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Clinical Investigation: Metastases

Relationship Between *HER2* Status and Prognosis in Women With Brain Metastases From Breast Cancer

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Summary

Amplification of the gene for human epidermal growth factor receptor type 2 (HER 2) is a well-established prognostic indicator in breast cancer. This retrospective study on a cohort of women with brain metastases from breast cancer showed that overall survival is better for those who are HER 2+ relative to those who are HER 2-, survival after diagnosis of brain metastases is longer, as is survival after treatment with stereotactic radiosurgery. This data suggests that HER 2 status may be a predictive factor for SRS.

Purpose: To analyze factors affecting outcomes in breast cancer patients with brain metastases (BM) and characterize the role of *HER*2 status.

Methods and Materials: We identified 264 breast cancer patients treated between 1999 and 2008 for BM. *HER*2 status was known definitively for 172 patients and was used to define cohorts in which survival and risk factors were analyzed.

Results: Kaplan-Meier survival analysis demonstrated improved mean overall survival (105.7 vs. 74.3 months, $p < 0.02$), survival after diagnosis of BM (neurologic survival, NS) (32.2 vs. 18.9 months, $p < 0.01$), and survival after treatment with stereotactic radiosurgery (RS) (31.3 vs. 14.1, $p < 0.01$) in *HER*2+ patients relative to those with *HER*2− breast cancer. *HER*2+ status was an independent, positive prognostic factor for survival on univariate and multivariate hazard analysis (hazard ratio: overall survival = 0.66, 0.18; NS = 0.50, 0.34). Additionally, subgroup analysis suggests that stereotactic radiosurgery may be of particular benefit in patients with *HER*2+ tumors.

Conclusions: Overall survival, NS, and RS are improved in patients with *HER*2+ tumors, relative to those with *HER*2− lesions, and *HER*2 amplification is independently associated with increased survival in patients with BM from breast cancer. Our findings suggest that the prognosis of *HER*2+ patients may be better than that of otherwise similar patients who are *HER*2− and that stereotactic radiosurgery may be beneficial for some patients with *HER*2+ lesions.

Keywords: Stereotactic radiosurgery, Whole-brain radiotherapy, Surgery, Survival, Trastuzumab, Lapatinib, Kaplan-Meier analysis, Hazards analysis

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Introduction

Central nervous system (CNS) metastases are the most common malignant brain tumors, with an annual incidence in the United States of up to 170,000 cases per year (1). Risk factors for brain metastases from breast cancer include young age, African American ethnicity, tumor grade, *BRCA1* phenotype, and receptor status (2–8). Historically, survival after diagnosis of brain metastases in women with breast cancer has averaged 3–9 months; fewer than 20% of patients survive beyond 1 year (9).

Recently, amplification of the gene for human epidermal growth factor receptor type 2 (*HER*2), a 185-kDa transmembrane tyrosine kinase (10, 11), has been identified as a prognostic marker. Before the advent of chemotherapeutic agents targeted to this receptor, lymph node–positive patients whose tumors were *HER*2 positive (*HER*2+) had a lower overall 10-year survival than those who were *HER*2 negative (*HER*2−) (11–14). Amplification of *HER*2 predicts response to the monoclonal antibody trastuzumab (15) and similar forms of adjuvant chemotherapy directed at the receptor (13), making it a valuable predictive marker (16) and a useful guide to systemic therapy. Therapy targeted at the *HER*2 receptor has significantly improved survival in *HER*2+ patients (11, 17).

The relative proportion of brain metastases in patients with *HER*2+ breast cancer is unknown. Figures of approximately 10–25% are common; some estimates approach 40%. These rates vary with the extent of the primary disease but are, in general, higher than in patients who are *HER*2− (11, 18–27). This difference is believed to be attributable both to treatment-related effects and to biological factors. Recent studies of CNS progression of *HER*2+ primary breast cancer indicate that more than two-thirds of patients with symptomatic CNS disease presented at a time when their systemic disease was controlled or was responding to trastuzumab (21). Because trastuzumab does not penetrate the CNS, these findings suggest that the brain may serve as a sanctuary site. Regarding biological factors, studies conducted in the pre-trastuzumab era demonstrated increased cumulative risk (6.8% vs. 3.5%) and increased incidence of CNS disease as the first site of breast cancer relapse (2.5% vs. 1.0%) in *HER*2+ vs. *HER*2− patients. These findings suggest that differences in underlying tumor biology between these subgroups may influence the development of CNS disease (11, 18, 21, 28). Regardless of the relative proportionality of these effects, brain metastases remain a significant problem in patients with *HER*2+ breast cancer, particularly in the post-trastuzumab era.

Because systemic treatments have improved long-term survival in these patients (26, 29–31), preventing morbidity and mortality related to development of brain metastases is an important consideration. Several strategies attempt to address this issue. Whole-brain radiotherapy (WBRT) is known to improve survival (32) and to reduce the cumulative incidence of brain metastases and the risk of death, leading some to suggest prophylactic WBRT in patients with *HER*2+ breast cancer. This has been met with limited enthusiasm (24, 33) because of concerns for possible delayed neurocognitive effects of WBRT (34) and patient preferences. Small-molecule inhibitors, such as lapatinib, have also been considered as adjuvant chemotherapeutic agents. The potential, long-term benefits of lapatinib to treat brain metastases remain unknown (35–37). Stereotactic radiosurgery (SRS) represents an attractive option, because it offers single-session, outpatient therapy associated with low morbidity, fewer neurocognitive side effects, minimal recovery time, and little or no interruption of therapy for the primary malignancy (38). One published abstract (17) suggested an improved likelihood of 1-year survival in patients with *HER*2+ breast cancer treated with SRS, but there is no further understanding of the role of SRS in these patients. We analyzed the factors affecting outcomes in patients with brain metastases from breast cancer to characterize the role and the implications of *HER*2 status in the management of CNS disease and to assess the efficacy of SRS in a large series of patients with breast cancer metastatic to the brain.

Methods and Materials

We conducted an institutional review board–approved review of patients managed by the Brain Tumor and Neuro-Oncology Center at the Cleveland Clinic from 1999 to 2008. Patients with a histologic diagnosis of breast adenocarcinoma and one or more brain lesions consistent with metastases were eligible. All primary histologic diagnoses of breast cancer were made from breast tissue obtained by either biopsy or resection. Assessment of *HER*2 status was independently performed on all tissue specimens by our institution's Department of Pathology and Laboratory Medicine on this tissue using a combination of immunohistochemistry and fluorescence in situ hybridization (39, 40) according to the American Society of Clinical Oncology/College of American Pathologists guidelines (41) (see Supplementary Methods and Materials [available online] for additional details). Brain biopsies are generally not performed for confirmatory histology at our institution when the clinical history and radiographic findings suggest metastatic disease, and brain metastases were therefore treated with either surgical resection, WBRT, SRS, or a combination thereof. Patients were excluded if they were aged <18 years or if metastases to the spine or leptomeningeal carcinomatosis represented their only form of CNS metastatic disease. Patients were treated with single-session SRS according to Radiation Therapy Oncology Group 95-08 standards (42). Overall survival (OS) is defined as the interval from the initial diagnosis of the primary breast cancer to the time of death; neurologic survival (NS) is the interval from initial radiographic diagnosis of brain metastasis(es) to the time of death; and survival after radiosurgery (RS) is the interval from SRS to time of death. Patients alive at the time of data analysis had a censored survival point entered. Standard statistical analyses were performed using SPSS. See Supplemental Methods and Materials for additional details.

Results

Study population

The study group comprised a total of 264 patients treated between January 1, 1999 and December 31, 2008 for brain metastases from breast cancer. The mean age at diagnosis was 47.1 years (σ = 0.6), the median was 46 years, and the range was 21–76 years. The median interval from initial diagnosis of the primary malignancy to radiographic diagnosis of CNS disease was 36 months (range, −2 to 407 months; −2 indicates brain metastases diagnosed 2 months before primary malignancy). At initial diagnosis of the primary malignancy, 38 patients (14.4%) were classified as Stage I, 75 (28.4%) as Stage II, 38 (14.4 %) as Stage III, and 24