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Breast Cancer

Central Nervous System Metastases in HER-2–Positive Metastatic Breast Cancer Patients Treated with Trastuzumab: Incidence, Survival, and Risk Factors

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Key Words. CNS metastasis incidence • HER-2–positive breast cancer • Prognosis • Risk factors

ABSTRACT

Background. **A higher incidence of central nervous system (CNS) metastases in HER-2–positive metastatic breast cancer (MBC) has recently been reported.**

Materials and Methods. **Aims of this observational study were to evaluate the incidence of CNS metastases in HER-2–positive MBC patients, to define the outcome of patients with CNS metastases, and to identify the risk factors for CNS relapse.**

Results. **Between April 1999 and June 2005 we treated 122 consecutive HER-2–positive MBC patients with chemotherapy and trastuzumab. At a median follow-up of 28 months from the occurrence of metastatic disease, 43 patients (35.2%) developed CNS metastases. The median time to death from the diagnosis of CNS metastases was 23.46 months. At multivariate analysis we found that only premenopausal status at diagnosis of breast cancer and visceral metastases as the dominant site at relapse were significantly associated with a higher risk for CNS metastases.**

Conclusion. **The CNS metastasis incidence is very high in HER-2–positive MBC, but the survival after CNS relapse in these patients is longer than in patients unselected for HER-2 status, because of the better control of extracranial disease obtained by trastuzumab. The identified risk factors for CNS relapse could allow us to select a subgroup of HER-2–positive MBC patients as candidates for active surveillance for CNS progression (by computed tomography or magnetic resonance imaging) and/or as candidates for accrual in trials of prevention of CNS relapse.** ***The Oncologist*** 2007;12:766–773

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Introduction

The human epidermal growth factor receptor 2 (HER-2) is an oncoprotein composed of an intracellular tyrosine kinase portion, a short transmembrane section, and an extracellular ligand-binding domain (ECD, p105). Overexpression of the HER-2 protein, which arises predominantly through amplification of the *her-2/neu* oncogene, is implicated in oncogenic transformation and tumor genesis and occurs in 20%–25% of breast cancers [1, 2]. This alteration is associated with greater biological aggressiveness and poor prognosis [1, 3]. Trastuzumab, a humanized monoclonal antibody directed against HER-2, is a novel targeted therapy for patients with HER-2–positive breast cancer. Trastuzumab monotherapy has demonstrated antitumor activity in metastatic disease when used in patients previously treated with chemotherapy (12%–15% response rate) [4, 5] and when used in the first-line setting (26% response rate) [6]. Based on preclinical data of additive or synergistic activity of trastuzumab and various antiblastic drugs [7–9], trastuzumab in combination with chemotherapy has been evaluated in many phase II trials, with response rates of up to 70%–80%. In a phase III trial, the addition of trastuzumab to chemotherapy was also associated with a longer median survival time than with chemotherapy alone [10]. These results have led to an increased use of trastuzumab in clinical practice.

Recently, some authors have observed that 25%–50% of patients with HER-2–positive metastatic breast cancer (MBC) treated with trastuzumab-based therapy developed central nervous system (CNS) metastases [11–17]. This incidence of CNS metastases in HER-2–positive metastatic disease is higher than that reported in historical (10%–15%) [18] and autoptic (29.6%) [19] series.

The aims of this retrospective study were to evaluate, in a large group of patients with HER-2–positive MBC treated with trastuzumab, the proportion of patients who develop CNS metastases, to define the outcome of patients with CNS metastases, and to correlate the incidence of CNS disease with some clinical and biopathological variables.

Materials and Methods

Patients with HER-2–positive MBC who received trastuzumab with or without chemotherapy from April 1999 to June 2005 at three Italian institutions were identified using pharmacy records.

Data on patient and tumor characteristics were abstracted from medical records. The extracted information also included sites of disease at the time of metastatic disease diagnosis and status of disease (stable, responding, progressing) at the time of CNS metastases. CNS disease included one or more parenchymal brain metastases or leptomeningeal carcinomatosis.

A normal left ventricular ejection fraction (>50%), as determined by echocardiography, was required to treat patients with trastuzumab.

Statistical Analysis

The overall survival (OS) time was measured from the diagnosis of breast cancer (OS1), from the occurrence of metastatic disease (OS2), and from the development of CNS metastases (OS3) to death from any cause and was estimated according to the Kaplan-Meier method [20]. For all analyses, time was censored at the last follow-up date if no event/death was observed.

Differences in time distributions were evaluated using the log-rank test [21] and Cox's proportional hazard regression [22].

A multivariate analysis was performed using the dichotomous, categorical, or continuous variables that resulted in a p-value $\leq .10$ in the univariate analysis.

All p-values are derived from two-sided significance tests. SPSS, version 11.5, software was used for statistical analyses (SPSS Inc., Chicago, IL).

Results

We reviewed the occurrence of CNS metastases in 122 consecutive HER-2–positive MBC patients treated with chemotherapy and trastuzumab between April 1999 and June 2005. The characteristics of the patients included in the study are summarized in Table 1. In 10 patients with HER-2 2+ tumors, the slides for fluorescence in situ hybridization amplification were not available. The median age of the patients was 48 years (range, 28–79 years). Tumor characteristics included G3 grading in 71 patients (58.1%) and estrogen receptor (ER)- and progesterone receptor (PgR)-negative status in 61 patients (50.0%). The disease-free interval was <24 months in 59 patients (48.3%) and ≥24 months in 63 patients (51.7%). Visceral metastatic disease was the dominant site of relapse in 82 patients (67.2%). Trastuzumab associated with chemotherapy represented the first line of treatment in 66 patients (54.0%), the second line in 35 patients (28.6%), and the third line or greater in 21 patients (17.2%).

The median follow-up time was 56 months (range, 2–230 months) from the initial diagnosis of breast cancer and 28 months (range, 2–167 months) from the occurrence of metastatic disease.

Incidence of CNS Metastases

At a median follow-up of 28 months (range, 2–167 months) from the occurrence of metastatic disease, 43 patients (35.2%) had developed CNS metastases, confirmed by computed tomography (CT) or magnetic resonance imag-

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Table 1. Patient characteristics ($n = 122$)

Characteristic	*n*	%
Age		
Median (range)	48 years (28–79 years)	
Menopausal status		
Premenopausal	60	49.1
Postmenopausal	62	50.8
Tumor size		
≤2 cm	44	36.0
2–5 cm	49	40.1
>5 cm	15	12.2
Undetermined	14	11.4
Axillary lymph node status		
Negative	22	18.0
Positive	86	70.4
Unknown	14	11.4
Receptor status (cutoff ≥10%)		
ER status		
Positive	54	44.2
Negative	67	54.9
Unknown	1	0.8
PgR status		
Positive	74	60.6
Negative	45	36.8
Unknown	3	2.4
ER/PgR status		
ER and PgR negative	61	50.0
ER and/or PgR positive	60	49.1
Unknown	1	0.8
Grade		
G1	3	2.4
G2	27	22.1
G3	71	58.1
Unknown	21	17.2
HER-2 status		
IHC 2+	10	8.1
IHC 3+	92	75.4
FISH amplified	20	16.3
Dominant metastatic disease site at relapse		
Soft tissue	21	17.2
Bone	19	15.5
Visceral	82	67.2
Lung	41/82	50.0
Liver	47/82	57.3

Abbreviations: ER, estrogen receptor; FISH, fluorescence in situ hybridization; HER-2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; PgR, progesterone receptor.

ing (MRI) (Table 2). In 10 patients, a single brain metastasis was observed and in 32 patients multiple parenchymal brain metastases occurred; leptomeningeal carcinomatosis was observed in only one patient. Neurological symptoms were present in 90.6% of these patients. CNS metastasis development occurred at the diagnosis of metastatic disease in 9 of 43 patients: in five patients as the only metastatic site and in four patients associated with other disease sites. In the remaining 34 patients, CNS metastases were diagnosed during treatment for metastatic disease (Table 2). In 26 of these 34 patients (76.4%), CNS metastasis development occurred during trastuzumab treatment. Eighteen of 34 patients (52.9%) who developed CNS metastases during treatment for metastatic disease were still responding in other metastatic sites and three patients (8.8%) had stable disease: in these patients the CNS represented the only site of progression. Disease progression at other sites at the time of CNS relapse was documented in 11 patients; two patients were not evaluable.

The median time of occurrence of CNS metastases from the diagnosis of metastatic disease was 12 months (range, 0–78 months). In the 34 patients who developed CNS metastases during treatment for metastatic disease, the median time to CNS development from the start of trastuzumab-based therapy was 8.3 months (range, 1–41 months).

Treatment of CNS Metastases

Following the diagnosis of cerebral metastases, 4 of 10 patients with a single cerebral lesion underwent surgery followed by whole brain radiotherapy and one patient was treated with stereotactic radiotherapy. In the 32 patients with multiple cerebral lesions, whole brain radiotherapy was administered in 30 patients and stereotactic radiotherapy was administered in 2 patients. No radiotherapy was delivered in the patient with leptomeningeal carcinomatosis. After the diagnosis of CNS metastases, trastuzumab with or without chemotherapy was administered in 17 patients (39.5%), cytotoxic chemotherapy was administered in 17 patients (39.5%), and nine patients (21.0%) received best supportive care only (Table 3).

Overall Survival

The median survival duration from the initial diagnosis of breast cancer (OS1) was 113 months (range, 2.1–230.3 months) in the overall population, 74.9 months (range, 7–170 months) in patients with CNS metastases, and 190.7 months (range, 2–230.3 months) in patients without CNS metastases ($p = .0056$). In the multivariate analysis (Cox's regression), young age as a continuous variable at diagnosis ($p = .028$) and presence of metastatic disease at diagnosis

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Table 2. CNS metastasis incidence

	n	%
n of all patients	122	100.0
CNS metastasis incidence[a]		
Total	43/122	35.2
At diagnosis of metastatic disease	9/43	20.9
During the treatment for metastatic disease	34/43	79.0
Neurological symptoms	39/43	90.6
Response at other sites at CNS relapse[b]		
CR + PR	18/34	52.9
SD	3/34	8.8
NV	2/34	5.8
PD	11/34	32.3
CNS as the only site of progression		
CR + PR + SD	21/34	61.7

The median follow-up was 28 months from the diagnosis of metastatic disease.
The median time of occurrence of CNS metastases was 12 months (range, 0–78 months).
[a] Confirmed by computed tomography or magnetic resonance imaging.
[b] In 34 patients (nine patients with CNS metastases at the time of first diagnosis of metastatic disease were excluded).
Abbreviations: CNS, central nervous system; CR, complete response; NV, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

($p = .001$) were significantly associated with worse survival (Fig. 1).

The median survival time from the occurrence of metastatic disease (OS2) was 51.2 months (range, 1.9+ to 167.4 months) in the overall population and 35 months (range, 4–105 months) in patients with CNS metastases. In the present analysis, the median OS time had not yet been reached in patients without CNS metastases ($p = .0024$) (Fig. 2). In the multivariate analysis (Cox's regression), CNS metastases ($p = .034$) and young age, as a continuous variable, at the diagnosis of metastatic disease ($p = .022$) were significantly associated with worse OS in this series.

The median time to death from the diagnosis of CNS metastases (OS3) was 23.46 months (range, 0.03–52.13+ months) (Fig. 3).

No statistically significant difference related to line of trastuzumab-based treatment (first line versus second line versus third line or greater) in the median survival time measured from the initial diagnosis of breast cancer (OS1), from the occurrence of metastatic disease (OS2), or from the diagnosis of CNS metastases (OS3) was found.

Risk Factors for CNS Metastases

To evaluate the risk factors for CNS metastasis development, logistic regression was performed first using univariate analysis. The following covariates were considered: menopausal status at diagnosis, age at diagnosis, lymph node status at diagnosis, ER and PgR status, dominant site of relapse (visceral, bone, and soft tissue), lung metastases, and liver metastases. Menopausal status at diagnosis ($p = .001$), age at diagnosis ($p = .003$), ER status ($p = .047$), and visceral metastases ($p = .04$) were significantly associated with a greater risk for CNS metastases (Table 4). Lymph node status at diagnosis ($p = 0.881$), PgR status ($p = .341$), lung metastases ($p = .826$), and liver metastases ($p = .343$) were not predictive of development of CNS metastases. A multivariate logistic regression model was built using the significant covariates. It showed that only premenopausal status at diagnosis ($p = .001$) and visceral metastases as the dominant site of disease at relapse ($p = .023$) significantly predicted the development of CNS metastases.

Discussion

In recent years, many authors have reported a higher risk for CNS metastases in HER-2–positive MBC patients.

At a median follow-up of 28 months from the occurrence of metastatic disease, we observed a 35.2% incidence of CNS metastases, similar to that reported in other trials [11–13, 15]. The median time from the diagnosis of metastatic disease to CNS recurrence in our experience was 12 months, overlapping with the median times of 11.5 months and 16.0 months found by Heinrich et al. [13] and Bendell et al. [12], respectively. Results from our study confirm that CNS metastases are a common event among HER-2–positive MBC patients, and this may result from several factors.

It has been postulated that HER-2 overexpression/amplification might predispose to CNS spread. In retrospective studies, HER-2 overexpression was significantly associated either with visceral and CNS involvement [23] or with "occult" CNS metastases in patients screened for participation in clinical trials [24]. In another series of 92 patients treated with paclitaxel and epirubicin for metastatic or locally advanced breast cancer, HER-2 overexpression was retrospectively associated with CNS relapse [25].

The superior metastatic disease control and longer survival obtained by trastuzumab-based treatment give the tumor more opportunity to occur and to become evident in the "sanctuary" of the CNS. High concordance (100%) for HER-2 status was also detected between a primary breast

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Table 3. Treatment of CNS metastases (n = 43 patients)

Treatment	*n* (%)
Local treatment	
Single cerebral lesion (n = 10 patients)	
Surgery followed by WBRT	4 (40.0%)
Stereotactic radiotherapy	1 (10.0%)
WBRT	4 (40.0%)
No radiotherapy	1 (10.0%)
Multiple cerebral lesions (n = 32 patients)	
WBRT	30 (93.7%)
Stereotactic radiotherapy	2 (6.2%)
Leptomeningeal carcinomatosis (n = 1 patient)	
Local treatment not administered	1 (100%)
Systemic treatment (n = 43 patients)	
Trastuzumab with or without further chemotherapy	17 (39.5%)
Cytotoxic chemotherapy	17 (39.5%)
Symptomatic medical therapy	9 (21.0%)

Abbreviations: CNS, central nervous system; WBRT, whole brain radiotherapy.

tumor and CNS metastases [26, 27]. Moreover, during i.v. weekly trastuzumab treatment, only a minimal amount of monoclonal antibody penetrates the cerebrospinal fluid (CSF) and trastuzumab levels in the CSF are 300-fold lower than serum levels [28].

The median survival time of our patients after CNS metastasis development was 23.4 months (range, 0.03–52.13+ months), higher than that reported in the literature in HER-2 – positive patients [11–13]. In patients with CNS metastases, unselected for HER-2 status, the median overall survival duration after whole brain radiotherapy is very poor, only 4–6 months [29, 30], and few trials have explored the use of chemotherapy, which in most circumstances is reserved for patients whose CNS disease has

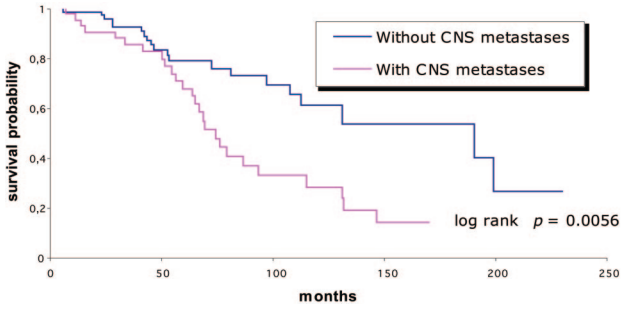

Figure 1. Overall survival from the time of diagnosis of breast cancer (n = 122 patients).
Abbreviation: CNS, central nervous system.

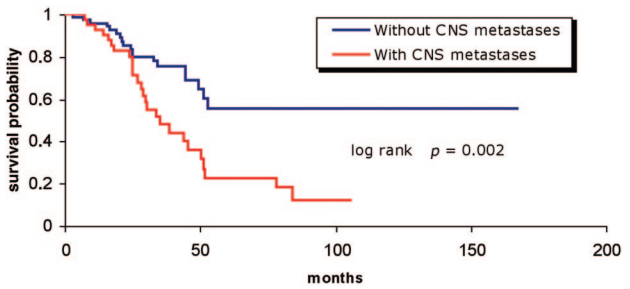

Figure 2. Overall survival from the time of diagnosis of metastatic disease (n = 122 patients).
Abbreviation: CNS, central nervous system.

progressed despite radiotherapy [30]. In our study, following the diagnosis of cerebral metastases, radiotherapy was delivered to 95% (41 of 43) of HER-2–positive patients; trastuzumab with or without chemotherapy was administered in 39.5% (17 of 43) of the CNS metastatic patients and chemotherapeutic treatment was administered in 39.5% (17 of 43) of the patients (Table 3). Moreover, we found that in 61.7% of our patients the CNS was the only site of progression. Our data confirm previous observations [11–13] that a high percentage of patients (71%–79%) who develop CNS metastases have responsive or stable disease at other metastatic sites. The better control of extracranial disease reported in HER-2–positive patients treated with trastuzumab is probably the cause of the longer survival of these CNS metastatic patients. In a recent publication, patients with HER-2–positive tumors had a significantly longer survival time after the diagnosis of brain metastases than patients with HER-2–negative tumors (22.4 versus 9.4 months from date of brain metastases, respectively; p = .0002 by log-rank test) [31]. This prolonged survival advantage may be correlated with better control of extracranial systemic disease resulting from trastuzumab-based treatment, administered in 77% of CNS metastatic patients. Moreover, the patients with HER-2–positive tumors who did not receive trastuzumab had a survival duration similar

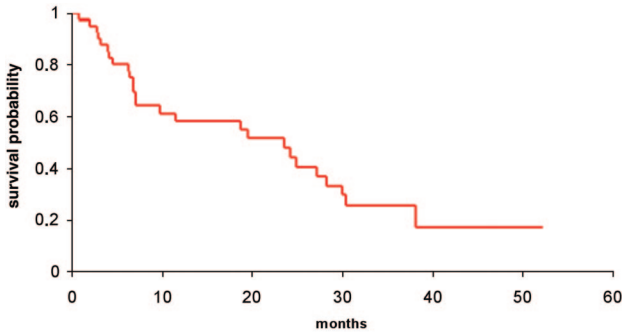

Figure 3. Overall survival from the time of diagnosis of central nervous system (CNS) metastases (n = 43 patients).

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Table 4. Risk for central nervous system metastasis development using variables found to be significant in the univariate analysis

Variable	CNS metastasis incidence	*p*-value
Menopausal status at diagnosis		
Premenopausal	50.0%	.001
Postmenopausal	21.0%	
Age at diagnosis		
≤50 years	46.4%	.003
>50 years	20.8%	
Estrogen receptor status		
Negative	43.3%	.047
Positive	25.9%	
Visceral metastases at relapse		
Yes	41.5%	.04
No	22.5%	

to that of patients with HER-2–negative tumors [31]. Also, in a randomized trial [32], longer survival with aggressive therapy was obtained in patients with a single metastasis only if extracranial disease was controlled. Interestingly, Kirsch et al. [31] suggested that the survival advantage does not correlate with better control of the brain metastases, but may be a result of better control of extracranial systemic disease in patients with HER-2–positive tumors who receive trastuzumab, as also reported by others [33, 34].

Because the overall survival duration of HER-2–positive patients who develop CNS metastases is very long, adequate treatment of brain disease and extracranial disease is necessary. Local therapy (surgery, whole brain radiotherapy, stereotactic radiotherapy) is indicated for CNS metastasis treatment. If disease is responsive or stable at other sites, it is necessary to continue trastuzumab-based therapy to obtain prolonged control of extracranial disease.

The prognosis for patients with HER-2–positive MBC changed with the introduction of trastuzumab, which has also prolonged the survival of patients who develop CNS disease. For these reasons, it is important to know the subgroup of HER-2–positive MBC patients at risk for CNS metastases, who may be candidates for serial radiological screening to detect asymptomatic brain metastases or for CNS prophylaxis strategies. For these reasons, we analyzed the risk factors for CNS metastasis development. In previous experience, negative hormone receptor status [35–37] and lung metastases as the first site of relapse [24, 25, 36] were identified as predictive factors for brain metastases in patients with MBC, unselected for HER-2 status. In our study, we conducted a multivariate analysis in 122 HER-2–positive MBC patients and we showed that premenopausal status at the time of diagnosis of breast cancer and visceral metastases as the dominant site at relapse are independent factors that significantly predict the development of CNS disease progression in HER-2–positive metastatic patients. This information could allow the selection of subgroups of HER-2–positive MBC patients as candidates for active surveillance with CT or MRI for CNS relapse and as candidates for enrollment in trials of CNS metastasis prevention with prophylactic cranial irradiation or with drugs that target HER-2 and cross the blood–brain barrier. Lapatinib, an oral dual-kinase inhibitor with specificity for both ErbB-1 and ErbB-2, demonstrated, in a phase II trial, a clinical effect in HER-2–positive breast cancer patients with CNS metastases pretreated with trastuzumab and radiotherapy [38], and other trials are ongoing in this subset of patients.

A phase III trial of lapatinib and capecitabine versus capecitabine alone also showed a lower incidence of brain metastases as the site of progression in the lapatinib–capecitabine arm [39]. In the future, we could have active therapies in the treatment and prevention of CNS metastases in HER-2–positive disease.

Conclusion

Although our study is retrospective, and only trastuzumab-treated patients were analyzed, our data confirm that the CNS metastasis incidence is very high in HER-2–positive MBC patients (35%). Furthermore, the survival duration after CNS relapse in these patients is longer (24 months) than in patients unselected for HER-2 status, because of the better control of extracranial disease obtained by trastuzumab.

In our experience, the risk factors for CNS metastasis development in HER-2–positive MBC patients are premenopausal status at the time of diagnosis of breast cancer and visceral metastases as the dominant site at relapse. These characteristics could allow us to select a subgroup of HER-2–positive MBC patients as candidates for active surveillance for CNS progression (by CT or MRI) and/or as candidates for accrual in trials of prevention of CNS relapse.

Disclosure of Potential Conflicts of Interest

The authors indicate no potential conflicts of interest.

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Stefania Gori, Simonetta Rimondini, Verena De Angelis, Mariantonietta Colozza, Giancarlo Bisagni, Gabriella Moretti, Angelo Sidoni, Carlo Basurto, Cynthia Aristei, Paola Anastasi and Lucio Crinò

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