The Breast 23 (2014) 623–628

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Original article

Metastatic breast cancer subtypes and central nervous system metastases

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ARTICLE INFO

Article history:
Received 31 January 2014
Received in revised form
16 May 2014
Accepted 8 June 2014
Available online 30 June 2014

Keywords:
Breast neoplasms
BC subtypes
Brain metastases
Survival outcome

ABSTRACT

Background: Breast cancer (BC) subtypes have different survival and response to therapy. We studied predictors of central nervous system metastases (CNS-M) and outcome after CNS-M diagnosis according to tumor subtype.

Patients and methods: 488 patients with diagnosis of metastatic BC were retrospectively evaluated. According to the combination of hormone receptors (HR) and HER2 status, tumors were grouped in: Luminal (Lum), Luminal/HER2+, pure HER2-positive (pHER2+) and triple negative (TN). Time to CNS progression, CNS-M free interval and Overall Survival (OS) after CNS-M occurrence were compared by the log-rank test. Cox-proportional hazard models were used to study predictor factors associated with CNS progression, including tumor subtype and all potentially clinical relevant variables.

Results: 115 patients (pts) developed CNS-M with a median time to CNS progression of 31 months. The rate of CNS-M by subtype was: Lum 14%, Lum/HER2+ 35%, pHER2+ 49%, TN 22% ($p < 0.001$). Compared with Lum tumors, Lum/HER2+ (HR 2.514, $p < 0.001$), pHER2+ (HR 6.799, $p < 0.0001$) and TN (HR = 3.179, $p < 0.001$) subtypes were at higher risk of CNS-M. Median OS in months after CNS-M was: Lum 7.4, Lum/HER2+ 19.2, pHER2+ 7, TN 4.9 ($p < 0.002$). Belonging to the Lum/HER2+ subtype (HR 0.48, $p < 0.037$) and having isolated CNS (HR 0.37, $p < 0.004$) predicted significantly reduced risk of death.

Conclusions: After CNS-M, the Lum/HER2+ subtype appears associated with the longest OS. Prospective clinical trials would be required for evaluating the potential role of screening for asymptomatic CNS lesions and of more aggressive CNS-M treatment in Lum/HER2+ subtype.

Introduction

The incidence of symptomatic central nervous system metastases (CNS-M) in women with breast cancer (BC) was reported in the range of 10%–16% in historical series [1,2]. While these figures referred to CNS-M presenting clinically during the course of metastatic disease, the real incidence of this metastatic localization has been known to be higher. In fact, on account of autopsy series, rates as high as 30% in patients dying from BC without clinically overt CNS-M have been reported [1,3]. Indeed, CNS-M generally occur as a late event in the natural history of metastatic BC. For this reason, and since the improvement in systemic treatments contrasts with the relative lack of efficacy of antitumor agents in the CNS, the incidence of clinically overt CNS-M seems to have raised significantly in the last two decades [4]. As a consequence, the optimal management of patients at risk of, or with diagnosed CNS-M is an unmet medical need and a major focus for research [4]. The prognosis of patients with CNS-M is, in fact poor, with survival rates of only 20% at one year from first diagnosis and less than 2% at two years [5]. Furthermore, CNS involvement is often associated with neurological complications that have a major impact on patients' quality of life. [4] There is increasing recognition that breast cancer is a collection of heterogeneous diseases. A seminal paper by Perou and colleagues has revealed that at least 4 major breast cancer subtypes can be identified based on distinct gene expression

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http://dx.doi.org/10.1016/j.breast.2014.06.009
0960-9776/

patterns [6]. Although more recent work in the field has added complexity to this classification [7], it is clear that tumor subtype influences all aspects of the natural history, pattern of relapse and response to treatments of breast cancer [8]. Indeed, single biological factors as estrogen receptor (ER) and/or progesterone receptor (PgR) status and human epidermal growth factor receptor 2 (HER2) overexpression have proven to be associated the risk of developing CNS-M in the past [9–11]. These immunohistochemical (IHC) markers may be combined to achieve a reasonable approximation of the molecularly defined subtypes [12]. Consequently, several authors have recently analyzed the impact of breast cancer subtype defined by ICH on incidence of CNS-M and subsequent survival [13–17]. Overall, these analyses identify the triple-negative (ER and PgR and HER2 negative) and the HER2-positive subsets as those at the highest risk of CNS-M. However, while overall survival is shortest for triple-negative breast cancer, it results particularly long, usually in the range of 15–17 months, in HER2-positive patients, especially when systemic treatment is feasible after the diagnosis of CNS-M [13–21]. Differently from what thought in the relatively recent past, heterogeneity of HER2-positive tumors according to HR expression has now been fully recognized [22–24]. Both the HER2 and the HR pathway concur to the peculiar biology of this distinct entity and to its clinical behavior in adjuvant and metastatic setting. With these premises we sat out to analyze predictors of CNS-M and the outcome after CNS recurrence according to tumor IHC-defined subtypes, with a focus on possible differences in the HER2-positive subset according to hormone receptor status.

Material and methods

Clinical records of 488 patients starting first-line chemotherapy for metastatic disease between June 1999 and March 2012 were identified from the medical charts of our Outpatient Clinic. All patients with HER2-positive disease received anti-HER2 treatment in addition to chemotherapy for metastatic disease. Median follow-up was 34 months (2–210 months). For each patient we collected the following data: date of first breast cancer diagnosis, stage at first diagnosis, ER and/or PgR expression, HER2 status, neo-adjuvant/adjuvant chemotherapy and/or hormone therapy, exposure to anthracycline or taxanes as adjuvant treatment, exposure to endocrine therapy as adjuvant treatment and/or for metastatic disease, date and site of first metastatic recurrence, first chemotherapy or trastuzumab based treatment for HER2-positive disease, date of further metastatic recurrences, date of the first CNS-M diagnosis, treatments for CNS-M, status at last follow-up date or date of death. According to the combination of HR and HER2 status, tumors were grouped as follows: Luminal (Lum): HR+ (i.e. ER+ and/or PgR+)/HER2−, Luminal/HER2+ (Lum/HER2+): HR+/HER2+, pure HER2-positive (pHER2+): HR−/HER2+, and triple negative (TN): HR−/HER2−.

ER and PgR status was determined by immunohistochemical (IHC) analysis, with 1% cut off for positive result according to current guidelines [25]. The HER2 status determined by immunohistochemical (IHC) staining by the Dako HercepTest, with a 3+ score identifying positive cases. Uncertain results (2+ at IHC) were further analyzed with fluorescent in situ hybridization (FISH). A *HER2*/Cep17 ratio ≥2 was chosen to define *HER2* amplification.

Statistical analyses

Comparisons between categorical variables were accomplished by the Fisher's or the Chi-square test, as appropriate. The following end points were evaluated by Kaplan Meier analysis: overall survival (OS), which was calculated from the date of first metastatic diagnosis to the date of death or last follow-up for alive patients; time to CNS progression, which was calculated from the date of the first diagnosis of metastatic breast cancer to that of the first documented CNS-M or last follow-up in patients without CNS-M; CNS-M free interval, which was calculated from the date of the first diagnosis of metastatic breast cancer to that of the first documented CNS-M restricted to patients who developed the event: OS after CNS-M, which was calculated from the date of the first CNS-M diagnosis to date of death or last follow-up for alive patients. Kaplan Meier curves were compared by the log-rank test. Factors associated with CNS progression and OS after CNS-M were evaluated by Cox hazard analysis where the effect of tumor subtype was analyzed together with that of other potentially relevant clinical variables. These included: age at diagnosis of metastatic breast cancer, stage at first diagnosis, disease free survival (from first localized disease to metastatic progression), exposure to adjuvant chemotherapy and to neoadjuvant or adjuvant regimens containing anthracyclines and/or taxanes, pattern and number of metastatic sites, and type of first-line chemotherapy or trastuzumab containing treatment. Because of the relatively small number involved and the exploratory nature of this analysis, we did not test for multiple comparisons. Statistical analyses were performed using the SPSS software 17.0. For all analysis statistical significance was set at $p < 0.05$.

Results

Patients and overall survival from the first diagnosis of metastatic disease

A total of 488 metastatic BC patients receiving chemotherapy between June 1999 and March 2012 were analyzed and Table 1 summarizes their relevant demographic characteristics. Median age at first breast cancer diagnosis was 51 years and median age at first metastatic recurrence was 55 years. A total of 267 (55%), 75 (15%), 79 (16%) and 64 (13%) patients had Lum, Lum/HER2+, pHER2+ and TN cancers, respectively. In 3 (1%) patients the tumor subtype could not be determined. A total of 249 (51%) patients had received adjuvant chemotherapy and 274 (56%) had received adjuvant hormonal therapy. Of the 154 patients with HER2-positive disease, a total of 15 (10%) who underwent breast cancer surgery after September 2005 (when adjuvant trastuzumab was registered for adjuvant use in Italy), received adjuvant trastuzumab added to chemotherapy.

Table 2 summarizes the types of first-line chemotherapy received by patients. All patients with HER2-positive metastatic BC received trastuzumab-based treatment, with most of them receiving continuous trastuzumab beyond disease progression, in combination with alternative chemotherapy agents or hormonal therapy. At the time of the analysis, 343 patients had died because of disease progression. The median OS from first metastatic progression was 40.5 months (95% C.I. 37.2–43.8). Fig. 1 shows the Kaplan Meier curves of OS according to subtype. Median OS for patients with Lum, Lum/HER2+, p-HER2+ and TN tumors was 44.4 months (95% 37.7–51.2), 55.3 months (95% C.I. 37.4–73.3), 35.9 months (95% C.I. 29.7–42.1) and 27.1 months IC (95% C.I. 22.6–31.6), respectively (overall log-rank test, $p = 0.0001$).

CNS progression and subsequent outcome

At the time of the analysis 115 patients (24%) had developed CNS-M. In all cases CNS-M were diagnosed following CNS imaging performed because of neurological symptoms. The proportion of CNS-M in each tumor subtype was: 14%, 35%, 49%, and 22% in Lum, LUM/HER2+, pHER2+ and TN tumors, respectively (Table 3, $p < 0.001$). Isolated CNS-M (no concomitant disease progression in