoma overexpressing Her2 (3+ by IHC) with estrogen receptors (90%) and without progesterone receptors. Staging exams revealed bone and liver metastasis. She received weekly paclitaxel (90 mg/m<sup>2</sup>) associated to trastuzumab (8 mg/kg loading dose, then 6 mg/kg) from September 2006 to April 2007 followed by trastuzumab alone (6 mg/kg dose) from April 2007.

In June 2007 she consulted the Center for progressively worsening headaches and vomiting. A brain scan revealed multiple secondary parenchymal cerebral and cerebellar lesions. Otherwise, staging exams showed stability of the liver and the bone metastasis. WBI (30 Gy/10 fractions/2 weeks) was performed. Tolerance was correct and clinical symptoms decreased quickly. Trastuzumab monotherapy was continued. Clinical and cerebral MRI monitoring was then performed every 3 months. A year later, in June 2008, the patient had new episodes of headache. An MRI confirmed cerebral recurrence, while the thoraco-abdomino-pelvic CT remained stable. Treatment with capecitabine 2,000 mg/m<sup>2</sup>/day (days 1–14) and lapatinib 1,250 mg/day (5 pills of 250 mg/day) was then started.

The neurologic symptoms decreased very quickly. After the third cycle, the cerebral MRI reevaluation showed a very significant regression (>90%) of the whole lesions. The persistent lesions were very limited including a small enhancement in the left frontal cortex.

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The dose of lapatinib was reduced to 4 pills/day (1,000 mg/day) after the third cycle because of vomiting (grade 1) and diarrhea (grade 2). The dose of capecitabine was not modified. Despite this dose adjustment and well-conducted symptomatic treatment, an accelerated transit (3–4 loose stools/day) persisted, well tolerated by the patient.

Nine subsequent cycles were then conducted at the same dose of lapatinib (1,000 mg/day) and capecitabine (2,000 mg/day, days 14–21) until March 2009. At that time, the clinic and paraclinic evaluation was stable and capecitabine was stopped after discussion with the patient in order to improve their quality of life. Lapatinib monotherapy was continued at 1,000 mg/day.

In July 2009, the clinical neurological examination remained stable but the MRI performed in the follow-up showed a further increase in an isolated BM. The association of capecitabine and lapatinib was then reintroduced at the dose of 1,000 mg/day of lapatinib and 2,000 mg/day (days 14–21) of capecitabine.

In February 2010, the situation was stable and the patient developed a paronychia of the left big toe. The treatment was stopped for 1 month and lapatinib was restarted (1,000 mg/day).

In June 2010, the patient complained of headaches, and MRI confirmed a new disease progression in the brain. Capecitabine (2,000 mg/day, days 14–21) was then reintroduced in combination with lapatinib (5 pills/day) for 4 months until October 2010, and the dose of lapatinib was reduced to 1,500 mg/day because of recurrence of digestive disorders.

Six months later, in December 2010, mucocutaneous jaundice with liver biologic abnormalities and digestive disorders were recorded. CT scan showed a stability of the lesions of the liver. The hypothesis of an iatrogenic cause was therefore made, and treatment with lapatinib and capecitabine was interrupted for 4 weeks. After the resolution of liver biologic abnormalities and improvement of the gastrointestinal symptoms, monotherapy of capecitabine (2,000 mg/day, days 14–21) was reintroduced in January 2011 after discussion with the patient, who did not wish to resume anti-Her2 therapy. However, while the clinical examination was stable, a control MRI performed in March 2011 brought to light a discrete progression of cerebellar lesions. Lapatinib was associated again. In April 2011 the patient presented a rapid and significant alteration of the general condition with clinical hepatic disease progression and occurrence of seizures. No imaging was performed given the rapid deterioration of general condition leading to patient death within a few days.

## Discussion

The standard treatment for newly diagnosed multiple BM is currently WBI. However, systemic treatments are playing an increasingly important role before or after radiotherapy. The Landscape study showed the benefit of the association of capecitabine and lapatinib in some Her2-positive patients with BM before WBI [10]. The passage of systemic agents through the BBB remains limited [11]. In cases of BM, the BBB has alterations around the metastatic sites as shown by contrast enhancements on MRI. Changes occur in the BBB after WBI and may favor the passage of various agents. Some agents have shown some efficacy in parenchymal metastases. The main chemotherapies used are: CMF, FEC, cisplatin, carboplatin, capecitabine, temozolomide, topotecan, irinotecan, methotrexate, liposomal doxorubicin [4]. Capecitabine appears to have a particular interest with activity reported in several case reports or small series, and sometimes complete and durable responses including patients sometimes heavily pretreated [12]. The anti-Her2 have widely demonstrated their interest in case of brain metastatic disease. Currently, patients can receive

multiple lines of chemotherapy and targeted therapy after WBI. In a phase II study, Lin et al. [13] evaluated the response rate obtained with lapatinib, a small-molecule inhibitor of tyrosine kinase, as monotherapy in 39 patients with Her2 tumor in brain progression (after WBI in 95% of cases). All patients had previously received treatment with trastuzumab and at least 2 lines of chemotherapy. The objective response rate evaluated by RECIST was 2.6% (1 case), while the volumetric analysis, performed on 34 patients, showed 3 responses equal or greater than 30% and 7 responses between 10 and 30%. Progression-free survival was 3 months. A second phase II study was then performed on 242 patients to evaluate the benefit of lapatinib in BM from Her2-positive cancer patients pretreated with WBI and having already received 1 line of treatment with trastuzumab. Patients had also received at least 2 lines of chemotherapy in 81% of cases. The main objective was response rate defined according to criteria involving volumetric reduction >50% on MRI in the absence of increase of steroids, of progression of neurological symptoms or of extracerebral progression. The objective response was 6% [14]. This response rate corresponds to that observed in phase II studies evaluating lapatinib in extracerebral metastases in evolution after trastuzumab [15]. Some cohorts have evaluated lapatinib in combination with various chemotherapy regimens in case of BM progression after chemotherapy + trastuzumab and WBI. The results showed the efficacy of the lapatinib-capecitabine association with responses ranging from 18 to 38% [6].

The development of new anti-Her2 therapies is ongoing: trastuzumab-maytansine (T-DM1), pertuzumab, tanespimycine, neratinib, afatinib. The combination of lapatinib + trastuzumab has also shown interesting results [16].

Two studies on breast cancer BM progression after trastuzumab are ongoing: neratinib (HKI-272), whose promoter is Dana-Farber Institute, and afatinib (BIBW 2992) EudraCT 2010-02141515-16 (promoter Boehringer Ingelheim).

Other associations of chemotherapy and targeted agents are studied in BM of breast cancer: trastuzumab + bevacizumab + carboplatin (Lin, Dana-Farber Institute, NCT 01004172) and bevacizumab + cisplatin + etoposide (Lu, National Taiwan University Hospital, NCT 01281696).

In our case, treatment was regularly adjusted with the objective of controlling systemic and neurological disease and maintaining the patient's quality of life. This case illustrates the need for close monitoring of these patients in order to adapt the sequence and the dose of the treatment based on MRI and clinical evaluations and to manage their side effects according to the related toxicities. The objective of the management of BM is twofold: survival and quality of life.

## Conclusion

In conclusion, systemic treatments are playing an increasingly important role in breast cancer BM. Clinicians have to know the different associations which are henceforth possible and manage the toxicities of the new agents in order to obtain the best benefit-risk ratio for these often fragile patients. Soon, new encouraging perspectives should be studied.

## Disclosure Statement

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