The Oncologist®

Breast Cancer

Clinicopathological and Treatment-Associated Prognostic Factors in Patients with Breast Cancer Leptomeningeal Metastases in Relation to Tumor Biology

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Breast cancer • Leptomeningeal disease • Human epidermal growth receptor 2 • Prognosis • Treatment

Abstract

Background. Breast cancer (BC) is one of the solid tumors most commonly associated with leptomeningeal disease (LMD). LMD carries a devastating prognosis; however, disease presentation and prognostic factors are uncertain.

Subjects, Materials, and Methods. In order to describe patient characteristics, treatment patterns, and factors associated with survival in a contemporary multicentric cohort, 153 consecutive BC patients diagnosed with LMD at two European institutions (2002–2017) were included. Time to LMD and overall survival (OS) after LMD diagnosis were evaluated using the Kaplan-Meier method and Cox proportional hazards models.

Results. Median age at LMD diagnosis was 58 years (25–84). Tumor phenotype distribution was as follows: hormone receptor (HR) positive (HR+)/human epidermal growth receptor 2 (HER2) negative 51.0%, triple-negative 15.0%, HR+/HER2 positive (HER2+) 13.1% and HR negative/HER2+ 7.2%. Most patients received active anticancer treatments (radiation therapy [RT] n = 42, systemic therapy n = 110, intrathecal treatment n = 103).

Median OS was 3.9 months (95% confidence interval [CI] 2.4–5.5). Eastern Cooperative Oncology Group performance status (ECOG PS) >2, high white blood cells count, low glucose, and high protein in cerebrospinal fluid (CSF) were poor prognostic factors. Having received RT or systemic treatment was associated with better prognosis. In multivariate analysis, ECOG PS (hazard ratio 2.22, 95% CI 1.25–3.94), CSF glucose levels (hazard ratio 1.74, 95% CI 1.05–2.88), and having received systemic treatment (hazard ratio 0.17, 95% CI 0.09–0.32) were confirmed as independent prognostic factors. In HER2+ BC patients, having received systemic HER2-targeted therapy was the only factor maintaining independent prognostication (hazard ratio 0.12, 95% CI 0.02–0.67) in multivariate analysis.

Conclusion. Despite being limited by their retrospective nature, these results highlight the need for clinical trials in BC LMD, stratified on tumor biology. ***The Oncologist*** 2018;23:1289–1299

Implications for Practice: Leptomeningeal disease (LMD) is a devastating complication of breast cancer (BC), and its optimal therapy is still not defined. Here, patient characteristics, treatment patterns, and prognostic factors from a contemporary cohort of 153 BC-related LMD patients are reported. In multivariate analysis, Eastern Cooperative Oncology Group performance status, cerebrospinal fluid glucose levels, and having received systemic treatment were confirmed as independent prognostic factors in the overall population, whereas in human epidermal growth receptor 2 (HER2) positive BC patients, having received systemic HER2-targeted therapy was the only factor maintaining independent prognostication in multivariate analysis. These results highlight the need to consider stratification on tumor biology in the treatment of BC LMD.

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Introduction

Among solid tumors, breast cancer (BC) is one of the most frequently associated with central nervous system (CNS) involvement. Together with lung cancer and melanoma, it represents one of the most common causes of leptomeningeal disease (LMD) [1,2]. The incidence of LMD in metastatic BC is reported to be approximately 5% [2]; however, this rate is probably underestimated due to nonspecific symptoms and signs and to the poor sensitivity of diagnostic methods. LMD generally occurs in the context of advanced systemic disease and is often associated with the presence of brain metastases (BM; 33%–54% of cases) [1,3].

Therapeutic options in LMD patients are scanty, and with limited efficacy. Therefore, the survival of BC patients diagnosed with LMD is extremely poor (usually limited to 6–8 weeks in the absence of tumor-specific treatment and 1.5–4.5 months when treated) [1,2]. Current treatment options include systemic treatment and local therapies such as radiotherapy (RT) and intrathecal (IT) chemotherapy. However, as BC patients diagnosed with LMD often undergo rapid deterioration of performance status, identifying appropriate candidates for active treatments represents a major challenge. Data from clinical trials to support treatment decisions in this scenario are scarce [1,4]. IT chemotherapy is frequently used in BC LMD, but its use is not supported by consistent efficacy data [4,5].

To date, there are no specific guidelines regarding systemic treatment for BC LMD. A variety of chemotherapy agents are used [6], and occasional responses of LMD to hormonal agents have been reported [7,8]. In human epidermal growth receptor 2 (HER2) positive (HER2+) BC with LMD, the European guidelines suggest to consider HER2-targeted treatment in combination with chemotherapy. However, these recommendations are based on uncontrolled case series and expert opinion rather than data from randomized clinical trials [1].

The objectives of this retrospective study were to describe patient characteristics and treatment patterns in a contemporary multicentric cohort of patients with BC diagnosed with LMD, and to determine factors associated with survival.

Material and Methods

Patients

A retrospective review of medical records was conducted in order to identify BC patients with LMD diagnosed between January 2002 and June 2017 in two European cancer centers: Montpellier (Montpellier Regional Cancer Institute) in France and Padova (Istituto Oncologico Veneto) in Italy.

Inclusion criteria were as follows: histologically proven invasive BC, age >18 years, and diagnosis of BC-related LMD (based on positive cytology performed on cerebrospinal fluid [CSF] or on the combination of typical neuroimaging findings and clinical signs [1]).

Patient demographics, Eastern Cooperative Oncology Group performance status (ECOG PS), primary tumor characteristics, and dates of diagnosis of primary BC and LMD were collected and included in a dedicated database. Presence of extra-CNS and parenchymal BM at time of LMD diagnosis, the technique used for LMD diagnosis (imaging vs. CSF cytology), treatments received after LMD diagnosis, and follow-up data were also recorded. When available, evaluation of white blood cells (WBC), glucose, and proteins in CSF was recorded.

Estrogen receptor and progesterone receptor expression in the primary tumor was determined by immunohistochemistry; positivity was defined as immunohistochemistry staining in at least 1% of tumor cells. HER2 status was defined as positive in case of immunohistochemistry score 3+ and/or by the presence of amplification of the HER2 gene by fluorescent in situ hybridization.

This study was approved by the local institutions' ethics committees. All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments, or comparable ethical standards. Considering the retrospective, noninterventional nature of this study, formal consent was not deemed necessary.

Statistical Analysis

Descriptive statistics including percentages, medians, and ranges were performed for patients' demographics and clinical characteristics. The Pearson's chi-square test was used to study the association between categorical clinicopathological variables. For WBC, glucose, and proteins in CSF, the median value in this study cohort was used to categorize patients in two groups for further survival analysis.

Time to LMD was defined as the time interval from diagnosis of primary nonmetastatic BC to diagnosis of LMD. Time to LMD from diagnosis of metastatic BC was defined as the time interval from diagnosis of metastatic BC to diagnosis of LMD. Overall survival (OS) was defined as the time interval from LMD diagnosis to death from any cause. Patients alive without event at the cut-off date of the analysis (July 10, 2017) were censored at date of last follow-up. Median time to LMD and OS were estimated using the Kaplan-Meier method and reported with 95% confidence intervals (95% CIs). Univariate Cox regression modeling for proportional hazards was used to calculate hazard ratios and their 95% CI. All reported p values were two-sided, and significance level was set at 5% ($p < .05$). Significant variables at univariate analysis were subsequently tested in multivariate analysis using Cox regression modeling for proportional hazards to calculate hazard ratios and their 95% CI. Analyses were performed using IBM SPSS, version 24 (IBM, Armonk, NY).

Results

Patient Characteristics

Overall, we identified 153 BC patients with LMD meeting the inclusion criteria. All were included in the analysis. Table 1 summarizes patient and tumor characteristics.

The median age was 50 years (range 18–72) at BC diagnosis and 58 years (25–84) at time of LMD diagnosis. Most

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Table 1. Patient and tumor characteristics at time of LMD diagnosis

Characteristics	Patients	
Age at BC diagnosis, years, median (range)	50	18–72
Age at LMD diagnosis, years, median (range)	58	25–84
Age at LMD diagnosis, *n* (%)		
<50 years	47	30.7
≥50 years	106	69.3
Tumor histology, *n* (%)		
Ductal	99	64.7
Lobular	39	25.5
Other histology[a]	10	6.5
Histologic grade, *n* (%)		
G1–G2	71	46.4
G3	67	43.8
Gender, *n* (%)		
Female	153	100.0
HR status, *n* (%)		
Positive	114	74.5
Negative	36	23.5
ER status, *n* (%)		
Positive	109	71.2
Negative	38	24.8
PgR status, *n* (%)		
Positive	84	54.9
Negative	62	40.5
HER2 status, *n* (%)		
Positive	32	20.9
Negative	101	66.0
Molecular subtype, *n* (%)		
TN	23	15.0
HR+/HER2−	78	51.0
HR−/HER2+	11	7.2
HR+/HER2+	20	13.1
ECOG PS, *n* (%)		
0	7	4.6
1	40	26.1
2	50	32.7
3	48	31.4
4	3	2.0
Symptoms at LMD diagnosis[b], *n* (%)		
Yes	137	89.5
No	14	9.2
Technique used to diagnose LMD, *n* (%)		
Radiology and cytology (both positive)	73	47.4
Cytology (radiology negative)	20	13.1
Radiology (cytology negative)	32	20.9
Radiology (cytology not done)	28	18.3
Presence of extra-CNS disease, *n* (%)		
Present	135	88.2
Absent	18	11.8
Presence of parenchymal brain metastases, *n* (%)		
Present	66	43.1
Absent	87	56.9

[a]The majority of tumors categorized as other histology (*n* = 6) were mixed ductal-lobular carcinomas.
[b]Symptoms presented at time of LMD diagnosed are further detailed in supplemental online Table 4.
Abbreviations: BC, breast cancer; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; HER2, human epidermal growth receptor 2; HR, hormone receptor; LMD, leptomeningeal disease; NA, not available; PgR, progesteron receptor; TN, triple-negative.

patients were diagnosed with invasive ductal carcinoma (*n* = 99, 64.7%); nevertheless, lobular histology was well represented (*n* = 39, 25.5%). Ten patients (6.5%) were diagnosed with another histological type of BC (mostly ductal-lobular mixed tumors). The majority of patients (51%) had hormone receptor (HR) positive (HR+)/HER2 negative (HER2−) tumors. Most patients had an ECOG PS ≤2 at LMD diagnosis (*n* = 97, 65.5%). Dismal PS (ECOG PS 3 or 4) was mostly caused by LMD (*n* = 44, 86.3%), and only in rare cases was it prevalently attributable to systemic disease or to parenchymal cerebral metastases that predated LMD (*n* = 4, 7.8% and *n* = 3, 5.9%, respectively). Concomitant extra-CNS metastases were present in 88.2% of the population (*n* = 135; median time from stage IV BC to LMD 19.8 months, 95% CI 14.0–25.5). Sixty-six patients (43.1%) presented with parenchymal BM at time of LMD diagnosis (42.4% of these patients, *n* = 28, were diagnosed with BM more than 30 days before LMD diagnosis). Lobular histology was more frequently associated with LMD in the absence of BM (72.5%) as compared with ductal histology (52.5%; Pearson's chi-square test $p = .031$).

The biochemical characteristics of CSF are summarized in supplemental online Table 1.

Time to LMD Diagnosis

Median time from BC diagnosis to LMD (patients with stage IV BC at first diagnosis excluded) was 55.3 months (95% CI 45.8–64.8) and was significantly different according to HR status (supplemental online Fig. 1), tumor histologic grade, tumor stage at diagnosis, and having received neo/adjuvant treatment for primary BC (supplemental online Table 2). However, only HR status and tumor stage at diagnosis maintained independent prognostication at multivariate analysis. HER2 status did not significantly affect time to LMD (median 47.1 vs. 44.2 months for HER2− and HER2+ tumors, respectively; log-rank $p = .727$; supplemental online Fig. 2).

Median time from metastatic BC to LMD was 19.8 months (95% CI 14.0–25.5) in the whole cohort. Patients with triple-

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Table 2. Treatment received by patients after diagnosis of LMD

Treatment	Patients	
	n	%
Surgical derivation		
Yes	15	9.8
No	138	90.2
Radiotherapy		
Yes	42	27.5
No	111	72.5
Type of radiotherapy		
WBRT	31	20.3
Spinal RT	10	6.5
Other RT	6	3.9
Intrathecal treatment		
Yes	103	67.3
No	50	32.7
Type of intrathecal treatment		
Methotrexate	94	92.2
Depocyte	3	2.9
Trastuzumab	1	1.0
Methotrexate followed by depocyte	2	2.0
Methotrexate followed by thiotepa	2	2.0
Any systemic treatment[a]		
Yes	110	71.9
No	43	28.1
Anti-HER2 therapy in HER2+ BC		
Yes	22	68.8
No	10	31.3
Type of anti-HER2 therapy received		
Pertuzumab-Trastuzumab	3	9.4
T-DM1	10	31.3
Lapatinib	7	21.9
Trastuzumab	17	53.1
Trastuzumab-Lapatinib	3	9.4

[a]Systemic treatment received after LMD diagnosis is further detailed in supplemental online Table 5.
Abbreviations: BC, breast cancer; CT, chemotherapy; HER2, human epidermal growth receptor 2; LMD, leptomeningeal disease; NA, not available; RT, radiotherapy; SRS, stereotactic radiosurgery; WBRT, whole-brain radiotherapy.

negative (TN) BC experienced a significantly shorter time from metastatic BC to LMD compared with those with HR+/HER2+ tumors (median 7.2 months, 95% CI 0.0–18.2; supplemental online Table 3).

Treatment Modalities

The majority of patients received at least one treatment modality, either local or systemic or both, whereas only 15 patients (9.8%) were treated with best supportive care alone (Table 2).

A total of 110 patients (71.9%) received at least a systemic treatment, namely chemotherapy, endocrine therapy, or targeted therapy (supplemental online Table 5). In the HER2+ population (n = 32), 68.8% received a systemic HER2-targeted therapy. One hundred three patients (67.3%) received at least one line of intrathecal treatment. Almost one third of patients received some form of RT to the CNS after the diagnosis of LMD (n = 42, 27.5%). Only a minority of the patients underwent surgical derivation procedures.

Prognostic Factors for OS After LMD Diagnosis

At the time of last follow-up, 136 patients (88.9%) had died. With a median follow-up of 36.5 months, the median OS from LMD diagnosis in the study cohort was 3.9 months (95% CI 2.4–5.5 months).

The impact of several factors on OS was investigated using univariate Cox regression (Table 3). OS after LMD diagnosis was not significantly affected by BC phenotype, although HER2+ patients showed a trend toward better prognosis (median OS 8.4 months in HER2+ patients vs. 3.2 months in HER2− patients, p = .066). Median OS was 2.0 (95% CI 0.0–4.3), 3.2 (95% CI 1.9–4.5), 11.4 (95% CI 0.0–24.0), and 6.6 (95% CI 0.4–12.7) months in TN, HR +/HER2−, HR negative/HER2+, and HR+/HER2+, subgroups, respectively (log-rank p = .264). Among clinical parameters evaluated at time of LMD diagnosis, ECOG PS was shown to significantly affect patients' prognosis: Patients with an ECOG PS >2 had a significantly shorter median OS than patients with ECOG PS ≤2 (hazard ratio 2.35, 95% CI 1.64–3.37, p < .001; Fig. 1A). Patients with high WBC (≥2 cells/mm^3), low glucose levels (<3 mmol/L), and high protein levels (≥1 g/L) in CSF also had a significantly shorter median OS.

Having received RT or systemic treatment was significantly associated with better prognosis (hazard ratio 0.65, 95% CI 0.45–0.95, p = .027 for RT; hazard ratio 0.16, 95% CI 0.10–0.24, p < .001 for systemic treatment; Fig. 1B). Patients treated with IT therapy showed a trend toward better prognosis without reaching statistical significance (hazard ratio 0.71, 95% CI 0.49–1.02, p = .061). Because ECOG PS may affect the physician's therapeutic approach, we tested the association between ECOG PS and the administration of local or systemic treatment. As expected, patients with deteriorated PS (ECOG PS >2) were less likely to receive systemic treatment (57% vs. 78%, p = .006) and RT (10% vs. 37%, p < .001) after LMD diagnosis as compared with patients with ECOG PS ≤2. Patients with ECOG PS >2 were also less likely to receive IT treatment; however, the association was not statistically significant (57% vs. 72%, p = .060). Nevertheless, in multivariate analysis, conserved ECOG PS (hazard ratio 2.22, 95% CI 1.25–3.94), high glucose levels in CSF (hazard ratio 1.74, 95% CI 1.05–2.88), and having received systemic treatment (hazard ratio 0.17, 95% CI 0.09–0.32) all confirmed their independent positive prognostic value.

Prognostic Factors for OS After LMD Diagnosis in HER2+ Population

In consideration of the different treatment options available for HER2+ and HER2− BC, prognostic factors for OS and treatment impact were assessed separately in the HER2+ (n = 32) and HER2− (n = 101) populations. Biochemical characteristics of CSF at time of LMD diagnosis were

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Table 3. Impact of prognostic factors on OS from time of LMD diagnosis in univariate and multivariate analysis in the overall population (*n* = 153)

		Univariate		Multivariate
Prognostic factors	**Median OS, months (95% CI)**	**Hazard ratio (95% CI)**	***p* value**	**Hazard ratio (95% CI)**
Tumor histology				
Ductal	3.9 (1.6–6.2)	Ref	.775	
Lobular	3.9 (2.1–5.8)	1.06 (0.72–1.56)		
HR status				
Positive	3.9 (2.4–5.4)	0.96 (0.64–1.42)	.832	
Negative	3.3 (0.0–11.0)	Ref		
HER2 status				
Positive	8.4 (2.3–14.5)	0.66 (0.42–1.03)	.066	
Negative	3.2 (1.9–4.5)	Ref		
Molecular subtype				
TN	2.0 (0.0–4.3)	1.63 (0.84–3.15)	.266	
HR+/HER2−	3.2 (1.9–4.5)	1.58 (0.90–2.77)		
HR−/HER2+	11.4 (0.0–24.0)	1.03 (0.45–2.38)		
HR+/HER2+	6.6 (0.4–12.7)	Ref		
Histologic grade			.128	
G1–G2	5.3 (3.8–6.8)	Ref		
G3	2.4 (1.3–3.5)	1.15 (0.96–1.37)		
Age at LMD diagnosis, years			.220	
≥50	4.2 (2.4–6.0)	0.80 (0.55–1.15)		
<50	3.3 (1.5–5.2)	Ref		
ECOG PS				
>2	1.8 (1.5–2.1)	2.35 (1.64–3.37)	**<.001**[a]	**2.22 (1.25–3.94)**
≤2	6.3 (3.3–9.4)	Ref		Ref
Presence of parenchymal BM				
Yes	2.9 (1.4–4.3)	1.26 (0.90–1.78)	.181	
No	5.3 (3.5–7.1)	Ref		
Presence of extra-CNS disease				
Yes	4.2 (2.5–5.9)	0.86 (0.50–1.48)	.585	
No	2.8 (1.6–4.0)	Ref		
White blood cells in CSF (available for *n* = 96)				
≥2 cells/mm^3	3.4 (1.8–5.0)	1.82 (1.16–2.84)	**.009**	1.38 (0.84–2.26)
<2 cells/mm^3	8.4 (4.2–12.5)	Ref		Ref
Glucose in CSF (available for *n* = 101)				
<3 mmol/L	2.8 (1.5–4.1)	1.84 (1.18–2.88)	**.007**	**1.74 (1.05–2.88)**
≥3 mmol/L	7.4 (4.7–10.0)	Ref		**Ref**
Proteins in CSF (available for *n* = 100)				
≥1 g/L	2.4 (0.6–4.3)	2.15 (1.39–3.34)	**.001**	1.35 (0.78–2.33)
<1 g/L	7.4 (4.1–10.7)	Ref		Ref
Treatment of LMD: Surgical derivation				
Yes	3.3 (0.0–7.6)	1.34 (0.78–2.30)	.284	
No	3.9 (2.5–5.4)	Ref		
Treatment of LMD: Any CNS RT				
Yes	7.6 (3.9–11.3)	0.65 (0.45–0.95)	**.027**	0.67 (0.38–1.18)
No	2.5 (0.9–4.1)	Ref		Ref

(continued)

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Table 3. (continued)

Prognostic factors	Median OS, months (95% CI)	Univariate		Multivariate
		Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)
Treatment of LMD: Intrathecal treatment				
Yes	5.3 (3.5–7.1)	0.71 (0.49–1.02)	.061	
No	1.5 (0.3–2.8)	Ref		
Treatment of LMD: Systemic treatment				
Yes	7.4 (5.0–9.8)	0.16 (0.10–0.24)	**<.001**	**0.17 (0.09–0.32)**
No	1.2 (0.8–1.6)	Ref		**Ref**

The presence/absence of symptoms linked to LMD at time of diagnosis was not tested due to the limited number of asymptomatic patients.
[a]Bolded values are statistically significant.
Abbreviations: BM, brain metastases; CI, confidence interval; CNS, central nervous system; CSF, cerebrospinal fluid; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth receptor 2; HR, hormone receptor; LMD, leptomeningeal disease; OS, overall survival; RT, radiotherapy; TN, triple-negative.

not tested in these analyses because of the limited number of patients with available data.

The association between spontaneous prognostic factors, treatments, and OS from LMD diagnosis in the HER2+ population is reported in Table 4. ECOG PS was the only clinical parameter to significantly affect patients' prognosis in univariate analysis (hazard ratio 2.78, 95% CI 1.21–6.38, $p = .016$). Having received systemic treatment and systemic HER2-targeted treatment significantly affected survival (hazard ratio 0.18, 95% CI 0.06–0.51, $p = .001$ and hazard ratio 0.11, 95% CI 0.04–0.33, $p < .001$, respectively). Survival curves according to HER2-targeted therapy are represented in Fig. 1C. Having received systemic HER2-targeted therapy was the only factor that maintained an independent role in multivariate analysis (hazard ratio 0.12, 95% CI 0.02–0.67).

Prognostic Factors for OS After LMD Diagnosis in HER2− Population

The association between prognostic factors, treatments and OS from LMD diagnosis in the HER2- population is reported in Table 5. ECOG PS and tumor histologic grade significantly affected patients' prognosis in univariate analysis (hazard ratio 2.16, 95% CI 1.40–3.35, $p = .001$ for ECOG PS >2; hazard ratio 1.77, 95% CI 1.15–2.73, $p = .009$ for grade 3). In this subgroup, both IT treatment (hazard ratio 0.42, 95% CI 0.27–0.65, $p < .001$) and systemic treatment (hazard ratio 0.16, 95% CI 0.10–0.27, $p < .001$) showed a significant association with prognosis. All four factors remained significantly associated with OS in multivariate analysis.

Discussion

In this study, we report the clinical characteristics, treatment modalities, and outcomes of one of the largest contemporary cohorts of consecutive patients diagnosed with BC-related LMD.

In accordance with literature data, lobular histology was overrepresented in our cohort (25.5%) as compared with a general population of metastatic BC patients not selected for LMD, confirming a greater propensity of lobular cancer for LMD [9].

We found that time from BC diagnosis to LMD is influenced by the HR status, but not the HER2 status. This is consistent with previous data from our team on the time to BM occurrence [10]. Median time from first diagnosis of metastatic BC to LMD was significantly shorter for the TNBC subgroup, also confirming previous results [11]. These results suggest that, similarly to what has been described for parenchymal BM, tumor biology might play a role in determining the timing of LMD involvement in BC [10,12,13]. This observation might possibly be related to the different efficacy of systemic treatment in BC subgroups and to the diverse capacity of chemotherapy, endocrine therapy, and HER2-targeted treatment to diffuse into the CSF [14,15].

Our results confirm that BC patients diagnosed with LMD have a dismal prognosis, with a median OS of 3.9 months only [16–18]. The major clinical characteristic impacting prognosis was ECOG PS (in the overall population, as well as in the HER2+ and HER2− cohorts separately), consistently with reports from previous studies [3,9,11,18–20]. Other authors have also reported age and tumor subtype (according to HR and HER2 status) as clinical prognostic factors [11,16–18], but these results were not confirmed in our study population. However, in our study, HER2+ BC showed a trend toward better prognosis (median OS 8.4 vs. 3.2 months, statistical significance not reached, $p = .066$).

The negative prognostic impact of biochemical CSF parameters (high WBC, low glucose levels, and high protein levels) has been previously described in a cohort of 50 patients diagnosed with LMD of mixed origin (BC, lung cancer, and hematologic malignancies) [21]. Despite that some of these parameters, in particular protein and glucose levels, have been shown to be prognostic in some small and relatively old cohorts of BC-related LMD [22–24], data corroborating the prognostic relevance of these parameters in a large contemporary cohort of BC-related LMD are still lacking. In our study, CSF glucose level added independent prognostication beyond ECOG PS in multivariate analysis. If confirmed, these results may support the clinical use of glucose CSF, a simple biochemical parameter, to better define prognosis of BC patients diagnosed with LMD. This result

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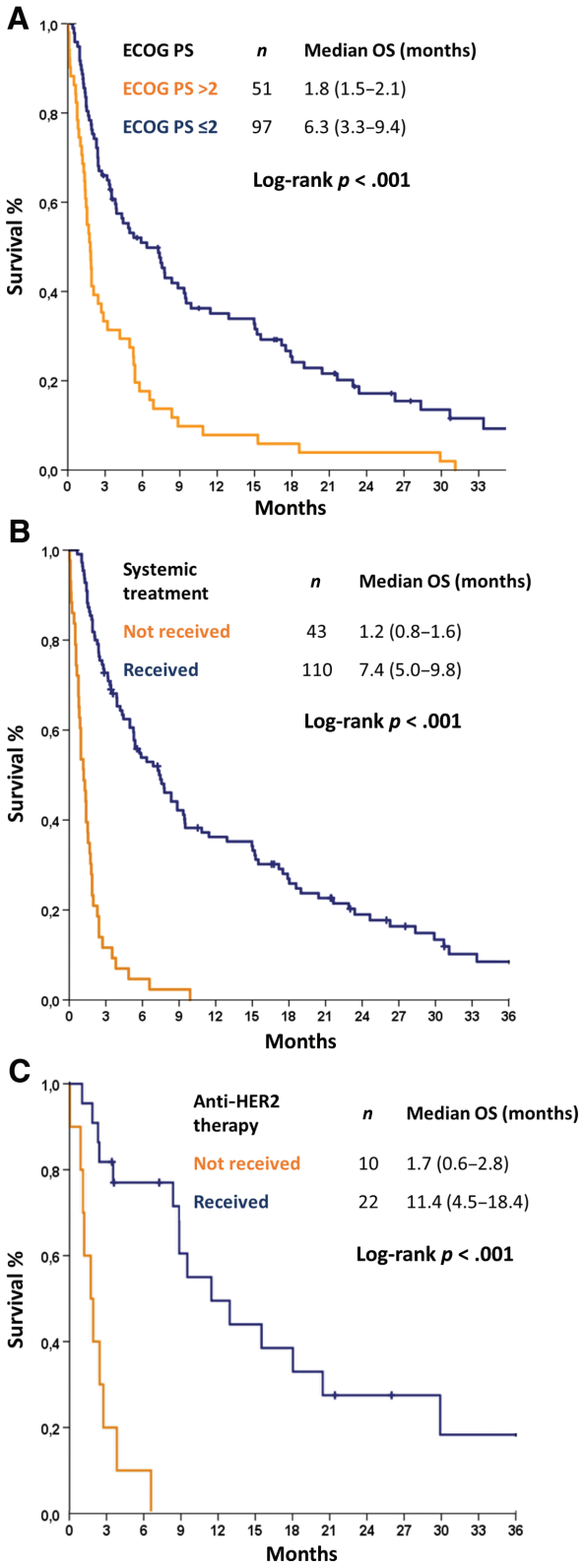

Figure 1. Overall survival curves from diagnosis of leptomeningeal disease according to clinical characteristics and treatment. Overall survival from diagnosis of leptomeningeal disease according to ECOG PS **(A)** or having received systemic treatment **(B)** in the overall population. Overall survival from diagnosis of leptomeningeal disease according to having received HER2-targeted treatment in the HER2 positive cohort **(C)**.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth receptor 2; OS, overall survival.

might be of particular interest in contexts in which, such as in Europe, CSF sampling at LMD diagnosis is strongly encouraged by guidelines and widely used by clinicians [1,6]. It should, however, be acknowledged that a number of limitations regarding the evaluation of these biochemical parameters in CSF are present in our study. In fact, data were missing for a consistent number of patients, as lumbar puncture was not performed in 19.6% of patients. In addition, because of the multicenter, retrospective nature of this study, a clear standardization of CSF collection (e.g., number and volume of samples) and processing is also missing. Moreover, the median value in this study cohort was used as a cutoff to categorize patients in order to evaluate the prognostic impact of these biochemical parameters. A deeper analysis conducted on a larger number of patients might help identify a more sensible and clinically useful cutoff. In the future, the use of new techniques to detect circulating tumor cells and circulating tumor DNA in the CSF [25,26], currently under evaluation in clinical trials (NCT03252912), might rapidly change the diagnostic approach as well as prognostic evaluation of BC-related LMD.

The main relevant result from our study is the prognostic impact of treatments: Systemic HER2-targeted treatment (for HER2+ patients) and both systemic treatment and IT therapy (for HER2− patients) were independent prognostic factors for OS after LMD. In view of the rapidly evolving scenario of available treatments for metastatic BC, it is crucial to acquire data from contemporary patient cohorts: The large majority of patients included in our study (n = 138, 90%) were diagnosed with LMD in or after 2009.

These results are particularly relevant considering the relative lack of evidence supporting treatment of BC-related LMD. In fact, only a few prospective interventional studies have been specifically conducted in BC-related LMD [1,4], and patients with LMD are often excluded from prospective studies testing new drugs for metastatic BC.

Evidence of the efficacy of HER2-targeted treatment in HER2+ BC BM exists, pointing out that this treatment is active in the CNS [27–30]. In addition, data from small clinical series have demonstrated that significant CSF concentrations of HER2-targeted agents, such as trastuzumab and lapatinib, can be achieved by systemic treatment in patients with a disruption of the blood-brain barrier [14,15]. Even if systemic treatment with anti-HER2 agents in HER2+ BC LMD is not uncommon [11], only a few case reports have described the activity of HER2-targeted agents in BC-related LMD [31–33]. This study presents, to our best knowledge, the first evidence of the impact of HER2-targeted therapy on survival in HER2+ BC LMD. Despite the small number of HER2+ patients included in this analysis (n = 32), HER2-targeted treatment remained independently associated with OS even when corrected for PS. Our observations are obviously limited by the retrospective nature of this study; however, as discussed, the majority of data in this clinical condition are retrospective in nature. Moreover, consistently with our findings, another retrospective study showed a longer median survival for HER2+ BC patients diagnosed with LMD after 2005 (coinciding with the use

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Table 4. Impact of prognostic factors on OS from time of LMD diagnosis in univariate and multivariate analysis in the HER2 positive population (n = 32)

Prognostic factors	Median OS months (95% CI)	Univariate		Multivariate
		Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)
HR status				
Positive	6.6 (0.4–12.7)	1.05 (0.45–2.44)	.909	
Negative	11.4 (0.0–24.0)	Ref		
Tumor histologic grade				
G1–G2	2.7 (0.6–4.8)	Ref	.286	
G3	8.8 (1.6–16.1)	0.79 (0.51–1.22)		
Age at LMD diagnosis, years				
≥50	8.8 (1.9–15.8)	0.88 (0.39–2.02)	.769	
<50	3.8 (0.0–12.6)	Ref		
ECOG PS				
>2	1.8 (0.0–3.8)	**2.78 (1.21–6.38)**[a]	**.016**	1.83 (0.76–4.41)
≤2	9.5 (5.3–13.7)	**Ref**		Ref
Presence of parenchymal BM				
Yes	6.6 (0.0–15.5)	1.51 (0.65–3.48)	.337	
No	11.4 (0.0–29.9)	Ref		
Presence of extra-CNS disease				
Yes	8.4 (2.7–14.0)	1.12 (0.38–3.28)	.841	
No	3.5 (0.0–11.9)	Ref		
Treatment of LMD: Surgical derivation				
Yes	1.8 (0.3–3.4)	1.85 (0.55–6.29)	.323	
No	8.4 (2.6–14.1)	Ref		
Treatment of LMD: Any CNS RT				
Yes	12.9 (1.8–24.0)	0.51 (0.23–1.14)	.101	
No	3.8 (0.0–11–5)	Ref		
Treatment of LMD: Intrathecal treatment				
Yes	3.8 (0–11.7)	1.20 (0.54–2.66)	.649	
No	8.4 (4.7–12.0)	Ref		
Treatment of LMD: Systemic treatment				
Yes	11.4 (5.7–17.2)	**0.18 (0.06–0.51)**	**.001**	1.16 (0.24–5.59)
No	2.3 (0.6–4.0)	**Ref**		Ref
Treatment of LMD: HER2 targeted treatment				
Yes	11.4 (4.5–18.4)	**0.11 (0.04–0.33)**	**<.001**	**0.12 (0.02–0.67)**
No	1.7 (0.6–2.8)	**Ref**		**Ref**

The presence/absence of symptoms linked to LMD at time of diagnosis was not tested due to the limited number of asymptomatic patients. Biochemical characteristics of CSF at time of LMD diagnosis were not tested due to the limited number of patients with available data.

[a]Bolded values are statistically significant.

Abbreviations: BM, brain metastases; CI, confidence interval; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth receptor 2; HR, hormone receptor; LMD, leptomeningeal disease; OS, overall survival; RT, radiotherapy; TN, triple-negative.

of lapatinib in the institution) compared with those diagnosed before 2005 [18].

IT administration of chemotherapy has been used by the majority of physicians treating LMD patients in Europe [6]. Consistently, we reported a vast use of IT treatment in our population (67.3% of patients). However, as the availability and efficacy of systemic therapy in metastatic BC has increased over the last decade, the role of IT treatment in BC LMD has been recently questioned by several authors [4,5]. In fact, the only randomized clinical trial specifically designed to assess the role of IT chemotherapy in BC-related LMD showed no benefit [34]. Data from a recent retrospective series suggest that the association of systemic therapy and radiation therapy with better prognosis might be stronger than that of intrathecal therapy [35]. These results are consistent with our data showing that both systemic treatment and radiotherapy associated with better outcome at univariate analysis in the overall population, whereas IT treatment did not. In our study, IT therapy

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Table 5. Impact of prognostic factors on OS from time of LMD diagnosis at univariate and multivariate analysis in the HER2 negative population (n = 101)

		Univariate		Multivariate
Prognostic factors	**Median OS, months (95% CI)**	**Hazard ratio (95% CI)**	***p* value**	**Hazard ratio (95% CI)**
Tumor histology				
Ductal	2.7 (0.4–4.99)	Ref	.916	
Lobular	3.4 (1.97–4.8)	0.98 (0.63–1.53)		
HR status				
Positive	3.2 (1.90–4.5)	0.98 (0.61–1.58)	.932	
Negative	1.97 (0.0–4.34)	Ref		
Histologic grade				
G1–G2	5.3 (3.6–7.0)	**Ref**[a]	**.009**	**Ref**
G3	1.9 (1.4–2.3)	**1.77 (1.15–2.73)**		**1.35 (1.08–1.69)**
Age at LMD diagnosis, years				
≥50	3.2 (0.78–5.6)	0.86 (0.56–1.32)	.477	
<50	2.9 (1.01–4.7)	Ref		
ECOG PS				
>2	1.7 (1.3–2.1)	**2.16 (1.40–3.35)**	**.001**	**1.93 (1.21–3.107)**
≤2	4.9 (2.2–7.5)	**Ref**		**Ref**
Presence of parenchymal BM				
Yes	2.0 (0.7–3.2)	1.28 (0.85–1.94)	.24	
No	4.9 (2.6–7.2)	Ref		
Presence of extra-CNS disease				
Yes	3.4 (1.5–5.3)	0.76 (0.40–1.44)	.399	
No	2.1 (0.0–4.9)	Ref		
Treatment of LMD: Surgical derivation				
Yes	5.3 (0.9–9.6)	1.02 (0.54–1.92)	.948	
No	2.9 (1.5–4.2)	Ref		
Treatment of LMD: Any CNS RT				
Yes	6.3 (1.9–10.8)	0.73 (0.45–1.17)	.190	
No	2.1 (1.3–3.0)	Ref		
Treatment of LMD: Intrathecal treatment				
Yes	5.3 (3.8–6.7)	**0.42 (0.27–0.65)**	**<.001**	**0.60 (0.37–0.97)**
No	1.3 (1.0–1.5)	**Ref**		**Ref**
Treatment of LMD: Systemic treatment				
Yes	5.4 (3.4–7.4)	**0.16 (0.10–0.27)**	**<.001**	**0.17 (0.10–0.29)**
No	1.2 (0.5–1.8)	**Ref**		**Ref**

The presence/absence of symptoms linked to LMD at time of diagnosis was not tested due to the limited number of asymptomatic patients. Biochemical characteristics of CSF at time of LMD diagnosis were not tested due to the limited number of patients with available data.

[a]Bolded values are statistically significant.

Abbreviations: BM, brain metastases; CI, confidence interval; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth receptor 2; HR, hormone receptor; LMD, leptomeningeal disease; OS, overall survival; RT, radiotherapy; TN, triple-negative.

was an independent prognostic factor, along with systemic treatment, for HER2− patients, but not for HER2+ patients. In HER2+ disease, the increasing availability of effective targeted systemic treatments prevails, whereas in the HER2− setting, available systemic treatments are probably less effective and rely mainly on chemotherapy, as tumors are often resistant to hormonal therapy at time of LMD diagnosis. However, this may rapidly change in the next few years as several highly effective targeted agents are entering clinical practice. In this context, results from trials evaluating the systemic use of agents such as the CdK4/6 inhibitor abemaciclib (NCT02308020), epothilone B (NCT00450866), 2B3-101 (glutathione PEGylated liposomal doxorubicin; NCT01818713), and high-dose systemic methotrexate (NCT02422641) in BC-related LMD will be of great importance. Further data regarding the use of IT chemotherapy might come from the ongoing randomized trial evaluating the IT use of liposomal

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cytarabine in BC-related LMD (NCT01645839). In HER2+ BC LMD, current research has been focusing on the systemic and IT use of HER2-targeted agents. The feasibility of trastuzumab IT administration has been described in a few small studies [36,37], and its efficacy is currently being evaluated in phase II studies (NCT01325207, NCT01373710). Intermittent high-dose lapatinib and capecitabine is currently being investigated in another ongoing study (NCT02650752).

Conclusion

LMD remains a highly problematic site of progression of metastatic BC. Our results confirm that BC-related LMD carries poor prognosis. However, we found that the use of systemic HER2-targeted treatment in HER2+ BC LMD and of systemic and IT treatment in HER2− BC LMD is associated with better prognosis. Even if these results are limited by their retrospective nature, they highlight the urgent need for prospective clinical trials in BC-related LMD in order to improve treatment and outcome for these patients.

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Final approval of manuscript: Gaia Griguolo, Stephane Pouderoux, Maria Vittoria Dieci, William Jacot, Céline Bourgier Federica Miglietta, Nelly Firmin, Pierfranco Conte, Marie Viala, Valentina Guarneri, Amélie Darlix

Disclosures

The authors indicated no financial relationships.

References

1. Le Rhun E, Weller M, Brandsma D et al. EANO-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of patients with leptomeningeal metastasis from solid tumours. Ann Oncol 2017;28:iv84–iv99.
2. Grossman SA, Krabak MJ. Leptomeningeal carcinomatosis. Cancer Treat Rev 1999;25: 103–119.
3. Le Rhun E, Taillibert S, Zairi F et al. A retrospective case series of 103 consecutive patients with leptomeningeal metastasis and breast cancer. J Neurooncol 2013;113:83–92.
4. Dudani S, Mazzarello S, Hilton J et al. Optimal management of leptomeningeal carcinomatosis in breast cancer patients-A systematic review. Clin Breast Cancer 2016;16:456–470.
5. Lee YC, Hsieh CC, Chuang JP et al. The necessity of intrathecal chemotherapy for the treatment of breast cancer patients with leptomeningeal metastasis: A systematic review and pooled analysis. Curr Probl Cancer 2017;41: 355–370.
6. Le Rhun E, Ruda R, Devos P et al. Diagnosis and treatment patterns for patients with leptomeningeal metastasis from solid tumors across Europe. J Neurooncol 2017;133:419–427.
7. Almajed MM, Esfahani K, Pelmus M et al. Complete response and long-term survival of leptomeningeal carcinomatosis from breast cancer with maintenance endocrine therapy. BMJ Case Rep 2016;2016:bcr2016215525.
8. Zoghi B, Elledge R. Endocrine therapy for leptomeningeal metastases from ER-positive breast cancer: Case report and a review of the literature. Breast J 2016;22:218–223.
9. Niwinska A, Rudnicka H, Murawska M. Breast cancer leptomeningeal metastasis: Propensity of breast cancer subtypes for leptomeninges and the analysis of factors influencing survival. Med Oncol 2013;30:408.
10. Darlix A, Griguolo G, Thezenas S et al. Hormone receptors status: A strong determinant of the kinetics of brain metastases occurrence compared with HER2 status in breast cancer. J Neurooncol 2018;138:369–382.
11. Torrejon D, Oliveira M, Cortes J et al. Implication of breast cancer phenotype for patients with leptomeningeal carcinomatosis. Breast 2013;22:19–23.
12. Berghoff A, Bago-Horvath Z, De Vries C et al. Brain metastases free survival differs between breast cancer subtypes. Br J Cancer 2012;106:440–446.
13. Griguolo G, Dieci MV, Giarratano T et al. Beyond breast specific-Graded Prognostic Assessment in patients with brain metastases from breast cancer: Treatment impact on outcome. J Neurooncol 2017;131:369–376.
14. Stemmler HJ, Schmitt M, Willems A et al. Ratio of trastuzumab levels in serum and cerebrospinal fluid is altered in HER2-positive breast cancer patients with brain metastases and impairment of blood-brain barrier. Anticancer Drugs 2007;18:23–28.
15. Gori S, Lunardi G, Inno A et al. Lapatinib concentration in cerebrospinal fluid in two patients with HER2-positive metastatic breast cancer and brain metastases. Ann Oncol 2014; 25:912–913.
16. Kingston B, Kayhanian H, Brooks C et al. Treatment and prognosis of leptomeningeal disease secondary to metastatic breast cancer: A single-centre experience. Breast 2017;36:54–59.
17. Abouharb S, Ensor J, Loghin ME et al. Leptomeningeal disease and breast cancer: The importance of tumor subtype. Breast Cancer Res Treat 2014;146:477–486.
18. Morikawa A, Jordan L, Rozner R et al. Characteristics and outcomes of patients with breast cancer with leptomeningeal metastasis. Clin Breast Cancer 2017;17:23–28.
19. Scott BJ, Oberheim-Bush NA, Kesari S. Leptomeningeal metastasis in breast cancer - A systematic review. Oncotarget 2016;7:3740–3747.
20. Jo JC, Kang MJ, Kim JE et al. Clinical features and outcome of leptomeningeal metastasis in patients with breast cancer: A single center experience. Cancer Chemother Pharmacol 2013; 72:201–207.
21. Palma JA, Fernandez-Torron R, Esteve-Belloch P et al. Leptomeningeal carcinomatosis: Prognostic value of clinical, cerebrospinal fluid, and neuroimaging features. Clin Neurol Neurosurg 2013;115:19–25.
22. Boogerd W, Hart AA, van der Sande JJ et al. Meningeal carcinomatosis in breast cancer. Prognostic factors and influence of treatment. Cancer 1991;67:1685–1695.
23. Yap HY, Yap BS, Rasmussen S et al. Treatment for meningeal carcinomatosis in breast cancer. Cancer 1982;50:219–222.
24. Fizazi K, Asselain B, Vincent-Salomon A et al. Meningeal carcinomatosis in patients with breast carcinoma. Clinical features, prognostic factors, and results of a high-dose intrathecal methotrexate regimen. Cancer 1996;77:1315–1323.
25. Lin X, Fleisher M, Rosenblum M et al. Cerebrospinal fluid circulating tumor cells: A novel tool to diagnose leptomeningeal metastases from epithelial tumors. Neuro Oncol 2017;19: 1248–1254.
26. De Mattos-Arruda L, Mayor R, Ng CK et al. Cerebrospinal fluid-derived circulating tumour DNA better represents the genomic alterations of brain tumours than plasma. Nat Commun 2015;6:8839.
27. Jacot W, Pons E, Frenel JS et al. Efficacy and safety of trastuzumab emtansine (T-DM1) in patients with HER2-positive breast cancer with brain metastases. Breast Cancer Res Treat 2016; 157:307–318.
28. Bachelot T, Romieu G, Campone M et al. Lapatinib plus capecitabine in patients with previously untreated brain metastases from HER2-positive metastatic breast cancer (LANDSCAPE): A single-group phase 2 study. Lancet Oncol 2013;14:64–71.
29. Braccini AL, Azria D, Thezenas S et al. Prognostic factors of brain metastases from breast cancer: Impact of targeted therapies. Breast 2013;22:993–998.

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30. Lin NU, Winer EP. Brain metastases: The HER2 paradigm. Clin Cancer Res 2007;13: 1648–1655.

31. Lavaud P, Rousseau B, Ajgal Z et al. Bi-weekly very-high-dose lapatinib: An easy-to-use active option in HER-2-positive breast cancer patients with meningeal carcinomatosis. Breast Cancer Res Treat 2016;157: 191–192.

32. Onishi H, Morisaki T, Nakafusa Y et al. Objective response with lapatinib in patients with meningitis carcinomatosa derived from HER2/HER1-negative breast cancer. Int J Clin Oncol 2011;16:718–721.

33. Ricciardi GRR, Russo A, Franchina T et al. Efficacy of T-DM1 for leptomeningeal and brain metastases in a HER2 positive metastatic breast cancer patient: New directions for systemic therapy - A case report and literature review. BMC Cancer 2018;18:97.

34. Boogerd W, van den Bent MJ, Koehler PJ et al. The relevance of intraventricular chemotherapy for leptomeningeal metastasis in breast cancer: A randomised study. Eur J Cancer 2004; 40:2726–2733.

35. Niwinska A, Pogoda K, Michalski W et al. Determinants of prolonged survival for breast cancer patient groups with leptomeningeal metastasis (LM). J Neurooncol 2018;138:191–198.

36. Zagouri F, Sergentanis TN, Bartsch R et al. Intrathecal administration of trastuzumab for the treatment of meningeal carcinomatosis in HER2-positive metastatic breast cancer: A systematic review and pooled analysis. Breast Cancer Res Treat 2013;139: 13–22.

37. Figura BN, Long W, Yu M et al. Intrathecal trastuzumab in the management of HER2+ breast leptomeningeal disease: A single institution experience. Breast Cancer Res Treat 2018; 169:391–396.

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Megan J. McKee, Kevin Keith, Allison M. Deal et al. A Multidisciplinary Breast Cancer Brain Metastases Clinic: The University of North Carolina Experience. ***The Oncologist*** 2016;21:16–20.

Implications for Practice:
Patients with breast cancer brain metastases often require unique multidisciplinary care to meet the numerous and uncommon challenges associated with their conditions. Here, the development and characteristics of a clinic designed specifically to provide for the multidisciplinary needs of patients with breast cancer brain metastases are described. This clinic may serve as a model for other institutions interested in creating specialty clinics with similar objectives.

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