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Sites of Distant Relapse and Clinical Outcomes in Patients with Metastatic Triple-Negative Breast Cancer: High Incidence of Central Nervous System Metastases

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Abstract

Purpose—To characterize the outcomes of patients with metastatic triple negative breast cancers, including the risk and clinical consequences of central nervous system (CNS) relapse.

Patients and Methods—Using pharmacy and pathology records, a study group of 116 patients treated for metastatic triple negative breast cancer at Dana-Farber Cancer Institute from January 2000 to June 2006 was identified.

Results—The median survival from time of metastatic diagnosis was 13.3 months. Sixteen patients (14%) were diagnosed with CNS involvement at the time of initial metastatic diagnosis; overall, 46% of patients were diagnosed with CNS metastases prior to death. Median survival after a diagnosis of CNS metastasis was 4.9 months. The age and race-adjusted rate of death for patients whose first presentation included a CNS metastasis was 3.4 times (95%CI:1.9, 6.1) that of patients without a CNS lesion at first metastatic presentation. Of 53 patients who developed brain metastases, only 3 patients were judged to have stable or responsive systemic disease in the face of progressive CNS disease at the last follow up prior to death.

Conclusion—Triple negative breast cancer is associated with poor survival after recurrence. CNS relapse is common, but death as a direct consequence of CNS progression in the setting of controlled systemic disease is uncommon. Thus, it does not appear that the high rate of CNS involvement is due to a sanctuary effect, but rather to the lack of effective therapies in general for this aggressive subtype of breast cancer. New treatment strategies are needed.

Keywords

Triple-negative breast cancer; basal-like breast cancer; brain metastases

Introduction

For years, clinicians have appreciated that breast cancer is not one disease, but a family of diseases, each with a distinct natural history and response to treatment. More recently, molecular interrogation of human breast cancers has led to the identification of at least four

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distinct tumor subtypes distinguished by their gene expression profiles: luminal A, luminal B, HER2-positive, and basal-like.¹⁻³

When patterns of gene expression are analyzed by hierarchical clustering, the basal-like subgroup consistently segregates as a distinct cluster, characterized by expression of keratins 5/6 and 17, and by lack of hormone receptor and HER2 overexpression.⁴ Although expression profiling is not routinely performed in a clinical context, approximately 80% of tumors that are ER, PR, and HER2 negative (i.e. “triple-negative”) demonstrate the basal-like gene expression pattern. Therefore, use of these commonly performed markers can act as a reasonable surrogate of the basal-like phenotype.

Previous reports have indicated that patients with early-stage basal-like or triple-negative breast cancers experience reduced disease-free and overall survival, relative to other breast cancer subtypes.^{2,5,6} In a retrospective study led by Haffty et al, triple-negative subtype was an independent predictor of distant relapse and shortened cause-specific survival in patients with early-stage breast cancer.⁶ However, it is unclear whether the worse cause-specific survival in this cohort could be solely explained on the basis of the higher distant relapse rate, or whether the inferior survival of women with triple-negative breast cancer relative to other breast cancer subtypes is also due to a shorter survival after the diagnosis of metastatic disease. In CALGB 9342, women with metastatic breast cancer were randomized to one of three doses of paclitaxel. Those women with triple negative had a shorter overall survival from study entry compared to all other patients.⁷

There are limited data regarding specific sites of metastasis and clinical course over time of patients with triple-negative, metastatic breast cancer. One potential metastatic site of concern is the central nervous system (CNS). Tsuda et al compared the clinical features of 20 high-grade carcinomas with large, central acellular zones to 40 matched high-grade carcinomas without these zones. The presence of acellular zones appeared to be highly correlated to a myoepithelial immunophenotype, and these tumors were more likely to metastasize to the brain and lung.⁸ An apparent increased incidence of CNS metastases has also been observed in African-Americans and BRCA1 mutation carriers, two populations of patients who have a relatively higher incidence of triple negative disease.⁹⁻¹³ Finally, in a study of 55 patients who developed brain metastases, the frequency of ER-negative, cytokeratin 5/6 positive, and epidermal growth factor receptor (EGFR)-positive tumors was higher than that observed in a comparison group of patients who did not have brain metastases.¹⁴ As systemic therapies have improved for patients with HER2-positive metastatic breast cancer, neurological progression has become a major source of morbidity and mortality.¹⁵⁻¹⁷ However, it is unknown whether the same is true of patients with triple-negative cancers, or whether the aggressive nature of their cancers dominates in both CNS and non-CNS sites.

The objective of this retrospective study was to characterize the sites of distant relapse and clinical outcomes in a cohort of patients with metastatic, triple-negative breast cancer. We further described the clinical course of the subset of patients who developed CNS disease, in order to explore the prognostic significance of CNS relapse.

Patients and Methods

Approval for this study was obtained from the institutional review board of Dana-Farber/Harvard Cancer Center (DF/HCC). Using computerized order entry systems, patients with breast cancer who were treated at Dana-Farber Cancer Institute (DFCI) between January 1, 2000 and June 30, 2006 and for whom at least one dose of the following chemotherapy drugs was ordered were identified: paclitaxel, docetaxel, liposomal doxorubicin,

gemcitabine, vinorelbine, carboplatin, bevacizumab. Patients whose only chemotherapy included doxorubicin plus cyclophosphamide (AC), or dose-dense AC followed by paclitaxel were excluded, as these regimens are rarely given in the metastatic setting. Patients who had received trastuzumab were also excluded. A total of 1,042 patients were identified initially. Pathology records were reviewed to determine the ER, PR, and HER2 status of the primary tumor and/or metastatic biopsy, if available. Patients were included if the primary tumor was negative for all three markers, or, if biopsy of a metastatic lesion was negative for all three markers. HER2 was considered negative if 0-1+ by immunohistochemistry (IHC) and/or FISH-negative (defined as HER2:cen17 ratio <2.0). Patients with any of three markers positive were excluded (n=851), as were patients with missing marker data (n=6). Patients were then excluded for the following reasons: a) non-metastatic breast cancer on further review of medical records (n=43), b) unusual breast cancer histology (n=2, metaplastic carcinoma), c) history of second (non-breast) malignancy (n=7), or d) inadequate follow-up (i.e. lost to follow-up less than 6 months following diagnosis of metastatic disease; n= 17). This left a total of 116 patients for analysis. Follow-up information was available through June 30, 2007.

Medical records from each patient included in this analysis were reviewed for the following information: date and stage of diagnosis of initial breast cancer, date of diagnosis of metastatic disease, initial staging workup at time of metastatic diagnosis, previous chemotherapy regimens, site(s) of initial and subsequent recurrence, status of metastatic disease at time of CNS diagnosis (if applicable), therapy for CNS disease, vital status, date of death (or date last seen), status of CNS and non-CNS at time of death, and cause of death. For patients with bilateral breast cancer (n=7), date of initial diagnosis was defined as date of primary breast cancer diagnosis closest to date of distant recurrence. CNS disease was defined as radiographic evidence of parenchymal metastases and/or clinical or radiographic evidence of leptomeningeal metastases. Isolated intraspinal or epidural metastases were not included in the definition of CNS metastases because of the difficulty in a retrospective study of distinguishing between true CNS involvement versus local extension from bony disease. A line of CNS-directed therapy was defined as a discrete plan of therapy given within a consecutive period. For example, a patient who underwent craniotomy followed by whole brain radiotherapy (WBRT) was classified as having one line of CNS-directed therapy. In contrast, a patient who underwent WBRT followed several months later by stereotactic radiosurgery (SRS) for a progressive lesion, was considered to have received two lines of CNS-directed therapy. Response was evaluated according to the interpretation of the primary oncologist from findings on physical examination and imaging studies, supplemented by review of radiology reports, when available. Attempts were not made to verify response or progression according to Response Evaluation Criteria in Solid Tumors (RECIST). Patients were characterized as responding, having stable disease, or progressing at the time of diagnosis of CNS metastases. In addition, patients were categorized as having been treated at DFCI prior to the diagnosis of metastatic breast cancer or referred to DFCI after a diagnosis of metastatic breast cancer had been made.

The primary outcome variable was time to death as measured in years. Comparison of cases by descriptor variables was done using a chi-square or Fisher's exact test for discrete variables and a t-test for continuous variables. Estimates of survival probabilities (with 95% confidence intervals) were calculated using Kaplan-Meier product limit methodology and compared using a Wilcoxon log rank test. Hazard rates were computed using a Cox proportional hazards model¹⁸ and were adjusted for age and race. All analyses were completed using the SAS statistical software package.¹⁹

Results

Description of Study Population

Table 1 illustrates the clinical characteristics for the patient sample. The mean age at diagnosis was 47.5 (standard deviation 9.9). The majority of patients were white (85%). Sixty percent of patients presented with Stage I or II disease; 11% of patients had evidence of distant disease at initial presentation. As expected, the vast majority of patients had grade 3 invasive ductal carcinomas. Of patients without metastatic disease at initial presentation, 81% received adjuvant chemotherapy. BRCA status was known in only 12 patients, of which 5 were confirmed carriers of deleterious mutations. Two-thirds of patients (75/116) had been treated at DFCI prior to the diagnosis of metastatic disease. The remainder of patients were referred for care after a diagnosis of distant metastasis had been made.

Median length of follow-up was 34.1 months from time of initial breast cancer diagnosis. At the time of this data analysis, 104 deaths were recorded, 11 patients were confirmed alive, and 1 patient was lost to follow-up. The median time from initial breast cancer diagnosis to diagnosis of metastatic disease was 19.9 months. Of patients who initially presented with Stage I-III disease, seventy-five percent of recurrences occurred within 3 years of breast cancer diagnosis (Figure 1). Patients received a median of three lines of chemotherapy prior to death; the distribution of regimens is detailed in Table 2. Approximately 30% of patients received bevacizumab; the high degree of usage reflects the existence of two phase 2 trials including this drug that were open during the time period of this retrospective study and the greater use of bevacizumab after results of the E2100 trial were presented in June 2005.²⁰⁻²²

The most common sites of involvement upon diagnosis of metastatic disease were lung (41% of patients), liver (29%), bone (24%), and breast or chest wall (22%) (Table 2). In terms of all sites of metastasis (initial + subsequent), lung and liver remained the two most common sites. Fifty-three (46%) patients were noted to have a CNS metastasis at some point, with 16 (14%) having a CNS metastasis at first metastatic presentation and 4 with an isolated CNS metastasis at initial metastatic presentation.

Characteristics of Patients with CNS Disease

The majority of patients with CNS disease presented with parenchymal brain metastases; leptomeningeal involvement without parenchymal disease was less common (Table 3). Neurological symptoms precipitated the initial diagnostic study in 77% of patients; the remainder of patients were found to have asymptomatic CNS metastases at the time of a screening study obtained to fulfill eligibility requirements of a clinical trial, prior to the use of bevacizumab, or as part of routine breast cancer staging. At the time of CNS diagnosis, systemic (i.e. non-CNS) disease was stable or responding to therapy in only 9 (17%) patients. In 83% of patients, CNS metastases were diagnosed concurrently with new or progressive systemic metastases. Most patients were treated with whole brain radiotherapy, either alone, or in conjunction with surgical resection, stereotactic radiosurgery, or intrathecal chemotherapy. Only 13 (24%) patients received more than one line of CNS-directed therapy.

We attempted to ascertain the cause of death of patients with CNS metastases. Because of the retrospective nature of this study, we were unable to assign a cause of death for 11 of 53 patients with CNS metastases who died during the study period. Of the remaining 42 patients, 12 died primarily of systemic disease progression, 11 died primarily of CNS disease progression, 17 died of both systemic and CNS progression, and one patient died of other causes (infection). We also characterized patients according to the status of CNS and non-CNS disease at the last follow-up prior to death. When analyzed in this way, only 3

patients were judged to have stable or responsive systemic disease in face of progressive CNS disease.

Prognostic Factors for Overall Survival

The median overall survival from time of metastatic diagnosis was 13.3 months. Survival did not significantly differ by age, race, initial stage, or time of presentation to DFCI. Patients who were ever diagnosed with a CNS metastasis at any time did not differ from those without such lesions by age, race, stage, time of presentation to DFCI, or overall survival. Patients whose first metastatic presentation included a CNS lesion also did not differ with respect any of the demographic or disease characteristics described above, but they did have shorter survival time than persons whose first metastasis did not include a CNS lesion (log-rank $p < 0.0001$). The age and race-adjusted rate of death for patients whose first presentation included a CNS metastasis was 3.4 times (95%CI:1.9, 6.1) that of patients without a CNS lesion at first metastatic presentation. The 1, 2 and 3 year survival rate for patients without a CNS lesion at initial presentation was 61.6% (se:4.9%), 21.8% (se:4.3%) and 14.4% (se:3.8%), respectively versus 18.8% (9.8%), 0% and 0% for patients with CNS lesions at presentation (Figure 1). Among the 53 patients with CNS metastases, median survival from time of diagnosis of first metastasis (CNS or non-CNS) was 11.6 months overall and 4.9 months from time of first CNS metastasis. Among those with a CNS lesion, survival did not vary by sex, race, stage, or time of presentation to DFCI.

Discussion

In this retrospective, single institution study, we found that the poor outcome of patients with triple-negative breast cancer persists in the metastatic setting. The median overall survival was only 13.3 months from the time of metastatic diagnosis, far shorter than the median survival reported for all-comers with metastatic breast cancer in population-based studies.²³ We also observed a strikingly high rate of CNS metastases in these patients. Patients with CNS involvement at the time of initial metastatic diagnosis fared particularly poorly. In addition, among the 53 patients with CNS metastases at any time during their disease course, median survival from the time of CNS diagnosis was only 4.9 months.

Historical series indicate a rate of CNS metastasis of approximately 10-16% in women with advanced breast cancer.^{9,24,25} Recently, Fulford et al published results of a retrospective study examining the outcomes of patients with CK14-positive tumors (a marker for myoepithelial/basal cells). Of the 443 tumors analyzed, 20% were CK14-positive, and of these, 37 were associated with metastatic recurrences. When compared to patients with CK-negative tumors, patients with CK14-positive tumors were more likely to develop brain metastases (HR 1.92; $p=0.05$).²⁶ Our data support and extend these findings: patients with metastatic disease from triple-negative or basal tumors appear to be at much higher risk for CNS involvement than unselected historical controls.

To date, HER2 positivity is the single risk factor that has been most prominently associated with an increased of CNS disease. We note several similarities and differences in the natural history of patients with HER2 positive brain metastases, as described in the literature, and in our study of patients with triple-negative tumors. First, as in patients with triple-negative breast cancer, CNS involvement is common among patients with advanced, HER2-positive tumors, with approximately one-third of patients diagnosed with brain metastases prior to death.^{15,27-29} This increase relative to unselected historical controls has been attributed to the combination of a biologic predisposition to CNS spread and a change in the natural history related to trastuzumab, which has afforded many women prolonged disease control outside of the brain.^{30,31} For example, in the series by Bendell et al, half of women had stable or responsive systemic disease at the time of CNS diagnosis.¹⁵ In contrast, we found

that in the triple-negative population, the diagnosis of CNS metastasis was typically made in the context of new and/or progressive systemic metastases and rarely occurred in the setting of stable systemic disease. Thus, it does not appear that the CNS involvement we observed is the result of a chemotherapy sanctuary effect. Rather, our data suggest that triple-negative tumors are particularly prone to CNS spread. The median survival after CNS diagnosis has been described in several retrospective studies as more favorable in HER2-positive, compared to HER2-negative patients.³²⁻³³ Many, though not all, studies have indicated a longer-than-expected median survival from CNS diagnosis, ranging from 13 to 23.5 months, in patients with HER2-positive breast cancer, treated in the post-trastuzumab era.³²⁻³⁵ There is a clinical need for salvage therapies after initial radiotherapy in this patient population, and it has been estimated that as many as half may die primarily of refractory CNS disease. Unfortunately, the results of our study, and of a recent study led by Nam et al, indicate that the prognosis for patients with CNS metastases from triple-negative breast cancer is almost uniformly poor.³⁶ Additionally, we found that death from isolated CNS progression was relatively uncommon. Our data, if confirmed, point to the need for improvements in systemic therapy for triple-negative breast cancer in general. At the same time, close attention to the CNS will be required to avoid the problem of isolated CNS progression which is now being observed in the HER2-positive population.

Strengths of this study are that we examined sites of both initial and subsequent metastasis and clinical outcomes in a large group of women with metastatic, triple-negative breast cancer, treated within a relatively narrow time period, with modern chemotherapy regimens. The majority of patients had received adjuvant chemotherapy, and one-third of patients received bevacizumab-based therapy in the metastatic setting. We had access to detailed clinic records and radiology reports. In all but one patient, we were able to document the use of chest, abdomen, and pelvis computed tomogram (CT) and/or PET-CT as part of initial staging, thus the characterization of the initial sites of disease is likely to be accurate. Although there was an increasing use of “screening” scans of the brain during this time period, largely reflecting the existence of clinical trials of angiogenesis inhibitors, the diagnosis of brain metastases still occurred as a result of neurological symptoms in 77% of patients. All but 12 patients were followed until death.

This study has several limitations. Patients were treated at a single, academic medical center, thus raising the possibility of referral bias. On the other hand, we did not observe any interaction between time of presentation to DFCI and either CNS relapse or overall survival. Next, consistent with clinical practice, the assignment of triple-negative phenotype was based upon the characteristics of the primary tumor in the vast majority of cases. Recent reports have indicated that discordance in hormone receptor and HER2 status between primary and metastatic lesions may occur.³⁷⁻³⁸ Because the majority of patients in this study did not undergo a biopsy of metastatic disease, we cannot rule out the possibility that some misclassification may have occurred. Finally, because patients were identified through pharmacy chemotherapy records, patients could enter the study population at any time during the course of their metastatic disease. As a result, this is not a true cohort study, which would require all patients to enter the cohort at the time of metastatic diagnosis. For this reason, we also did not include a comparison arm, as there could be a bias introduced if the time interval during which chemotherapy was administered was held constant, given differences in the typical timing of chemotherapy initiation for metastatic disease based upon tumor subtype. In addition, we were not able to calculate time to progression for each line or type of chemotherapy. To address some of these concerns, and based in part upon results from this study, we are in the process of analyzing sites of metastasis and clinical outcomes in a much larger cohort of patients dichotomized by triple-negative status.

In contrast to the current dilemma with HER2-positive disease, where the CNS appears to be an important sanctuary site, in this study, patients with triple-negative, metastatic breast cancer rarely experienced isolated CNS progression. In addition, death from CNS progression in the setting of controlled systemic disease was uncommon, and survival among patients with CNS involvement was uniformly short. These data underscore the need to develop better treatments for patients with triple negative breast cancer, irrespective of the presence or absence of brain metastases. Furthermore, any efforts to improve treatments for CNS disease in this patient population will need to consider the limited treatment options for extra-CNS disease and the fact that most patients with CNS involvement also have progression at other sites.

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Figure 1.
Time to metastatic disease by stage at initial presentation

Figure 2.
Time to death by presence/absence of CNS metastasis at first metastatic presentation (log-rank $p < 0.001$)

Table 1**Patient and Tumor Characteristics**

	Patients (N=116)	
	No.	%
Age at initial diagnosis, years		
Median	46	
Range	(31-75)	
Sex		
Female	116	100
Male	0	0
Race		
White	99	85
Black	12	10
Other	5	4
Stage at Diagnosis		
I	21	18
II	49	42
III	33	28
IV	13	11
Nodal Stage at Diagnosis		
N0	40	34
N1	37	32
≥N2	25	22
Nx	14	12
Histology		
Ductal	107	92
Lobular	1	<1
Mixed ductal and lobular	4	3
Medullary	1	<1
Carcinoma, type not specified	3	3
Nuclear Grade		
2	17	15
3	98	84
Unknown	1	<1
BRCA testing performed		
No	101	87
Yes	15	13
BRCA1 mutation (of n=15 tested)		
No	7	
Yes	5	
Result unknown	3	
Initial surgery		

	Patients (N=116)	
	No.	%
Lumpectomy	55	47
Mastectomy	46	40
None	15	13
Types of prior adjuvant chemotherapy exposure		
None	32	28
A-based	24	21
Both A- and T-based	44	38
Non-A based, non-T based	16	14
Adjuvant radiotherapy		
No	49	42
Yes	67	58

Table 2**Recurrence Characteristics**

	Patients (N=116)	
	No.	%
Disease-free interval		
Median	19.9 mo	
Range	0 to 134.7 mo	
Site(s) of Initial Recurrence/Metastasis		
Lung/pleura	48	41
Liver	34	29
Bone	28	24
Breast/chest wall	28	24
Soft tissue/distant lymph nodes	25	22
Regional lymph nodes	17	15
CNS	16	14
Site(s) of Initial and Subsequent Recurrence/Metastasis		
Lung/pleura	74	64
Liver	58	50
CNS	53	46
Bone	49	42
Breast/chest wall	38	33
Soft tissue/distant lymph nodes	37	32
Regional lymph nodes	22	19
# Lines of Metastatic chemotherapy		
Median	3	
Range	0-9*	
Metastatic chemotherapy		
Anthracycline	35	30
Taxane	74	64
Capecitabine	83	72
Vinorelbine	88	76
Gemcitabine	29	25
Platinum	18	16
Bevacizumab	35	30
Other	46	40

* Two patients did not receive chemotherapy for metastatic disease; one patient whose disease recurred on adjuvant chemotherapy and refused further chemotherapy, and one patient who died before receiving the first planned cycle of chemotherapy.

Table 3

Characteristics of CNS Disease (n=53)

	Patients (N=53)	
	No.	%
Site of CNS Metastasis		
Parenchymal only	40	75
Leptomeningeal only	8	15
Both parenchymal and leptomeningeal	5	9
Reason for Diagnostic Study		
Neurological symptoms	41	77
Prior to clinical trial or bevacizumab treatment	6	11
Staging of breast cancer in asymptomatic patient	6	11
Systemic disease status at time of CNS diagnosis		
Stable/responsive	9	17
Progressive	44	83
# Lines of treatment for CNS disease		
0	3	6
1	37	70
2	6	11
3+	7	13
CNS-directed therapy		
WBRT	47	89
SRS	7	13
IT chemotherapy	6	11
Craniotomy	5	9
Systemic therapy*	4	8
Other RT**	4	8
None	3	6

* Systemic therapy includes hormonal therapy, chemotherapy, or investigational agents.

** For example, radiation to the lumbar spine for symptomatic leptomeningeal metastases.