Incidence of and survival following brain metastases among women with inflammatory breast cancer

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Background: The purpose of this study was to determine the incidence of and survival following brain metastases among women with inflammatory breast cancer (IBC).

Methods: Two hundred and three women with newly diagnosed stage III/IV IBC diagnosed from 2003 to 2008, with known Human epidermal growth factor receptor 2 (HER2) and hormone receptor status, were identified. Cumulative incidence of brain metastases was computed. Survival estimates were computed using the Kaplan–Meier product limit method. Multivariable Cox proportional hazards models were fitted to explore the relationship between breast tumor subtype and time to brain metastases.

Results: Median follow-up was 20 months. Thirty-two (15.8%) patients developed brain metastases with a cumulative incidence at 1 and 2 years of 2.7% and 18.7%, respectively. Eleven (5.3%) patients developed brain metastases as the first site of recurrence with cumulative incidence at 1 and 2 years of 1.6% and 5.7%, respectively. Compared with women with triple receptor-negative IBC, those with hormone receptor-positive/HER2-negative disease [hazard ratio (HR) = 0.55, 95% confidence interval (CI) 0.19–1.51, P = 0.24] had a decreased risk of developing brain metastases, and those with HER2-positive disease (HR = 1.02, 95% CI 0.43–2.40, P = 0.97) had an increased risk of developing brain metastases, although these associations were not statistically significant. Median survival following a diagnosis of brain metastases was 6 months.

Conclusion: Women with newly diagnosed IBC have a high early incidence of brain metastases associated with poor survival and may be an ideal cohort to target for site-specific screening.

Key words: brain metastases, breast tumor subtypes, incidence, inflammatory breast cancer, risk, survival

Introduction

Inflammatory breast cancer (IBC) is a rare and aggressive form of breast cancer that accounts for ~1%–6% of all newly diagnosed cases of breast cancer in the United States [1]. Historically, this disease was considered to be uniformly fatal with <5% of women surviving beyond 5 years when treated with surgery and/or radiotherapy [2, 3]. However, with the introduction of a multimodal approach to the treatment of IBC incorporating anthracycline-based primary systemic chemotherapy, surgery and radiation therapy as essential components of treatment, the survival of women with IBC has improved considerably, with 5- and 10-year overall survival rates of 40% and 33%, respectively, being reported [4].

Data from large population-based epidemiological studies have shown that the incidence of IBC is increasing dramatically [1]. This fact, coupled with the improved survival rates attached with IBC and the known early recurrence of disease compared with non-IBC tumors [5], will likely result in a situation where more women with IBC will be alive with metastatic disease. It thus becomes imperative to study the patterns of recurrence, factors that predispose to recurrence and survival following recurrence among women with IBC.

Metastasis to the brain is an important site of distant metastatic disease occurring in ~10%–15% of women with breast cancer [6]. Although it is less common than other sites of visceral or bone metastases, it is typically associated with a comparatively poorer prognosis and recent data indicate a trend toward increased brain recurrence probably due to both increased use of sensitive methods of detection as well as alteration of the natural history of breast cancer from improved systemic treatments that are prolonging survival [7, 8]. Thus, the objective of this retrospective study was to study the incidence of and survival following diagnosis of brain metastases among women diagnosed with IBC.
patients and methods

patient population

Using a prospectively maintained database located at the Breast Medical Oncology Department of the University of Texas M. D. Anderson Cancer Center (MDACC), women with IBC diagnosed from 2003 to 2008 were identified. IBC was defined based on standard American Joint Committee on Cancer (AJCC) criteria that included a history of rapidly developing signs and symptoms of diffuse erythema, peau d’orange, and increasing size of the breast in <3 months duration [9]. In addition, all women had to have pathological confirmation of invasive carcinoma with or without evidence of dermal lymphatic invasion. Male patients and those with more than one primary cancer were excluded from the analysis. Moreover, all women included in the analyses had to have complete information on hormone receptor and HER2 status of their tumor specimens. All information extracted from the database was cross-checked with medical records to ensure accuracy of data. The Institutional Review Board of the MDACC approved the retrospective review of all medical records. Variables recorded include age at diagnosis, hormone receptor status, HER2 status, grade of disease, stage of disease, site of first metastases and development of brain metastases during the follow-up period of the study. Brain metastasis was defined as the presence of metastatic disease in the brain that was diagnosed via imaging studies (magnetic resonance imaging or computed tomography).

pathology and staging

Diagnosis of breast cancer was made via core needle biopsy of the affected breast. All specimens obtained were reviewed by the breast pathologists at the MDACC. Hormone receptor status and HER2 status were assessed on core biopsy specimens obtained at initial diagnosis. Hormone receptor status was assessed using an immunohistochemical staining method (IHC) on 4-μm sections of the paraffin-embedded tissue specimens. The mAb used to detect estrogen receptor was 6F11 (Novocastra, Burlingame, CA), and for progesterone receptor, it was 1A6 (Novocastra). Nuclear staining of ≥10% of all cells was considered a positive result. HER2 status was determined using either an IHC method or a fluorescence FISH technique. In brief, tumors that were HER2 positive exhibited 3+ staining by IHC and/or gene amplification by FISH. Of note, gene amplification was defined as a HER2 : CEP17 ratio of ≥2.0. Tumors that were HER2 negative exhibited no staining by IHC and/or absence of gene amplification by FISH. Tumors with 2+ staining on IHC needed FISH confirmation for either negative or positive status.

Staging of disease was based on the TNM (tumor-node-metastasis) criteria set forth in the sixth edition of the AJCC Cancer Staging Manual [9]. Accordingly, all patients with IBC were assigned a tumor designation of T4d. Histologic grade was assessed using the modified Black’s nuclear grading system [10].

statistical analysis

Patient and tumor characteristics were tabulated or described by their median and range, as appropriate. Breast tumors were grouped into three subtypes according to the hormone receptor status and HER2 status: (i) subtype 1 = hormone receptor positive/HER2 negative, (ii) subtype 2 = HER2 negative and (iii) subtype 3 = triple receptor negative. Median follow-up was computed as the median observation time for the whole cohort. All survival estimates were computed using the Kaplan–Meier product limit method and compared across groups using the long-rank statistic. The following survival estimates were calculated: (i) overall survival was defined from the date of diagnosis of IBC to the date of diagnosis from any cause or last follow-up date; (ii) time to brain metastases was defined from the date of diagnosis of IBC to the date of development of brain metastases or last follow-up (women who died before the development of brain metastases were censored at the time of their death) and (iii) survival following all brain metastases was defined from the date of diagnosis of brain metastases to the date of death or last follow-up. We also computed the cumulative incidence of brain metastases and considered death from any cause as a competing risk. Cumulative incidence of brain metastases as the first site of metastases was also computed considering both other sites of metastases and death as competing risks. Using the PROC PHREG procedure of SAS, the unadjusted relative risk of developing brain metastases stratified by a number of variables explored was computed. Multivariable Cox proportional hazards models were used to explore the association between breast tumor subtype and time to development of brain metastases. Variables inserted in the models were based on clinical significance rather than statistical significance observed on univariate analysis.

For these analyses, all statistical tests were two sided. P values <0.05 were considered to be statistically significant. Analyses were carried out using SAS 9.1 (SAS Institute, Cary, NC).

results

patient and tumor characteristics

Two hundred and three women with IBC diagnosed from 2003 to 2008 who fit eligibility criteria for this study were identified. Table 1 summarizes patient and tumor characteristics of the cohort studied. Median age at diagnosis was 51 years (range 23–81 years). Eighty-two (40.4%) women had de novo stage IV disease and 121 (59.6%) had stage III disease. Sixty (29.6%) women had hormone receptor-positive/HER2-negative disease, 70 (34.5%) had HER2-positive disease and 73 (36.0%) had triple receptor-negative disease. Of the 70 women with HER2-positive disease, 60 (85.7%) received trastuzumab as part of their treatment regimen. Thirty-two women (15.8%) developed brain metastases. Eleven (5.4%) women had brain metastases as the first site of distant metastases. Among women who developed brain metastases either as a first or as a subsequent site of recurrence, 8 (25%) had hormone receptor-positive/HER2-negative disease, 12 (37.5%) had HER2-positive disease and 12 (37.5%) had triple receptor-negative disease.

overall survival estimates

At the time of this analysis, 30 (15%) women had died. Median follow-up for the cohort is 20 months (range 0–68 months). Median overall survival for the whole cohort was not reached. Two-year overall survival for the whole cohort was 86% [95% confidence interval (CI) 78% to 90%]. Two-year overall survival was 89% (95% CI 76% to 95%) for women with hormone receptor-positive/HER2-negative disease, 92% (95% CI 80% to 97%) for women with HER2-positive disease and 76% (95% CI 62% to 85%) for women with triple receptor-negative disease (P = 0.10) (Figure 1).

development of brain metastases

Median time to development of brain metastases was 19 months (0–68 months). One- and 2-year cumulative incidences for the development of brain metastases among women with IBC were 2.7% and 18.7%, respectively. One- and 2-year cumulative incidences for the development of brain metastases as the first site of distant metastases were 1.6% and 5.7%, respectively.
Table 1. Patient characteristics

<table>
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<tr>
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<tr>
<td>Median age (range), years</td>
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Subtype 1 = hormone receptor positive/HER2 negative, subtype 2 = HER2 positive, subtype 3 = triple receptor negative. LVI, lymphovascular invasion.

respectively. We also analyzed separately the two groups of IBC patients with or without distant metastases at diagnoses. Among the 121 women with stage III IBC, 14 (11.6%) developed brain metastases and the overall 1- and 2-year cumulative incidences for the development of brain metastases were 1.8% and 13.7%, respectively. Among the 82 women with stage IV IBC, 18 (21%) developed brain metastases and the 1- and 2-year cumulative incidences of brain metastases as either a first or a subsequent site of metastases were 3.9% and 25%, respectively.

Table 2 summarizes the unadjusted relative risks of developing brain metastases stratified by various patient and tumor characteristics. No specific factor was significantly associated with the development of brain metastases. Table 3 summarizes the results of the multivariable model looking at the association of breast tumor subtype and time to development of brain metastases. The model was adjusted for age, stage of disease and lymphovascular invasion. Compared with women with triple receptor-negative breast cancer, those with hormone receptor-positive/HER2-negative disease [hazard ratio (HR) = 0.55, 95% CI 0.19–1.51, P = 0.24] had a decreased risk of developing brain metastases, although this association was not statistically significant. Compared with women with triple receptor-negative disease, those with HER2-positive disease (HR = 1.02, 95% CI 0.43–2.40, P = 0.97) had an increased risk of developing brain metastases, although this association was not statistically significant.

**survival following brain metastases**

Table 4 summarizes the median survival estimates stratified by patient and tumor characteristics following a diagnosis of brain metastases. Median survival following a diagnosis of brain metastases was 6 months (range 3–8 months) (Figure 2). Median survival following a diagnosis of brain metastases among women with stage III or IV IBC was 4 and 6 months, respectively (P = 0.69). In the unadjusted analysis, no specific variable was significantly associated with survival following the development of brain metastases (Figure 3). Median survival following a diagnosis of brain metastases as the first site of distant metastases was 6 months (range 4–10 months).

**discussion**

The current study is the first to analyze the incidence and outcome of brain metastases among women with newly diagnosed IBC that had received multimodality therapy for their disease. From the cohort studied, we observed a significant incidence of brain metastases in IBC, particularly during the first 2 years from diagnosis, contributing to a reduced survival. In fact, overall brain metastases occurred in 13.2% of the patients translating into cumulative incidences at 1 and 2 years of 2.7% and 18.7%, respectively. Interestingly, no specific patient or tumor characteristics were significantly associated with the development of brain metastases, although a trend toward a higher risk was observed among women with HER2-positive brain metastases, indicating that some of the peculiar biological features of IBC may contribute independently of subtypes. Median survival following a diagnosis of brain metastases as either the first or the subsequent site of metastases was observed to be 6 months, which is consistent with that reported historically for non-IBC tumors.

IBC is a particularly aggressive form of breast cancer that is associated with poorer outcome and earlier recurrence compared with non-IBC tumors. In a recent study, Cristofanilli et al. [5] looked at the cumulative incidence of recurrence among women with IBC tumors and compared it with women with non-IBC locally advanced tumors (LABC). The authors reported a 5-year cumulative incidence of recurrence of 64.8% among women with IBC and 43.4% among women with non-IBC LABC (P < 0.001). Gonzalez-Angulo et al. [11] looked at the incidence of CNS metastases among women with LABC, At
Among women diagnosed and treated from 1982 to 2000, 7.7% with non-IBC LABC and 10.2% with IBC developed brain metastases. In our present study, we observed that at a median follow-up of 20 months, 15.8% of women with IBC developed brain metastases as either the first or the subsequent site of metastases that translated into a cumulative incidence of 18.7% at 2 years. One explanation for the high early cumulative incidence could be attributed to the fact that nearly 50% of the women who developed brain metastases had stage IV disease at initial presentation, another observation to support the aggressive features of the disease. A second possible contributing factor to the high early incidence in HER-positive disease is that nearly 70% of women in this study with HER2-positive disease received trastuzumab. A number of studies have provided evidence of a higher risk of brain metastases among women with HER2-positive disease who receive trastuzumab, which has been attributed to increased control of systemic disease [8,12–14]. In our multivariable model, women with HER2-positive disease had a trend toward a higher risk of developing brain metastases compared with women with triple receptor-negative disease (HR = 1.02, 95% CI 0.43–2.40, P = 0.97). However, this association was not statistically significant, which could be attributed to the small sample size of the cohort resulting in a lack of power to detect a significant association. Although trastuzumab does not cross the blood–brain barrier, recent data have demonstrated modest activity of lapatinib, an oral inhibitor of both epidermal growth factor receptor and HER2, against brain metastases [15]. This evidence, coupled with the fact that lapatinib in combination with Taxol has been shown to have a nearly 95% clinical response rate among women with...
IBC [16], would make lapatinib an ideal agent to investigate among women with HER2-positive IBC and lapatinib is indeed currently under clinical trials for this cohort. A third factor to explain the high incidence of brain metastases may be a contributing role of chemokine receptors in breast tumor and their ligands in the host organ tissue (in this case, the brain) that play an important role in dissemination and progression of disease [17,18]. Looking at a cohort of 44 women with IBC, our group has previously reported a high expression of the chemokine receptors CXCR4 (40.9%) and CXCR7 (22.7%), which may contribute to the homing of IBC tumor cells toward the seeding in the brain [19]. However, this hypothesis will have to be confirmed in future studies.

Distinct intrinsic breast tumor subtypes have been identified including hormone receptor-positive, basal-like (triple-negative), and HER2-positive subtypes, each being associated with a distinct prognostic outcome [20,21]. Our group has previously reported on a cohort of 598 women with breast cancer and brain metastases and observed that the group of women with HER-negative disease had worse prognostic outcome compared with women with HER2-positive disease who received trastuzumab (HR = 1.66, 95% CI 1.31–2.12, \( P < 0.0001 \)) [22]. Nam et al. [23] recently reported on a cohort of 126 women with breast cancer and brain metastases. The authors reported median survivals of 4.0, 7.3, 3.1 and 3.4 months among women with luminal A, luminal B, hormone receptor-negative/HER2-positive (who had not received trastuzumab) and triple-negative disease, respectively (\( P = 0.0448 \)). In contrast, Svoboda et al. [24] reported that tumor phenotype did not significantly affect survival following a diagnosis of brain metastases among 187 women with breast cancer and brain metastases. In the present study, we observed that the median survival following a diagnosis of brain metastases among women with IBC was 4, 6.5 and 3 months among women with hormone receptor-positive/HER2-negative,
HER2-positive, and triple receptor-negative disease, respectively \((P = 0.58)\). Although differences are not statistically significant, which can be attributed to the small sample size of 32 women, a trend is observed with the highest median survival observed among women with HER2-positive disease. This is consistent with the results of our previous study where we looked at a cohort of 179 women with IBC and reported that in the presence of trastuzumab, HER2-positive disease could predict for improved prognostic outcome [25].

In conclusion, these results indicate that IBC is associated with a high early incidence of brain metastases. This observation supports the notion that IBC may be an ideal cohort to study measures that may allow early detection or preventive intervention to reduce the incidence of brain metastases. We acknowledge that this study, like any other retrospective study, is subject to all the inherent biases associated with this study design. Moreover, one of the biggest limitations of the study is its small sample size. As such, the

![Kaplan–Meier curves among women with IBC and brain metastases stratified by (A) HER2, (B) hormone receptor and (C) breast tumor subtype.](image-url)

IBC, inflammatory breast cancer.

Figure 3. Kaplan–Meier curves among women with IBC and brain metastases stratified by (A) HER2, (B) hormone receptor and (C) breast tumor subtype. IBC, inflammatory breast cancer.
The hypothesis generated by this study would have to be validated in larger prospective studies.

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**references**


