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Breast Cancer Res Treat (2009) 117:297–303
DOI 10.1007/s10549-008-0275-z

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Received: 8 October 2008 / Accepted: 9 December 2008 / Published online: 7 January 2009

Abstract Brain relapse is a common occurrence in HER2-positive breast cancer patients. However, the factors determining the risk of brain metastasis in these patients remain to be established. The aim of this study was to assess the impact of particular clinical and pathological factors on the risk of brain relapse in HER2-positive advanced breast cancer patients. The study group included 264 consecutive HER-2 positive metastatic breast cancer patients, most of whom (210; 80%) were administered trastuzumab, usually in combination with chemotherapy. Time from the diagnosis to distant relapse ranged from 0 to 142 months (median 16 months). The most common dominant site of metastatic disease was viscera (80%), followed by soft tissue (11%) and bones (10%). After a median follow-up of 3.1 years, the symptomatic brain relapse occurred in 103 patients (39%). Median time from treatment dissemination to brain relapse was 15 months (range, 0–81 months), and the cumulative 1-year, 3-year and 5-year risk of brain relapse was 17, 42 and 55%, respectively. The average annual risk of brain relapse for surviving patients during consecutive 7 years of follow-up was 10.0% (95% CI, 6.6–13.5%). In the univariate analysis the only variable significantly related to the increased risk of brain relapse was time from initial diagnosis to distant relapse shorter than 2 years (HR = 1.55, 95% CI, 1.03–2.33, $P = 0.034$). Patients with dominant site of disease in soft tissue or bones tended to have lower risk of relapse (HR = 0.54 and 0.62; $P = 0.098$ and 0.203, respectively) compared to patients with visceral metastases. Treatment with trastuzumab was not associated with reduced risk of brain relapse (HR = 0.91, 95% CI, 0.47–1.77, $P = 0.78$). In the multivariate analysis, time from initial diagnosis to distant relapse shorter than 2 years remained the only significant variable related to increased risk of brain relapse (adjusted HR = 1.62, 95% CI, 1.07–2.44; $P = 0.022$). HER2-positive breast cancer patients remain at high and continuous risk of brain relapse for a prolonged period of time after diagnosis of disease dissemination. Short time from initial diagnosis to distant relapse is related to increased risk of brain relapse. Molecular predictors are sorely needed to better characterize patients with high probability of early brain relapse.

Keywords Brain relapse · HER2-positive breast cancer · Trastuzumab · Brain-blood barrier

Presented in part in oral form at the 2007 European Cancer Conference, Barcelona, Spain.

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Introduction

Brain is among the most common sites of relapse in breast cancer, with the clinical and autopsy occurrence of 14–20% and 18–30%, respectively [1, 2]. Relapse in the brain is

related to high morbidity and mortality, with relatively few effective therapeutic options. This issue has emerged as an important clinical problem, since most cytotoxic agents used in breast cancer do not cross the blood–brain barrier, making brain a sanctuary site for the development of metastasis. Additionally, increased efficacy of systemic treatment in extracranial sites may allow more time for the development of brain metastasis. Indeed, some recent studies suggested increased risk of brain relapse in breast cancer patients administered taxanes and anthracyclines, the two most effective groups of anticancer agents in this malignancy [3, 4]. Another factor contributing to increasing occurrence of brain lesions are refined imaging methods, providing more effective detection.

Several studies demonstrated increased risk of brain relapse in breast cancer patients with overexpressed or amplified *HER2-neu* gene [5–8]. HER2 abnormalities occur in 20–30% of invasive breast cancers and are associated with more aggressive tumor growth, increased risk of relapse and shorter survival [9, 10]. Currently HER2-positive breast cancer patients are managed with trastuzumab, a monoclonal antibody against extracellular domain of HER2 receptor. Trastuzumab does not cross through the blood–brain barrier and is ineffective in preventing and treating brain lesions [11–17]. Recently, Food and Drug Administration (FDA) and European Medicines Agency (EMEA) granted approval to lapatinib, an anti-HER2 small-molecule tyrosine kinase inhibitor, for use in women with advanced HER2-positive breast cancer who have progressed on trastuzumab treatment.

In most instances brain metastases in breast cancer patients appear after another systemic disease has developed at other sites. With the increased treatment efficacy of extracranial lesions, poor control of brain lesions may largely influence prognosis. For example, in a recent series including metastatic breast cancer patients treated with trastuzumab, nearly half of deaths were due to progressive brain disease [11]. It is hoped that determining tumor and host risk factors for brain metastasis might allow selection of candidates for preventive strategies. Most studies addressing risk factors for brain relapse included unselected breast cancer patients [18–22], whereas little is known on this issue in HER2-positive breast cancer patients [23, 24]. In this study we assessed retrospectively the impact of selected clinical and pathological variables on the risk of brain relapse in a large, unselected group of patients with metastatic HER2-positive breast cancer.

Materials and methods

Patients

This series included 264 consecutive HER2-positive (immunohistochemistry 3+ or FISH-positive) pathologically confirmed metastatic breast cancer patients treated in six oncology centers between 1993 and 2007 (Table 1). Tumor diagnosis and cancer type were determined by two independent pathologists. Expression of estrogen and progesterone receptors was determined using immunohistochemistry, with 10% of nuclear staining considered as a positive result. HER2 protein expression was determined using semiquantitative immunohistochemistry (HercepTest, Dako A/S, Glostrup, Denmark). Only samples showing strong expression (scored 3+), defined as uniform, intense membrane staining of at least 10% of invasive tumor cells, were considered positive. The samples showing intermediate expression (scored 2+) were subjected to additional analysis of gene HER2 copy number using fluorescence in situ hybridization (FISH). Gene amplification by FISH was defined as a FISH ratio (*HER2*/centromeric probe for chromosome 17 ratio) of more than 2.0. FISH-positive patients were considered HER2-positive. Due to the retrospective nature of this study, tumor staging was performed using AJCC/UICC classification from 1997. Metastatic lesions were grouped into three categories: soft tissue, bones and viscera. For tumors involving more than one category, dominant site of distant disease was classified by the category associated with the worst prognosis, irrespective of the extent of involvement, in the following order of increasing gravidity: soft tissue, bones, viscera.

Seventy-two percent of the patients relapsed after previous curative surgery, and the remaining 28% were inoperable at the time of diagnosis (Table 1). Postoperative radiotherapy was applied in 93 patients (49% of those subjected to surgery). A total of 210 patients (80%) were administered trastuzumab for metastatic disease, usually in combination with chemotherapy. No patient received trastuzumab in the adjuvant setting. The time from the initial diagnosis to distant relapse ranged from 0 to 142 months (median 16 months). No screening for occult brain lesions was performed, therefore all metastases were symptomatic.

Statistical analysis

Continuous variables were described using the group size, variable mean or median and range. Qualitative variables were compared by chi-square test and exact Fisher's test, where appropriate. Median follow-up was calculated in accordance with Schemper and Smith [25]. Time to progression, time to brain relapse, and overall survival were estimated by the Kaplan–Meier method and compared using univariate log-rank tests. Hazard ratios and 95% confidence intervals for particular variables were calculated using univariate Cox's proportional model; reported *P* values were derived from Wald's test. Multivariate analysis was done with backward manual elimination based on likelihood-ratio statistics. Cumulative risk of

Table 1 Patent characteristics ($n = 264$)[a]

Variable	*n* (%)
Menopausal status	
Premenopausal	131 (50%)
Postmenopausal	130 (49%)
Unknown	3 (1%)
Age at diagnosis (years)	
Mean	49
Range	24–77
Dominant site of disease	
Visceral	210 (80%)
Soft tissue	28 (11%)
Bones	26 (10%)
Steroid receptor status	
ER+/PgR+	57 (22%)
ER+/PgR−	39 (15%)
ER−/PgR+	12 (5%)
ER−/PgR−	144 (55%)
Unknown	12 (5%)
Pathology type	
Ductal	210 (80%)
Lobular	16 (6%)
Ductal and lobular	9 (3%)
Other	8 (3%)
Not specified	21 (8%)
Grade	
G1	4 (2%)
G2	87 (33%)
G3	100 (38%)
Not specified	73 (28%)
Surgery	
Modified radical mastectomy	183 (69%)
Breast conservation	8 (3%)
None	73 (28%)
Chemotherapy[b]	
Induction only	15 (8%)
Adjuvant only	83 (43%)
Induction and adjuvant	74 (39%)
None	19 (10%)
Adjuvant endocrine therapy[b]	
Tamoxifen	78 (41%)
Aromatase inhibitors	3 (2%)
Tamoxifen and aromatase inhibitors	13 (7%)
None	97 (51%)
Adjuvant radiotherapy[b]	93 (49%)
Trastuzumab for advanced disease	210 (80%)

[a] Percentages may not sum up to 100 due to rounding

[b] Only in patients subjected to surgery

brain relapse was calculated using cause-specific hazard method with deaths considered as censored events [26]. We additionally performed cumulative incidence analysis using competing risk model with deaths as competing events [26]. The model was based on the assumption that longer survival of patients treated with trastuzumab may have resulted in higher chance of observing brain relapse. All reported tests were two-sided with significance level of $\alpha = 0.05$, with no adjustments for multiple comparisons. All calculations were performed using SPSS for Windows version 13.0 (SPSS Inc., Chicago, IL) and NCSS 2001 (NCSS Inc., Kaysville, UT).

Results

The median follow-up from the diagnosis of disease dissemination was 3.1 years (range, 0–11.4 years). 1-year and 2-year survival probabilities were 82% (95% confidence interval [CI], 77–86%) and 66% (95% CI, 60–72%), respectively. Symptomatic brain relapse occurred in 103 patients (39%). Seventeen patients (6%) presented with brain metastases at the time of dissemination occurrence. Median time from disease dissemination to brain relapse was 15 months (range, 0–81 months). Cumulative 1-year, 3-year and 5-year risk of brain relapse was 17% (95% CI, 13–22%), 42% (95% CI, 35–49%) and 55% (95% CI, 46–64%), respectively (Fig. 1). Cumulative hazard function of brain relapse was constant with time (data not shown). When 17 patients in whom first distant relapse

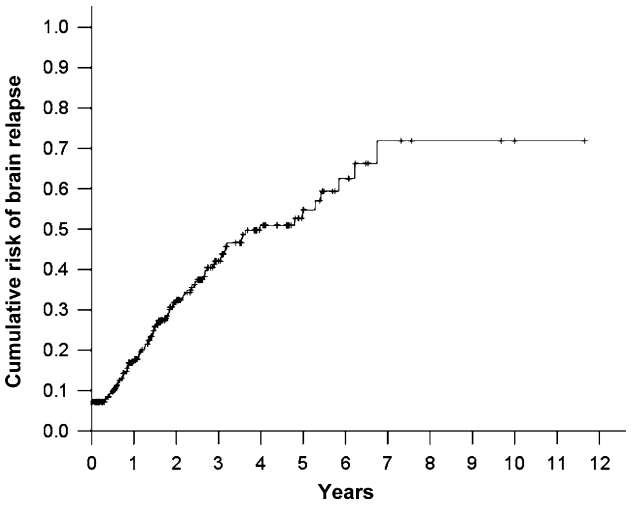

Fig. 1 Cumulative risk of brain relapse. Median time from disease dissemination to brain relapse: 15 months; cumulative 1-year, 3-year and 5-year risk of brain relapse: 17, 42 and 55%, respectively

included brain metastases were excluded from the analysis, the average annual risk of brain relapse for surviving patients during consecutive 7 years of follow-up was 10.0% (95% CI, 6.6–13.5%).

In the univariate analysis the only variable significantly related to the increased risk of brain relapse was time from initial diagnosis to distant relapse shorter than 2 years (HR = 1.55, 95% CI, 1.03–2.33; $P = 0.034$; Table 2; Fig 2). Cumulative 1-year and 3-year risk of brain relapse in postmenopausal patients was 15% (95% CI, 8–22%) and 37% (26–48%), compared to 19% (13–25%) and 45% (36–55%) in premenopausal patients, respectively. Patients with dominant site of disease in soft tissue or bones tended to have lower risk of relapse (HR = 0.54 and 0.62, respectively; $P = 0.098$ and 0.203, respectively) compared to patients with visceral metastases. Administration of trastuzumab was not associated with reduced risk of brain metastases (HR = 0.91, 95% CI, 0.47–1.77, $P = 0.78$; Table 2; Fig. 3). In the multivariate analysis, time to distant relapse from initial diagnosis shorter than 2 years remained the only significant variable related to increased risk of brain relapse (HR = 1.62, 95% CI, 1.07–2.44; $P = 0.022$; adjusted for histology, age and dominant site of disease). We also performed supplementary univariate analysis of risk factors for early brain relapse (within 3 years) by censoring all patients who survived without brain relapse for longer than 3 years. Results of this analysis were similar to those presented in Table 2.

In the competing risk analysis with deaths as censored events, the cumulative risk of brain relapse was similar in patients who did and did not receive trastuzumab, with a 3-year incidence of brain relapse of 20% (95%CI: 15–27%) and 29% (19–46%), respectively (figure not shown).

Table 2 The risk of brain relapse according to clinicopathological variables: univariate analysis

Variable	HR	95% CI	*P*
Menopausal status			
Postmenopausal	1.00		
Premenopausal	1.12	0.76–1.67	0.56
Age (continuous variable)	0.99	0.97–1.01	0.52
Pathology type			
Non-lobular	1.00		
Lobular	1.26	0.69–2.30	0.45
Grade			
G1	NA	NA	NA
G2	1.00		
G3	0.95	0.60–1.49	0.81
Time to distant relapse			
>2 years	1.00	1.03–2.33	0.034
≤2 years	1.55		
Dominant site of disease			
Viscera	1.00		
Soft tissue	0.54	0.26–1.12	0.098
Bone	0.62	0.30–1.29	0.203
ER			
Negative	1.00		
Positive	0.82	0.55–1.23	0.34
PR			
Negative	1.00		
Positive	0.95	0.61–1.47	0.81
Trastuzumab therapy[a]			
No	1.00		
Yes	0.91	0.47–1.77	0.78

NA—Not assessable due to insufficient number of patients

[a] Seventeen patients who initially presented with brain metastases were excluded

Discussion

Our study included a large series of HER2-positive advanced breast cancer patients, with relatively long follow-up. Cumulative 3-year risk of brain relapse of 42% is in the range found in other series of HER2-positive advanced breast cancer patients [11–17, 23]. In this cohort the average annual risk of symptomatic brain relapse for surviving patients during consecutive 7 years of follow-up was 10%, with no apparent plateau. Thus, HER2-positive advanced breast cancer patients remain at high and continuous risk of brain relapse for a prolonged period of time after diagnosis of disease dissemination, and the development of brain metastasis in this group appears to be a stochastic event.

High incidence of brain relapse in HER2-positive patients has been attributed to aggressive behavior of this subtype, including more rapid cell proliferation, increased angiogenesis, deficient apoptosis and increased metastasis formation [9, 10]. It is therefore possible that this phenotype also predisposes to brain metastasis. However, HER2-positive tumors may also have a specific predilection to central nervous system (CNS). Indeed, some studies demonstrated that CNS environment may facilitate migration and settling of HER2-positive cells [27, 28]. Recently, overexpression of HER2 has been found to increase the colonization of breast cancer cells in the brain in vivo [29].

The risk factors for the development of brain relapse in general breast cancer patient populations include younger age, aggressive tumor growth, dissemination to other distant sites and steroid receptor negativity [18–22]. The knowledge of the risk factors for brain relapse in a subset of HER2-positive advanced breast cancer patients has been limited, and our study is among the few investigating this issue [23, 24]. In the present analysis the only variable

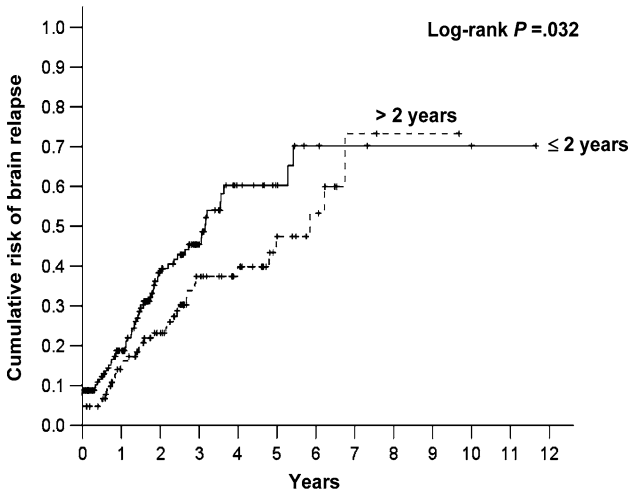

Fig. 2 Cumulative risk of brain relapse according to time from initial diagnosis to dissemination. Hazard ratio for patients with diagnosis to distant relapse interval ≤2 years:1.55 (95% CI, 1.03–2.33; $P = 0.034$; univariate analysis)

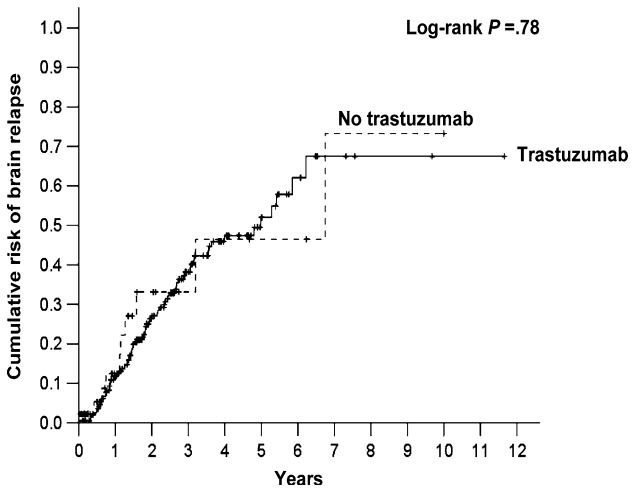

Fig. 3 Cumulative risk of brain relapse according to trastuzumab therapy. Hazard ratio for patients who received trastuzumab: 0.91 (95% CI, 0.47–1.77, $P = 0.78$; univariate analysis)

significantly related to the increased risk of brain relapse was short time from initial diagnosis to distant relapse, a well established indicator of tumor aggressiveness. In the earlier analysis performed on this series of patients, after a shorter follow-up and with lower cumulative incidence of brain relapse (28%), also premenopausal status was found to be significantly related to the risk of brain relapse, whereas lobular carcinoma was at borderline level [30]. With longer follow-up, during which several new events occurred (a cumulative incidence of 39%), these two additional factors have lost their significance.

In this series the steroid receptor status and tumor grade were not related to the risk of brain relapse. The lack of steroid receptor expression is considered an adverse prognostic factor in general breast cancer population, and also includes increased risk of brain relapse [18–22, 31]. The knowledge on the predictive value of steroid receptor status for brain metastases in HER2-positive advanced breast cancer patients is scarce. A recent study including patients administered trastuzumab did not demonstrate any association between ER status and the risk of brain relapse [17]. Pathological tumor grade in general breast cancer population is considered highly predictive for clinical behavior of breast cancer, including the risk of brain relapse [18]; however, the impact of this feature in HER2-positive patients is also not well recognized. Of note, typically for HER2-positive advanced breast cancers, our material included only a small proportion (2%) of well differentiated tumors. Visceral metastases in breast cancer are known to carry particularly ominous prognosis [18, 21]. In our material patients with dominant site of disease in soft tissue or bones had indeed lower risk of relapse compared to patients with visceral metastases. However, this difference did not reach statistical significance, probably due to the low number of patients in the two former subsets. Notably, this study included exclusively patients with earlier tumor dissemination, by definition selected by adverse prognostic factors. It is likely therefore that in such a selected group well established prognostic factors might have been confounded.

An important finding of the present study was no impact of trastuzumab therapy on the risk of brain relapse. The small number of patients not administered trastuzumab calls for cautious interpretation of this result, nevertheless resistance of brain lesions to trastuzumab therapy was consistently reported by others. Notably, several studies demonstrated the development of brain metastases despite the response to trastuzumab in extracranial sites, and no prophylactic effect of trastuzumab on brain relapse both in advanced disease and in the adjuvant setting [11–17]. Brain is the sole site of progression in about 10% of advanced breast cancer patients administered trastuzumab [16]. The most likely explanation for the inefficacy of trastuzumab to prevent brain metastases is impaired penetration of this drug through the blood–brain barrier due to the high molecular weight (145 kDa) of this antibody [32, 33].

Interestingly, despite ineffective delivery of trastuzumab imposed by the blood–brain barrier, some studies suggested that prolonged survival may also include patients who developed brain relapse while on therapy with this agent [14, 24, 34–39]. For example, in the study of Lower et al. [14] the mean survival in patients who developed brain relapse during trastuzumab therapy was 1,400 days, compared to 639 days in patients with brain relapse who were not applied this agent. Additionally, in that study the incidence of bone relapse in patients administered trastuzumab was significantly lower compared to those who did

not receive this compound (15 and 91%, respectively). However, other studies did not demonstrate survival benefit of trastuzumab in patients with brain relapse [16, 40].

The median survival in this series was 3.2 years and the median survival from the diagnosis of brain relapse—9 months. Despite adverse prognostic impact of HER2 overexpression or amplification, these results seem to be better compared to those reported previously in unselected series of advanced breast cancer [41–43]. This may be related to more effective systemic therapy of advanced breast cancer, particularly the use of trastuzumab, more effective management of brain metastases and improved supportive care.

Our study demonstrated the limited value of clinical and pathological factors in predicting brain relapse in advanced HER2-positive advanced breast cancer. Future studies on prediction of this event should include tests based on molecular tumor characteristics. Discovery of such tests can be envisioned on DNA level (comparative genomic hybridization arrays), RNA level (mRNA and microRNA profiling using array technology) and protein level (proteomics using mass spectrometry). These methods have already been found to better predict treatment outcome in breast cancer patients compared to standard clinicopathological factors [44, 45]. Most recently, we have developed a 13-gene molecular signature highly predictive for early brain relapse [46]. We believe that further refinement of molecular methods may identify categories of metastatic breast cancer patients with particularly high risk of brain relapse, in whom preventive strategies might be considered.

Acknowledgments The authors wish to thank Prof. Jacek Jassem for his contribution to study design, interpretation of results and numerous helpful discussions on the manuscript.

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