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CLINICAL INVESTIGATION **Brain**

PRELIMINARY RESULTS OF WHOLE BRAIN RADIOTHERAPY WITH CONCURRENT TRASTUZUMAB FOR TREATMENT OF BRAIN METASTASES IN BREAST CANCER PATIENTS

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Purpose: To assess the use of trastuzumab concurrently with whole brain radiotherapy (WBRT) for patients with brain metastases from human epidermal growth factor receptor-2–positive breast cancer.
Methods and Materials: Between April 2001 and April 2007, 31 patients with brain metastases from human epidermal growth factor receptor-2–positive breast cancer were referred for WBRT with concurrent trastuzumab. At brain progression, the median age was 55 years (range, 38–73), and all patients had a performance status of 0–2. The patients received trastuzumab 2 mg/kg weekly (n = 17) or 6 mg/kg repeated every 21 days (n = 14). In 26 patients, concurrent WBRT delivered 30 Gy in 10 daily fractions. In 6 patients, other fractionations were chosen because of either poor performance status or patient convenience.
Results: After WBRT, radiologic responses were observed in 23 patients (74.2%), including 6 (19.4%) with a complete radiologic response and 17 (54.8%) with a partial radiologic response. Clinical responses were observed in 27 patients (87.1%). The median survival time from the start of WBRT was 18 months (range, 2–65). The median interval to brain progression was 10.5 months (range, 2–27). No Grade 2 or greater acute toxicity was observed.
Conclusion: The low toxicity of trastuzumab concurrently with WBRT should probably not justify delays. Although promising, these preliminary data warrant additional validation of trastuzumab as a potential radiosensitizer for WBRT in brain metastases from breast cancer in the setting of a clinical trial. © 2011 Elsevier Inc.

Breast cancer, Trastuzumab, Radiosensitization, Whole brain radiotherapy.

INTRODUCTION

Symptomatic brain metastases occur in about 10–15% of breast cancer patients with metastatic disease and represent a major complication for which the treatment options remain suboptimal (1, 2). Whole brain radiotherapy (WBRT) remains the mainstay of palliative treatment of patients with multiple brain metastases who are not eligible for radical surgery or stereotactic radiosurgery. It improves survival by about 3–6 months (3) and provides efficient symptom relief. However, the prognosis of patients with brain metastases remains particularly poor, with a 1-year overall survival rate of about 20% (4). Recently, preliminary clinical data have suggested that local tumor control might be improved by combining WBRT with systemic agents acting as radiosensitizers (5).

Approximately 20% of breast cancer patients have human epidermal growth factor receptor 2 (HER2)-positive tumors. This status has been associated with both a poor clinical prognosis and a significantly increased risk of brain metastases (6, 7). However, it was demonstrated that the addition of the monoclonal antibody trastuzumab (Herceptin, Genentech, South San Francisco, CA) to conventional chemotherapy resulted in a survival advantage for patients with metastatic disease (8, 9). Consequently, the incidence of brain metastasis is increasing with the improvement in survival of cancer patients, particularly HER2-positive breast cancer patients. Although limited, evidence has shown that trastuzumab can cross the blood–brain barrier when it is impaired, because it occurs in cases of brain metastases or during WBRT (10–12). The preclinical results have suggested that RT could act synergistically with trastuzumab, demonstrating enhanced radiation-induced apoptosis of the cells in a HER2 level-dependent manner (13). These data encourage the use of trastuzumab concurrently with WBRT to improve the outcomes of breast cancer patients, particularly those with

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brain metastases, but they also suggest a potential for increased toxicity.

In the present study, we analyzed the efficacy and acute toxicity of trastuzumab and concurrent WBRT.

METHODS AND MATERIALS

Patient and tumor characteristics

We retrospectively reviewed the clinical records of 31 breast cancer patients who underwent WBRT and concurrent trastuzumab at the Institut Curie (Paris, France) between April 2001 and April 2007 for brain metastases from breast cancer. Local committees approved the study design.

At the initial presentation, the median age was 53 years (range, 36–67). Of the 31 patients, 26 had localized or locally advanced disease and 5 had presented with metastatic disease. All women had a confirmed histologic diagnosis of HER2-positive breast cancer by biopsy or surgery of their primary lesion. Positive HER2 was defined as immunohistochemistry staining of 3+ or positive fluorescent *in situ* hybridization in patients with 2+ immunohistochemistry staining. The patient and tumor characteristics at first presentation are listed in Table 1. The treatment delivered for primary breast tumor (*i.e.,* surgery type and neoadjuvant and adjuvant therapy) are listed in Table 2. Before brain progression, most patients had received several lines of chemotherapy for their systemic metastatic disease (median, four; range, one to six), and 25 patients had received trastuzumab in the metastatic setting ($n = 22$). Most patients included in our series had been treated before the demonstration that adjuvant trastuzumab improves the outcomes in this population. Consequently, only 3 patients received adjuvant trastuzumab. They developed brain metastases while receiving trastuzumab as adjuvant therapy. The treatment delivered before brain progression is reported in Table 2.

At brain progression, 25 patients were actively receiving trastuzumab. For the 6 remaining patients, trastuzumab was initiated at brain progression. All patients presented at late stages of their diseases but with newly diagnosed brain metastases. Of the 31 patients, 28 presented with systemic metastases before brain metastases, including 18 patients with multiple extracranial metastatic sites. The patient characteristics at brain progression are listed in Table 3.

Brain metastases were documented in all cases using gadolinium-enhanced magnetic resonance imaging and/or computed tomography. Most patients had multiple brain metastases. The median interval to the diagnosis of brain metastasis was 47 months (range, 10–156) after the initial diagnosis of breast cancer. The median

Table 1. Patient and tumor characteristics at first presentation

Characteristic	Value
Patients (*n*)	31
Age (y)	
Median	49
Range	36–65
Histologic type (*n*)	
Invasive ductal carcinoma	28 (90.4)
Invasive lobular carcinoma	1 (3.2)
Other	2 (6.4)
Clinical stage (*n*)	
I	5 (16)
II	9 (29)
III	12 (39)
IV	5 (16)
Tumor grade (*n*)	
I	2 (6)
II	13 (42)
III	12 (39)
Not reported	4 (13)
Mitotic index (*n*)	
Low	7 (23)
Intermediate	7 (23)
High	7 (23)
Not reported	10 (31)
Tumor estrogen receptor (*n*)	
Positive	12 (38.7)
Negative	19 (61.3)
HER2 status (*n*)	
IHC 3+	29 (94)
IHC 2+; FISH positive	2 (6)

Abbreviations: HER2 = human epidermal growth factor 2; IHC = immunohistochemistry; FISH = fluorescent *in situ* hybridization.
Data in parentheses are percentages.

Table 2. Treatment delivered before brain progression

Treatment	*n* (%)
Primary breast disease	
Primary surgical treatment	
Breast-conserving therapy	8 (26)
Modified radical mastectomy	18 (58)
No surgery	5 (16)
Neoadjuvant chemotherapy	
Yes	9 (32)
No	22 (68)
Adjuvant therapy	
Chemotherapy	22 (71)
Endocrine therapy	11 (35)
Trastuzumab	3 (10)
Breast/chest radiotherapy	27 (87)
Metastatic disease	
Chemotherapy plus trastuzumab	22 (81)
Chemotherapy alone	1 (4)
Endocrine therapy alone	1 (4)
Endocrine therapy plus chemotherapy	3 (11)
Chemotherapy cycles (adjuvant chemotherapy excluded)	
Median	4
Range	1–6

Table 3. Patient characteristics at brain progression

Characteristic	Value
Age (y)	
Median	55
Range	38–73
Performance status (*n*)	
0	8 (26)
1	18 (58)
2	5 (16)
Other metastatic sites ($n = 28$)	
Liver	16 (57)
Bone	19 (68)
Pleura/lung	14 (50)
Lymph nodes	4 (14)
Other	3 (11)
Carcinomatous meningitis	2 (7)

Data in parentheses are percentages.