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ORIGINAL ARTICLE

Central nervous system metastases in a cohort of metastatic breast cancer patients treated with trastuzumab

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Abstract
Background Several analyses suggest an increase of brain metastases in HER2 over-expressing breast cancers treated with trastuzumab as compared to historical series of unselected patients.
Patients and methods We analyzed the incidence of central nervous system (CNS) metastases in 78 patients with HER2 over-expressing breast cancer treated with trastuzumab between July 2000 and June 2006 at the Oncology Department of University Federico II in Naples. We also characterized and compared patients with and without CNS involvement.
Results The median follow-up was 35.3 months (95%CI 26.3–44); median overall survival was 56 months (95%CIs 46-nr); 5 patients showed CNS involvement before trastuzumab therapy while 31 developed CNS metastases during trastuzumab treatment. The median overall survival after CNS metastases was 25.4 months (95%CIs 15.2-nr); patients with CNS lesions showed worse overall survival than patients without CNS lesions (39.1 vs. 75 months, $p = 0.005$).
Conclusion CNS metastases are common events in patients with metastatic HER2 over-expressing breast cancer treated with trastuzumab; the impact on survival is detrimental even if survival after CNS metastases is longer than historical reports. Appropriate investigation of the role of CNS imaging screening and the prophylactic treatment strategies for CNS represents a priority research in this setting.

Keywords Trastuzumab · Breast cancer · HER2 · Survival · Central nervous system · CNS metastases

Introduction

Breast cancer is the second most common cause of central nervous system (CNS) metastases after lung cancer [1, 2], and the first solid tumor to exhibit leptomeningeal colonization [3]. Historical series show that, in unselected breast cancer patients, clinically overt CNS metastases occur in 10–16% of cases [4, 5], with a median time to development from the diagnosis of breast cancer and from the diagnosis of systemic disease of about 34 and 12 months, respectively [6]. Interestingly, the prevalence of CNS localizations in autopsy studies is higher, ranging from 18 to 30% [5, 7], thus suggesting that more than half of breast cancer patients who develop brain metastases die of systemic progression before such metastases become clinically evident.

The emergence of CNS metastases has traditionally been regarded as an indicator of impending overwhelming disease and their impact on survival is generally thought to be detrimental. Nonetheless, patients with CNS localizations from breast cancer make up a heterogeneous group, with

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some living relatively long time and the majority dying from extra-cranial progression. This variability depends on the extension of the CNS lesions, on the treatment applied to such lesions and on the control of extra-CNS metastatic disease.

Recently trastuzumab, a monoclonal antibody directed against the extra-cellular domain of the c-erbB2 receptor, has been introduced in the clinical armamentarium leading to improved survival of HER2-overexpressing breast cancer patients [8]. However, breast oncologists soon had the impression of a higher than expected incidence of CNS metastases for patients treated with trastuzumab. Several investigators have carried out retrospective analyses of trastuzumab-treated metastatic breast cancer to verify the hypothesis of an increased incidence of CNS localizations. Most, but not all, of these studies lend support to the initial clinical observations with a reported incidence of CNS metastases between about 25 and 50% [9–14]. In such a context, several new questions need to be addressed such as: (a) is this increase confirmed by additional data? (b) is there evidence that trastuzumab-treated patients should be screened for CNS disease? (c) is aggressive treatment of such localizations justified by the average clinical outcome? (d) should prophylactic cranial irradiation be exploited for such patients? (e) will new drugs crossing the blood–brain barrier overcome this issue? (f) could the identification of subgroups of patients at very high risk for CNS metastases aid define tailored diagnostic and therapeutic strategies?

To help solve such questions we present the results of a retrospective analysis aimed to investigate the incidence of CNS metastases in patients with HER2 over-expressing breast cancer treated with trastuzumab at our institution, to analyze risk factors that correlate to the development of such metastases and to describe their impact on survival.

Patients and methods

A total of 78 HER2 over-expressing breast cancer patients treated with trastuzumab were identified from pharmacy records at our institution. These patients had received trastuzumab-based therapy for metastatic breast carcinoma between July 2000 and June 2006 at the Oncology Department of University Federico II in Naples, Italy. All patients had received trastuzumab at 4 mg/kg as a loading dose then 2 mg/kg weekly or 8 mg/kg loading dose followed by 6 mg/kg thrice weekly. Trastuzumab therapy was continued beyond disease progression, either at CNS or at extracranial sites, according to our institution policy. The following information was abstracted from the medical records: previous adjuvant treatment, date of diagnosis of metastatic disease, date of diagnosis of CNS metastases, date on which trastuzumab was started, duration of trastuzumab therapy, date of last follow-up or death. HER2 status and oestrogen (ER) and progesterone receptor (PgR) status as assessed by immunohistochemistry (IHC) on the primary tumor. HER2-positivity was defined as 3+ score at polyclonal Dako test. For tumors scoring 2+ a fluorescence in situ hybridization (FISH) test was mandatory to confirm HER2 gene amplification. Some patients were tested by a monoclonal antibody (CB11) and were declared HER2-positive if they exhibited intense and diffuse membrane staining in more than 10% of tumor cells.

Central nervous system metastases were usually diagnosed through screening of asymptomatic patients by contrast-enhanced computerized tomography (CT) scan, according to our institution policy. Magnetic resonance imaging (MRI) scan was used to confirm unclear diagnoses.

Statistical methods

The end-point for this analysis was time-to-CNS localization, overall survival (OS) and post-CNS-OS. The time-to-CNS was defined as the time elapsed from the diagnosis of metastatic disease to the appearance of CNS localization. The time-to-CNS was also calculated from the start of trastuzumab therapy. OS was defined as the time elapsing from the diagnosis of metastatic disease to death. Post-CNS-OS was defined as the time elapsing from the diagnosis of CNS metastases to death.

The time-to-CNS, OS and post-CNS-OS were estimated by the Kaplan–Meier method. For time-to-CNS estimation, patients not developing CNS metastases during study follow-up were censored at the time of their last follow-up or death. For OS and post-CNS-OS surviving patients were censored at the time of their last follow-up.

The prognostic significance of CNS metastases on OS was evaluated taking into account the time-dependent nature of CNS appearance. Because CNSs do arise at variable time during follow-up, a potential temporal bias exists in classifying patients into the CNS-group or not, since the length of follow-up could affect the chance of CNS to develop. An appropriate analysis was therefore performed using a method first published by Mantell and Byar [15], in which subjects (CNS yes/no) are compared according to their CNS status at each time of the follow up. Similarly, the graphical representation of probability of survival according to CNS status was done taking into account the "time-dependent" classification of patients, according to Simon and Makuch [16].

To identify features that correlate to a high risk of developing CNS localizations a multivariate Cox model was fitted to time-to-CNS using all the available clinical–pathological characteristics as covariates.

All p values were two-sided and considered as significant if their value was <0.05.

Results

The characteristics of 78 patients of the study are shown in Table 1.

Five patients presented CNS lesions before starting trastuzumab while 31 patients developed CNS metastases during trastuzumab therapy, accounting for an overall prevalence of CNS localizations of about 46% (95%CI: 35–58%). If only patients free of CNS metastases were taken into account, the prevalence was similar (42%; 95%CI: 35–58%). A high proportion of these women had multiple CNS metastases, 42% of patients showed with computerized tomography (CT) and/or magnetic resonance imaging (MRI) either supratentorial or infratentorial lesions. The median time-to-CNS was 35.8 months from the diagnosis of metastatic disease and 30.3 months from the start of trastuzumab therapy.

The median age for patients with CNS metastases was lower than for patients without such lesions (47.5 vs. 56.0 years). Patients with CNS metastases had a greater proportion of hormonal receptor negative breast cancer than patients with no CNS disease (42 vs. 29%). The median duration of trastuzumab therapy in the CNS subgroup was 20.6 months (3–42.5) while it was 17.8 months (2–69) in the subgroup of patients without CNS lesions. The other analyzed characteristics, i.e., grade, nodal status and previous adjuvant chemotherapy were evenly distributed between the two groups.

As of 30th March 2007 when the median follow-up was 35.3 months the estimated median OS for all 78 patients was 56 months (95%CIs: 46-na), with an estimated proportion of surviving patients equal to 83% at 2 years (Fig. 1a). Of the 36 patients with CNS metastases, 17 died at the time of analysis. The overall survival was significantly better in patients without CNS lesions than in patients with CNS involvement, 75 versus 39.1 months, respectively ($p = 0.005$) (Fig. 1b).

Median post-CNS-OS was 25.4 months (95%CIs: 15.2-na), with an estimated proportion of surviving patients equal to 46% at 2 years after the diagnosis of CNS lesions (Fig. 1c).

For 19 patients (53%) the CNS was the first site of progression, and therefore they had stable disease or better response to trastuzumab therapy in sites other than the CNS.

A Cox proportional hazard model was used to analyze factors predicting a high risk of SNC metastases develop-

Table 1 Patients' characteristics according to the development of central nervous system (CNS) metastases

Patients' characteristics	CNS		No CNS	
	%	*N* (36)	%	*N* (42)
Age	Median 47.5 years (26–71)		Median 56.0 years (32–79)	
<50	53	19	29	12
>50	47	17	71	30
ER-PgR				
+/+	45	16	54	23
+/−	8	3	12	5
−/−	42	15	29	12
Unknown	5	2	5	2
Node				
Negative	11	4	14	6
Positive	61	22	60	25
Unknown	28	10	26	11
Grade				
1–2	14	5	17	7
3	50	18	52	22
Unknown	36	13	31	13
Adjuvant chemotherapy				
Anthracycline	45	16	43	18
Anthracycline/taxane	8	3	3	1
No anthracycline/taxane[a]	47	17	54	23
Trastuzumab regimen				
Monotherapy	6	2	5	2
Combination (hormonal or chemotherapy)	94	34	95	40

ER Oestrogen receptor, *PgR* progesterone receptor

[a] In this group included are patients who did not received adjuvant chemotherapy or who received other kinds of chemotherapy regimens

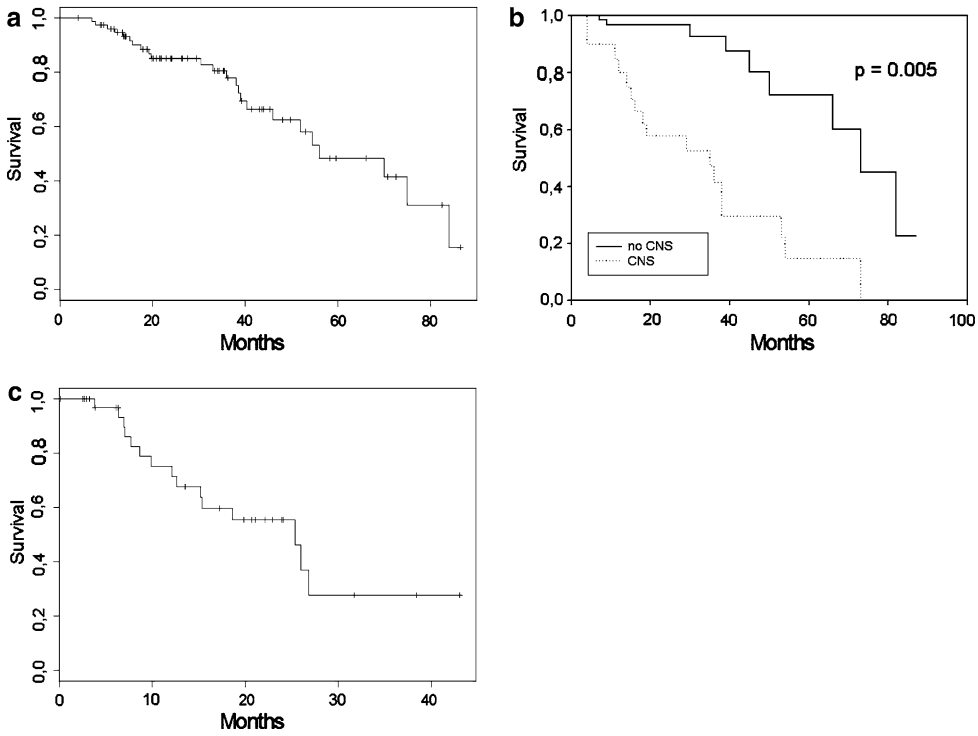

Fig. 1 **a** Kaplan–Meier overall survival plot for the whole study population. **b** Simon–Machuck overall survival plot according to the development of central nervous system (CNS) metastases. **c** Kaplan–Meier overall survival plot after the development of CNS metastases

ment. In the multivariate Cox analysis only younger age (<50 vs. ≥50) was significantly associated with the hazard of developing CNS localizations (HR: 2.7, 95%CIs: 1.35–5.39, $p = 0.0048$). However, a trend to increased risk of CNS metastases of borderline statistical significance was observed for patients with ER-negative tumors (HR: 2.2, 95%CIs: 0.97–5.10, $p = 0.058$). Neither tumor grade, adjuvant anthracycline use nor adjuvant taxane use correlated with the risk of CNS metastases.

Discussion

The results of our study confirm that the development of CNS metastases is a common event in women with HER2-positive breast cancer treated with trastuzumab. Of the 78 patients included in our series, 5 patients presented CNS lesions before starting trastuzumab while 31 patients developed CNS metastases during trastuzumab therapy, accounting for a prevalence of CNS localizations of about 46% in the overall series and of about 42% among patients who were CNS-free at the start of trastuzumab therapy. These figures are in agreement with most of the reported retrospective analyses in which the incidence of CNS metastases ranged from about 25 to 50% [9–14] and appears higher than what was reported among unselected patients [5]. Various hypotheses have been formulated to explain these figures.

First, HER2-overexpressing breast cancers have, on average, a more aggressive phenotype and, therefore, they have a higher tendency to metastasize in every organ, including CNS. In a recent large study conducted on newly diagnosed breast cancer not treated with trastuzumab, Pestalozzi et al. demonstrated that HER2-overexpression is, indeed, a significant risk factor for the development of brain metastases during follow-up [17]. Similarly, Gabos et al., in a series almost free of adjuvant trastuzumab, reported a higher incidence of CNS as first site of recurrence among HER2+ patients [18]. However, in both these studies HER2-positivity is also a significant risk factor for non-CNS metastases, thus suggesting that the increased risk of CNS localization may reflect a general tendency of HER2-positive tumors to metastasize.

Second, factors related to the biology of the HER2 signaling could be specifically responsible for an increased cerebral tropism, thus resulting in a preferential homing of HER2+ cancer cells at CNS sites. However, clinical data have so far failed to confirm this hypothesis. Tham et al. have analyzed a series of 2,685 trastuzumab-untreated patients who, differently from the series reported by Gabos et al. and Pestalozzi et al., were all metastatic [19]. This study, therefore, aims to specifically identify factors related to a preferential CNS tropism in a trastuzumab-free population. However, it shows that CNS metastases are not significantly associated with HER2-overexpression.

Finally, the increased incidence may simply reflect the trastuzumab-driven prolongation of disease control in all but CNS sites. Trastuzumab is, indeed, a large monoclonal antibody and does not seem to cross the blood brain barrier (BBB). Before trastuzumab became available, HER2-posi-

tive patients were probably dying from systemic progression earlier than CNS disease could develop; improved control of systemic disease by trastuzumab now allows them to live long enough to have occult CNS metastases to become clinically overt. Consistent with this hypothesis, in our analysis CNS was the first site of progression for 19 patients (53%), while they had stable disease or better response to trastuzumab in non-CNS sites. Similar results are reported by others [9, 13, 14, 23].

The development of CNS metastases is traditionally regarded as a marker of dismal prognosis in unselected patients; nonetheless their impact on survival for HER2-positive trastuzumab-treated patients is unclear. Our analysis showed that survival was statistically worse for patients with CNS involvement. This result is apparently in contrast with what is reported by other authors. In the study by Lower et al., for example, survival was similar for trastuzumab-treated patients irrespective of whether or not they developed CNS metastases [12]. However, these authors did not apply a specific statistical methodology for time-dependent prognostic factors, as we conversely did in our analysis, and this may have diluted the prognostic information related to CNS involvement.

Despite that CNS metastases had a negative impact on prognosis in our series, we reported a median post-CNS metastases survival of 25 months, which compares favorably with historical controls even if referred to patients unselected for HER2 status [20, 21, 24]. This encouraging outcome in our series may be related to the diagnosis of CNS disease at the asymptomatic stage for most patients, due to systematic CNS imaging screening and to the aggressive treatment of CNS metastases with stereotactic radiosurgery and conventional radiation therapy. Although survival in our study may have been partially inflated for a "lead-time bias" (i.e., anticipated diagnosis, rather than real prolongation), it appears so favorable to support the use of CNS imaging for trastuzumab-treated asymptomatic patients and the worth of such systematic CNS imaging screening should be appropriately evaluated by a randomized trial.

Not all trastuzumab-treated patients have the same risk of developing CNS metastases. In the multivariate analysis, some authors found that premenopausal status at diagnosis of breast cancer and visceral metastases as dominant site at relapse were significantly associated with a higher risk for CNS metastases [23]. In our study, at multivariate Cox analysis, age <50 appeared to be a significant risk factor in this regard (HR: 2.7, 95%CIs: 1.35–5.39, $p = 0.0048$) while a borderline statistical significance was observed for ER-negativity (HR: 2.2, 95%CIs: 0.97–5.10, $p = 0.058$). These results are in agreement with what reported by other authors [17–19] and may help identify subgroups of patients for whom the evaluation of CNS imaging screening and/or of aggressive prophylactic strategies should be warranted. In this regard, some authors have suggested that prophylactic cranial irradiation (PCI) could potentially prolong survival of patients with a major response to trastuzumab therapy at extra-CNS sites [10] and appropriate studies are underway about this issue. Alternatively, the preferential use of BBB-permeating anti-HER2 small molecules, such as lapatinib, should be considered in high risk subgroups [22].

Conflict of interest statement Michele De Laurentiis and Sabino De Placido declare speaking honararia from Roche Italia s.p.a. The other authors do not declare any conflicts of interest.

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