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CLINICAL TRIAL

Leptomeningeal metastases from breast cancer: intrinsic subtypes may affect unique clinical manifestations

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Abstract Leptomeningeal metastasis (LM) usually occurs late during the course of breast cancer. The aim of this study was to characterize the clinical features and outcomes of LM based on breast cancer subtypes in conjunction with brain parenchymal metastases. A retrospective study was performed of breast cancer patients with LM, who received palliative management at Samsung Medical Center between 1995 and 2008. Among the 272 metastatic breast cancer patients with central nervous system (CNS) involvement, 68 patients with LM were identified. The median age was 46 years (range, 24–72 years). The median survival duration from LM to death (LM-OS) was 4.5 months (range, 0.2–26.4 months). Patients surviving for 12 or more months were rarer among triple negative (TN) patients compared to other subtypes (21.7% for HR + ve vs. 27.8% for HER2 + ve vs. 72.7% for TN, $P = 0.217$). Death caused by CNS involvement appeared to be much more common in TN than in other subtypes (0% for HR + ve vs. 36% for HER2 + ve vs. 64% for TN, $P = 0.060$). Median survival time from distant metastasis was significantly different among the three groups (28.3 vs. 29.1 vs. 11.8 months, $P < 0.0001$). However, median survival time from LM did not differ (4.1 vs. 5.9 vs. 3.8 months, $P = 0.226$). Characteristic manifestations and treatment outcomes of LM may be affected by the unique biology of breast cancer intrinsic subtypes. The different roles of active combined treatment modalities including both systemic chemotherapy and local treatment modalities should be considered to improve outcomes.

Keywords Leptomeningeal metastases · Subtype · HER2 · Triple negative breast cancer

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Introduction

With improvements in the systemic treatment of cancer and in survival, the control of central nervous system (CNS) involvement from various cancers has become increasingly important for overall disease control [1, 2]. Leptomeningeal metastasis (LM) occurs in 4–15% of all the patients with solid tumors, whereas almost 20% of the patients with neurological symptoms and signs are found to have LM during autopsy [3, 4]. CNS metastases occur in 10–16% of the stage IV breast cancer patients, and LM is usually a late event during the course of the disease [5]. Improved neuroimaging, increasing numbers of breast cancer patients, and prolonged survival attributable to improved systemic treatment have significantly increased the frequency of LM [3, 6–8]. Better systemic control of cancer may delay the appearance of LM; however, once LM is established, the prognosis is poor, and intensive treatment is questionable [9, 10].

The aims of treatment of LM are improvement or stabilization of neurologic status and symptoms, maintenance of neurologic quality of life, and prolongation of life in some cases. Therapeutic modalities for LM include the combination of surgery, radiation, and local and/or systemic chemotherapy in most cases [5, 6, 10–16]. However, development of a standard therapeutic approach to LM is complicated because of the rare occurrence of the disease, the lack of prospective, randomized studies, and the difficulty of determining response to treatment. Moreover, LM has been reported to occur late in the course of illness and rarely occurs in isolation, but is frequently associated with extracranial systemic and brain parenchymal metastases [3, 10, 17–19]. Even after successful treatment of LM, progression of extracranial systemic and brain parenchymal metastases may lead to clinical deterioration and death. Because of the rarity of the circumstances and lack of understanding of the biological background, the value of each treatment option has to be evaluated in the context of the entire disease and the whole therapeutic concept.

It has become clear that breast cancer is not a single disease, but a heterogeneous group of diseases. Gene expression-profiling studies classify breast tumors into at least 4–5 distinct subtypes; luminal A, luminal B, human epidermal growth factor receptor-2 (HER2) positive, and basal-like subtype, each with a distinct natural history and response to treatment. Several reports have suggested a higher risk for brain metastasis in HER-2 positive and triple negative (TN) breast subtypes than in hormone receptor (HR) positive subtypes [20, 21]. However, factors associated with high risk of developing LM, especially in terms of breast cancer subtypes, have not been reported.

The aim of this study was to investigate how breast cancer heterogeneity based on subtype affects clinical presentations and courses of LM.

Materials and methods

Patients and methods

We retrospectively analyzed the medical records of the patients who were diagnosed with CNS metastasis of breast cancer from 1995 to 2008 at Samsung Medical Center (SMC). All the patients presented histologically confirmed adenocarcinoma of the breast. All the pathologic specimens were reviewed by two experienced pathologists who determined the primary tumor characteristics based on histologic and nuclear grades, tumor size, the presence of lymphovascular invasion (LVI), multiplicity (multifocal/multicentric disease), axillary nodal status, and the status of receptors by immunohistochemical staining (IHC) (estrogen receptor [ER], progesterone receptor [PgR], and HER2). ER and PgR positivity was defined as an Allred score of 3–8 by IHC using antibodies to ER (Immunotech, France) and PgR (Novocastra, UK). HER2 status was evaluated using antibody analysis (DAKO, CA, USA) and/or fluorescence in situ hybridization (FISH). Grades 0 and 1 for HER2 by IHC were defined as a negative result, and grade 3 as a positive result. Amplification of HER2 was confirmed by FISH if HER2 was rated 2 + by IHC. Triple negativity was defined as lack of ER, PgR, and HER2 expressions which was confirmed by FISH if HER2 was rated 2 + by IHC.

We diagnosed LM from breast cancer based on signs and symptoms, and the findings on cerebrospinal fluid (CSF) examination including cytology and/or imaging studies of the brain and/or spine. We suspected LM in cases based on clinical findings, and LM was confirmed by CSF cytology showing neoplastic cells. We repeated lumbar punctures up to 2–3 times if the cytological examination was negative upon initial examination in the case of clinical and/or radiological suspicion. All the patients underwent brain MRI with gadolinium enhancement and/or whole spine MRI if indicated for detection of LM. Our study protocol was approved by the Institutional Review Board of Samsung Medical Center.

Survival analysis

The time-to-LM (TTLM) was defined from the date of distant metastasis to the date of LM. The overall survival (LM-OS) was measured from the date of diagnosis of LM to death or to the final follow-up date. The date of diagnosis of LM was defined as the day on which LM was confirmed via imaging or cytological examination.

Comparisons of categorical variables among groups were conducted using chi-square and Fisher's exact tests. The LM-OS was calculated from diagnosis of LM and plotted using the Kaplan–Meier method. A comparison of survival according to prognostic factors was evaluated via log-lank test, and forward stepwise Cox proportional hazard models were employed to evaluate the joint effects of predictive variables. P values <0.05 were considered statistically significant. Data were analyzed using PASW version 18.0 statistical software.

Results

Patients

We searched our electronic database at the Department of Medicine, SMC, and retrospectively reviewed the records of 1,027 patients who received palliative treatment for metastatic breast cancer (MBC). Between January 1995

and June 2008, 285 of these patients were diagnosed with CNS metastasis from breast cancer. Thirteen patients without available clinical data were excluded from this study, and the remaining 272 patients were included. Among these 272 patients, 68 showed LM, representing our final cohort. Forty-seven patients (69.1%) had positive CSF cytology from lumbar puncture(s), and 21 patients (30.9%) had no demonstration of malignant cells in CSF, but clinical features, such as single or multiple neurologic deficits of cranial nerves and typical MRI findings strongly indicated LM, which include hydrocephalus without an identifiable mass lesion as well as leptomeningeal contrast enhancement [22]. CSF findings that were compatible with neoplastic meningitis consisting of lymphocytic pleocytosis, elevated protein, and normal or low CSF glucose, were also considered as meningeal carciomatosis in patients with MBC, because LM could not be ruled out by negative CSF cytology when typical clinical features and MRI findings were present.

IHC could be carried out for 65 of the 68 patients. Among them, 23 patients were HR+ (ER+ and/or PgR+ and HER2−), 18 were HER2+ (HER2+ regardless of ER and/or PgR), and 24 were TNBC (ER−, PgR−, and HER2−) (Table 1).

Patient characteristics

Comparison of clinical characteristics of patients with brain parenchymal metastases with or without LM LM (BM + LM vs. BM-LM)

Sixty-eight patients (25%) were identified as having LM. Among these, 65 patients were available IHC for subtype. We analyzed the patient and tumor characteristics of patients with BM + LM and BM-LM (Table 1). The median age of patients with BM − LM was greater than those with BM + LM (49 vs. 46 years, $P = 0.019$). Performance status (PS) appeared to be better in patients with BM − LM than in those with BM + LM. HER2+ patients were more commonly identified than other subtypes in patients with BM-LM (23.0% for HR+ vs. 47.1% for HER2+ vs. 29.9% for TN, $P = 0.049$). The rate of LM was lower in the HER2+ subtype compared to other subtypes among all the 272 patients with CNS metastases (46.3% for HR+ vs. 28.5% for HER2+ vs. 40.6% for TN, $P = 0.049$). Distribution of initial TNM staging, the status of systemic disease control, and metastatic sites other than CNS except bone were similar between BM patients, regardless of LM status. Bone metastasis was associated with BM + LM more often than with BM − LM (60.3% vs. 39.7%, $P = 0.001$). Time-to-CNS metastases and survival time from distant metastasis did not differ between the two groups. However, time to death from CNS metastasis (CNS-OS) was longer in patients with BM − LM than in those with BM + LM (8.7 vs. 5.8 months, $P = 0.025$ by log-rank test) (Table 1).

Patient and tumor characteristics at the time of LM according to breast cancer subtypes The median age of the 68 patients with LM was 46.3 years (range, 24–72 years). At the time of diagnosis of LM, parenchymal brain metastases were detected in 37 of the 68 patients (54.4%), and 53 of the 68 patients (79.1%) had metastatic disease at the sites other than LM, including the brain, lung, liver, skin, bones, lymph nodes, and the other sites. Sixteen patients (23.5%) presented with isolated CNS metastases (BM + LM and BM − LM without other systemic metastasis), and six patients (8.8%) developed isolated LM without evidence of metastatic disease in brain parenchyma and other systemic sites. Of these six patients, one patient was HR+, two patients were HER2+, and the remaining three patients were TN subtype. Twenty-six patients (38.2%) received greater than third-line chemotherapy before LM.

The characteristics of the 65 patients at the time of LM are shown according to subtype in Table 2. The percentage of patients with HR+, HER2+, and TN breast cancers in LM were 35.4, 27.7, and 36.9%, respectively. The median age was lower for patients in the TN subtype compared to the other subtypes ($P = 0.030$). Distributions of menopausal status, histology, and TNM staging were not significantly different among the three groups. Although bone metastasis was more commonly associated with the HR+ group, this difference was not statistically significant. However, the prevalence of spinal metastases was statistically significant in HR+ compared to other subtypes (56.5% for HR+ vs. 22.2% for HER2+ vs. 20.8% for TN, $P = 0.018$). Isolated CNS metastases were much more commonly found in TN than in other subtypes (4.3% vs. 33.3% vs. 41.7%, $P = 0.004$). TTLM from distant metastasis was much longer in HR+ than in other subtypes (20.4 vs. 12.2 vs. 7.0 months, $P = 0.001$, Fig. 1a). For 18 HER2+ patients, the TTLM in trastzumab-treated patients was much longer than in trastuzumab-naïve patients (9.9 vs. 15.2 months, $P = 0.008$).

Treatment of LM and outcomes according to breast cancer subtypes Most LM patients were treated with combinations of surgery, whole brain radiation therapy (WBRT), and local and/or systemic chemotherapy. An Ommaya reservoir was inserted in 52 patients (76.5%) as a port for intrathecal (IT) chemotherapy. Patients received single modality and/or combination of modalities for the treatment of LM (Table 3). Forty-seven patients (72.3%) received IT chemotherapy, among whom 10 patients received IT therapy only, principally with methotrexate

Table 1 Comparison of clinical characteristics of the patients with brain parenchymal metastasis with leptomeningeal metastases (LM) to the patients with brain parenchymal metastasis without LM ($n = 272$)

	Brain parenchymal metastases with LM ($n = 68$)	Brain parenchymal metastases without LM ($n = 204$)	P value
No. of the patients	68 (25.0%)	204 (75.0%)	
Median age (range)	46 (24–72)	49 (24–87)	0.019 (T test)
ECOG PS[a]			0.041
0–1	41 (60.3%)	148 (72.5%)	
2≤	27 (39.7%)	56 (27.5%)	
Menopausal status			0.053
Premenopause	43 (63.2%)	102 (50.0%)	
Postmenopause	13 (19.1%)	45 (22.1%)	
Unknown	12 (17.7%)	57 (27.9%)	
Subtype			0.049
HR + ve (ER + and/or PR + ,and HER2−)	24 (35.3%)	47 (23.0%)	
HER2 + ve (HER2 + regardless of ER and/or PgR)	19 (27.9%)	96 (47.1%)	
TN (ER−/PR−/HER2−)	25 (36.8%)	61 (29.9%)	
Histology			0.269
IDC	47 (69.1%)	153 (75.0%)	
ILC	3 (4.4%)	2 (1.0%)	
Others	5 (7.4%)	8 (3.9%)	
Unknown	13 (19.1%)	41 (20.1%)	
Initial TNM stage			0.080
1	7 (10.3%)	27 (13.2%)	
2	30 (44.1%)	64 (31.4%)	
3	21 (30.9%)	93 (45.6%)	
4	10 (14.7%)	20 (9.8%)	
Isolated CNS metastasis at diagnosis	57 (83.8%)	178 (87.3%)	0.444
Progression of extracranial Ds. at CNS	47 (69.1%)	162 (79.4%	0.087
Metastatic sites			0.001
Bone	41 (60.3%)	81 (39.7%)	
Lung	22 (32.4%)	92 (45.1%)	0.060
Liver	12 (17.6%)	40 (19.6%)	0.686
Distant lymph nodes	21 (30.9%)	43 (21.1%)	0.091
Pleura	9 (13.2%)	26 (12.7%)	0.967
Median number of chemotherapy regimens before diagnosis of CNS involvement	3	2	0.066 (T-test)
Trastuzumab for metastatic disease	3 (15.8%)	19 (19.8%)	0.323
Time to CNS from distant metastasis	12.1 months	11.6 months	0.386 (log-rank test)
Time to death from distant metastasis (Metastatic OS) (median)	20.5 months	24.0 months	0.669 (log-rank test)
Time to death from CNS metastases (CNS−OS) (median)	5.8 months	8.7 months	0.025 (log-rank test)

[a] *PS* performance status, *CNS-OS* from time of CNS metastasis to death

alone (44 of 47 patients, 93.6%) or in combination with hydrocortisone plus cytosine arabinoside (three of 47 patients, 6.4%). Thirty-two of the 47 patients (68.1%) treated with IT chemotherapy responded to treatment, and presented without any microscopically detectable malignant cells in CSF at two consecutive follow-up times. The median time to cytological negative conversion was 2.9 weeks (range, 0.0–17.3), and the mean duration time of IT treatment was 13 weeks. HR+ patients had a relatively lower rate of cytological negative conversion (Table 3). Twenty-two (33.8%) patients received systemic chemotherapy. Early death within 1 month occurred mainly in

Table 2 Characteristics of patients according to breast cancer subtypes at the time of LM ($N = 65$)

	HR positive (ER+ and/or PR+ and HER2−)	HER2 positive (HER2+ regardless of ER and/or PgR)	Triple negative (ER−/PR−/HER2−)	*P* value
No. of patients, *n* (%)	23 (35.4%)	18 (27.7)	24 (36.9)	
Median age at LM, years	52 (46–58)	47 (44–50)	43 (39–48)	0.030
ECOG PS[a] at LM				0.633
0–1	5 (21.7%)	6 (33.3%)	7 (29.2%)	
2≤	18 (78.3%)	12 (66.7%)	17 (70.8%)	
Menopausal status				0.801
Premenopause	13 (56.5%)	12 (66.7%)	16 (66.6%)	
Postmenopause	6 (26.1%)	2 (11.1%)	4 (16.7%)	
Unknown	4 (17.4%)	4 (22.2%)	4 (16.7%)	
Histology				0.445
IDC	17 (73.9%)	13 (72.2%)	17 (70.8%)	
ILC	0 (0%)	1 (5.6%)	1 (4.2%)	
Others	2 (8.7%)	0 (0%)	3 (12.5%)	
Unknown	4 (17.4%)	4 (22.2%)	3 (12.5%)	
Initial TNM stage				0.691
1	1 (4.4%)	3 (16.7%)	2 (8.3%)	
2	10 (43.5%)	9 (50.0%)	10 (41.7%)	
3	9 (39.1%)	5 (27.8%)	7 (29.2%)	
4	3 (13.0%)	1 (5.5%)	5 (20.8%)	
Metastatic sites at the LM				
Bone	16 (69.6%)	9 (50.0%)	11 (45.8%)	0.242
Spine	13 (56.5%)	4 (22.2%)	5 (20.8%)	0.018
Liver	3 (13.0%)	5 (27.8%)	3 (12.5%)	0.327
Lung	8 (34.8%)	6 (33.3%)	9 (37.5%)	0.979
Distant LNs	7 (30.4%)	7 (38.9%)	10 (41.7%)	0.678
Isolated CNS metastasis	1 (4.3%)	6 (33.3%)	10 (41.7%)	0.004
Isolated LM	1 (4.3%)	2 (11.1%)	3 (12.5%)	0.563
Median number of chemotherapy line at LM	4	3	2	0.094
Progression of systemic disease at LM	60.9%	41.2%	41.7%	0.285
Median time to LM from primary cancer	64.6	40.9	21.8	0.002
Diagnosis (range)	(1.2–168.6)	(21.4–139.5)	(3.1–145.2)	
Median time to LM from distant metastasis	20.4	12.2	7.0	0.001
(TTLM) (range)	(0.0–102.2)	(0.0–69.2)	(0.0–35.2)	

[a] *PS* performance status

HR+ patients (17.4% vs. 0% vs. 8.3%, $P = 0.082$). Long-term survivors of 12 months or more were found less frequently in the TN subtype compared to other subtypes (8.3% for TN vs. 22% for others $P = 0.045$). Death caused by CNS progression was also much more common in the TN subtype (64% for TN vs. 18%, $P = 0.046$). Median survival time from distant metastasis was significantly different among the three groups (28.3 vs 29.1 vs. 11.8 months, $P < 0.0001$, Fig. 1b). However, LM − OS did not differ among the subtypes (4.1 vs. 5.9 vs. 3.8 month, $P = 0.226$).

Prognostic factors analysis

The median LM − OS of the 68 patients was 4.1 months (range, 2.2–5.8), and the one-year survival rate was 13.2% (9 of 68 patients). Univariate analysis was performed on LM − OS by log-rank test (Table 4). Systemic disease control at LM ($P = 0.035$), isolated CNS metastasis ($P = 0.035$), cytological negative conversion to IT chemotherapy ($P = 0.001$), systemic chemotherapy after LM ($P = 0.002$), and combined treatment modality ($P = 0.008$) were identified as favorable risk factors for LM − OS.

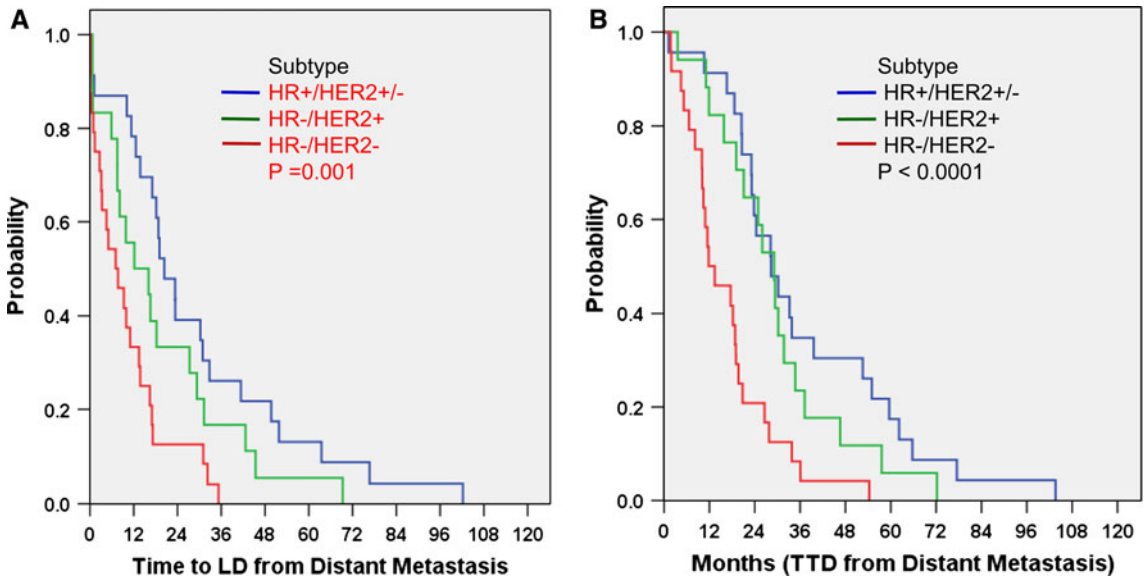

Fig. 1 Kaplan–Meier survival curves (**a**); Time to LM (TTLM) from distant metastasis according to subtypes (**b**); Time to death from distant metastasis (metastatic OS) according to subtypes

Table 3 Treatment modalities and outcomes for LM according to breast cancer subtypes ($n = 65$)

Treatment modalities	HR positive ($n = 23$)	HER2 positive ($n = 18$)	Triple negative ($n = 24$)	P value
				0.204
Single modality				
Intrathecal chemotherapy (IT)	4 (17.4%)	2 (11.1%)	4 (16.7%)	
Whole brain radiotherapy (WBRT)	4 (17.4%)	2 (11.1%)	4 (16.7%)	
Combination modality				
IT + WBRT	6 (26.1%)	5 (27.8%)	9 (37.5%)	
IT + Systemic chemotherapy	1 (4.3%)	0%	3 (12.5%)	
WBRT + Systemic chemotherapy	1 (4.3%)	4 (22.2%)	0%	
IT + WBRT + Systemic chemotherapy	5 (21.7%)	5 (27.8%)	3 (12.5%)	
No treatment (supportive care only)	2 (8.7%)	0%	1 (4.2%)	
Treatment outcome				
Intrathecal chemotherapy				
Cytologically negative conversion	53.3%	90.9%	73.7%	0.092
Clinical symptom improvement	43.5%	88.2%	66.7%	0.010
Median time to cytologic negative conversion (weeks)	1.3	3.9	3.9	0.562
Mean duration time of IT treatment (weeks)	9.9	19.0	15.6	0.426
Early death (<1 month) from LM	17.4%	0%	8.3%	0.082
Long term survivor (≥ 1 year) from LM	21.7%	27.8%	8.3%	0.217
Cause of death (CNS progression)	0%	36%	64%	0.060
Ommaya reservoir insertion	60.9%	82.4%	79.2%	0.235
Complications after Ommaya insertion	14.3%	6.7%	10.5%	0.795
Removal	0%	13.3%	15.8%	0.155
Change to shunt	0%	0%	15.8%	0.053
Time to death from distant metastasis	28.3	29.1	11.8	<0.0001
(metastatic OS) months (ranage)	(1.2–103.0)	(3.6–72.2)	(1.7–54.3)	
Time to death from LM	4.1	5.9	3.8	0.226
(LM − OS) months (range)	(0.4–35.7)	(2.8–27.8)	(0.6–22.1)	

Table 4 Univariate analysis for median survival time from LM to death (LM − OS) ($N = 65$)

Parameter	P value
Subtype	0.647
ECOG PS at LM	0.157
Systemic disease control at LM	0.035
Isolated CNS metastasis	0.035
Cytology negative conversion	0.001
Systemic chemotherapy	0.002
Combination therapy	0.008

Breast cancer subtype and PS were not identified as risk factors for survival (Fig. 2a, c). However, in the multivariate analysis, the results for the final model showed that cytological negative conversion (Hazard Ratio (HR) 0.416, $P = 0.023$), isolated CNS metastases (HR 0.420, $P = 0.028$), and combined treatment modality for LM (HR 0.238, $P = 0.004$) were independent prognostic factors for LM − OS (Table 5).

Discussion

This study investigated characteristic features of LM in breast cancer according to intrinsic subtypes. At first, patients with HR+ subtype showed different presentations and treatment outcomes. Isolated CNS metastasis appeared to be more uncommon compared to other subtypes ($P = 0.004$) (Table 2). In addition, progression of extracranial systemic disease was a more common finding, although statistical significance was not maintained (60.9% vs. 41.2% vs. 41.7%). Most importantly, TTLM from distant metastasis was much longer in HR+ than in other subtypes (20.4 vs. 12.2 vs. 7.0 months, $P = 0.001$). In addition, relatively low rates of death were caused by CNS compared to other subtypes. Furthermore, early death within 1 month from LM was a more common finding in HR+ patients than in other subtypes. The median TTLM from distant metastases was 89 months in four patients whose survival times from LM were within 1 month. The cause of death was usually progression of extracranial systemic disease, not LM. In the long run over the entire disease course, LM was merely a final consequence in HR+ patients. The median number of lines of chemotherapy administered before development of LM was higher in HR+ than in other subtypes. With respect to whole CNS involvement in breast cancer, LM seems to be a final event, as does brain parenchymal metastasis in HR+ patients, as a result of the long-lasting disease course. Interestingly, bone metastasis was closely related with BM + LM compared to BM-LM (Table 1). Considering the route by which cancer cells reach the pia-arachnoid in leptomeningeal carcinomatosis [6, 23], extensive metastatic bone lesions including spines seem to be the most likely locations for LM development. Consequently, our results showed a preference for spinal metastases in HR+ patients (Table 2). Therefore, development of LM in HR+ patients appears to be correlated with the end-stage of the whole disease course through extensive disseminated metastases, especially to the spine. Most of the patients in the HR+ group died of uncontrolled systemic disease, irrespective of LM control.

Owing to the delaying effects of trastuzumab or other chemotherapy on CNS involvement, the HER2+ subtype was reported to have a higher incidence of late onset CNS involvement [2, 24, 25]. TTLM in HER2+ patients was shown to be significantly longer than in TN patients, and was similar to that observed in HR+ patients. Limiting the analysis to 18 HER2+ patients, we found that TTLM in trastuzumab-treated patients was much longer than those in trastuzumab-naïve patients (9.9 vs. 15.2 months, $P = 0.008$). However, LM-OS did not show any significant differences among the three subtypes. Compared to TN subtype, early death was not observed in HER2+ patients and there were many long-term survivors of 12 months or more (Table 2), as well as longer TTLM from distant metastasis (Table 3). Interestingly, the proportion of HER2+ patients in the BM − LM subgroup was higher than that of other subtypes (22.8% vs. 47.2% vs. 29.9%, $P = 0.049$, Table 1). In fact, the rate of LM was lower in HER2+ patients than in other subtypes, among all the 272 patients with CNS metastases (46.3% for HR+ vs. 28.5% for HER2+ vs. 40.6% for TN, $P = 0.049$). A plausible explanation for this finding may be the differences in biological background and improvements in treatment related to HER2-targeted therapy.

In contrast, TTLM was much shorter in TN patients than in the other subtypes. For patients with the worst prognoses without any targeted therapy in TN breast cancer, the occurrence of LM may be associated with extremely poor prognoses. LM is a very late event in HR+ patients and is frequently associated with progression at other sites including the brain parenchyma, but it did not seem to be a late event in TN patients. Despite a similar prognosis of TN patients in terms of LM − OS compared to other subtypes, LM occurred early during the disease course of TN patients. The short TTLM accompanied by the worst outcomes in TN patients suggested that LM could occur abruptly at any time, representing aggressive tumor behavior. This finding reveals an urgent need for new, innovative therapeutic strategies for TNBC patients. The higher incidence of isolated CNS metastases, fewer lines of chemotherapy, and higher rate of death caused by CNS metastases support these conclusions. In HER2+ patients after trastuzumab treatment, development of CNS

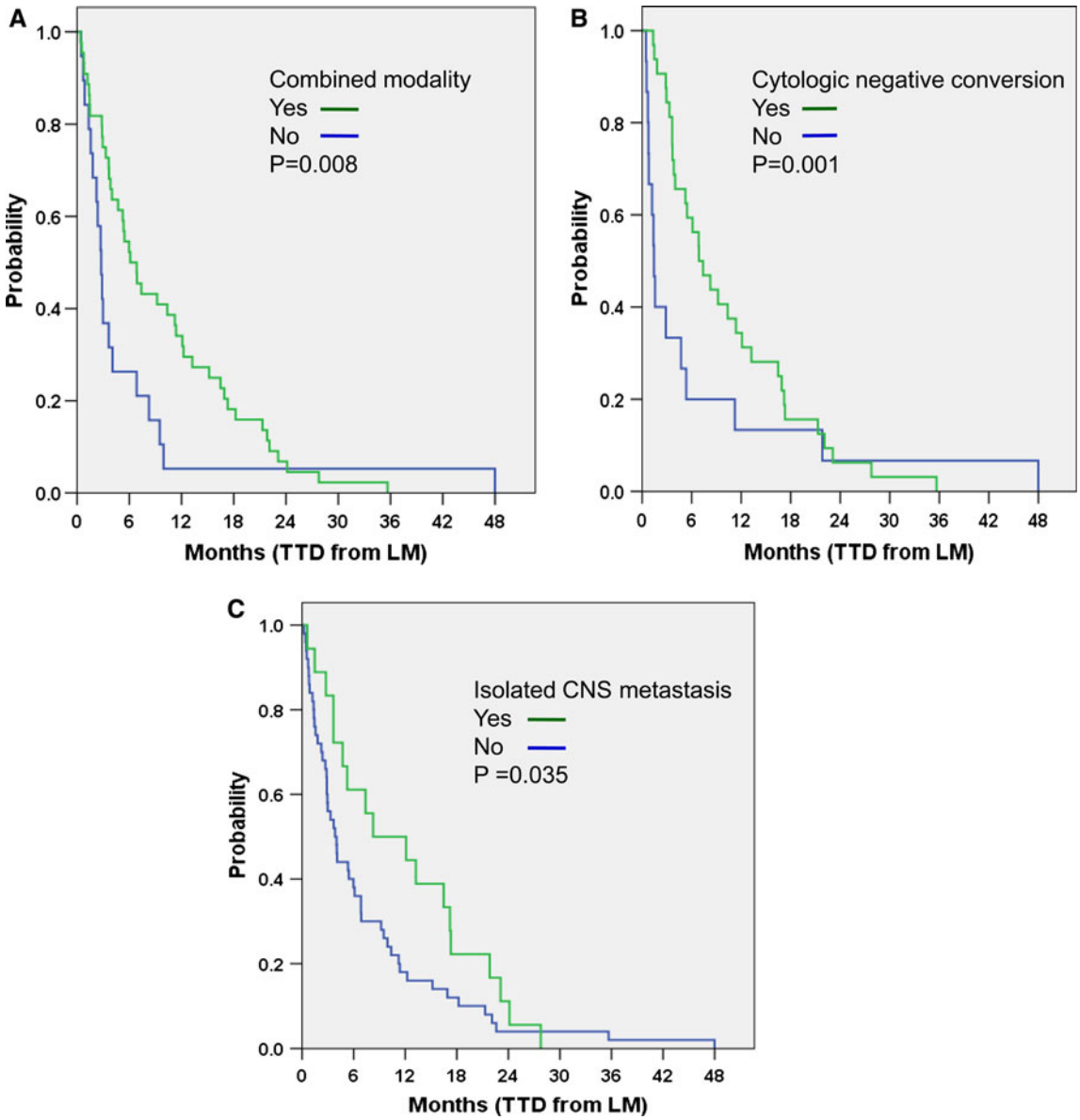

Fig. 2 Univariate analysis on time to death from LM (LM − OS) (**a**); LM − OS according to use of combined modality for treatment (**b**); LM − OS according to cytologic negative conversion status to IT chemotherapy (**c**); LM − OS according to presence of isolated CNS metastasis

Table 5 Multivariate Cox-regression analysis for survival from LM (LM-OS)

Parameter	*P* value	Hazard ratio (exp. B)	95% CI
Cytology negative conversion	0.023	0.416	0.195–0.887
Isolated CNS metastasis	0.028	0.420	0.194–0.908
Combined treatment modality for LM.	0.004	0.238	0.090–0.628
Progression of systemic disease at LM	0.801	1.103	0.514–2.370

involvement indicates the late course of the disease, although it may still be responsive to treatment. In other words, CNS involvement including LM implies eventual failure of disease control, but the clinical course is still reversible in nature. This may present the evidence that systemic chemotherapy plays a role in an advanced systemic disease setting. However, independent sudden onset of LM with highly aggressive clinical presentation in TNBC probably results in a completely different clinical course. In spite of frequent cytological conversions to IT chemotherapy, the prognosis of LM in TNBC was no better than other subtypes.

We note that our study has some limitations. This was a small retrospective study. There may have been heterogeneous treatment strategies, even though most of the patients were treated with multiple modalities. Thus, treatment factors were underestimated in our analysis. In addition, the diagnostic method of LM needs to be better defined.

In conclusion, clinical courses of LM were affected by breast cancer subtype: LM was an end-stage event in HR+ patients, BM − LM was more common in HER2+ than in other subtypes, and LM was a reflection of aggressive tumor behavior with worse outcomes in TN patients. Further studies to better understand the biology of LM and to improve therapeutic outcomes are warranted.

Conflict of Interest The authors have no conflicts of interest to declare.

References

1. Lin NU, Bellon JR, Winer EP (2004) CNS metastases in breast cancer. J Clin Oncol 22(17):3608–3617. doi:10.1200/JCO.2004.01
2. Park YH, Park MJ, Ji SH, Yi SY, Lim DH, Nam DH et al (2009) Trastuzumab treatment improves brain metastasis outcomes through control and durable prolongation of systemic extracranial disease in HER2-overexpressing breast cancer patients. Br J Cancer 100(6):894–900. doi:6604941
3. Chamberlain MC, Glantz M, Groves MD, Wilson WH. (2009) Diagnostic tools for neoplastic meningitis: detecting disease, identifying patient risk, and determining benefit of treatment. Semin Oncol. 36(4 Suppl 2):S35-45. doi:S0093-7754(09)00095-5
4. Chamberlain MC (2006) Neoplastic meningitis. Neurologist 12(4):179–187. doi:10.1097/01.nrl.0000219732.33321.cc
5. Mammoser AG, Groves MD (2010) Biology and therapy of neoplastic meningitis. Curr Oncol Rep 12(1):41–49. doi:10.1007/s11912-009-0079-2
6. Gleissner B, Chamberlain MC (2006) Neoplastic meningitis. Lancet Neurol 5(5):443–452. doi:S1474-4422(06)70443-4
7. Glantz MJ, Walters BC (1998) Diagnosis and outcome measures in trials for neoplastic meningitis: a review of the literature and clinical experience. Neurosurg Focus 4(6):e4. doi:040604
8. Jaeckle KA (2006) Neoplastic meningitis from systemic malignancies: diagnosis, prognosis and treatment. Semin Oncol 33(3):312–323. doi:S0093-7754(06)00190-4
9. Jayson GC, Howell A (1996) Carcinomatous meningitis in solid tumours. Ann Oncol 7(8):773–786
10. Rudnicka H, Niwinska A, Murawska M (2007) Breast cancer leptomeningeal metastasis—the role of multimodality treatment. J Neurooncol 84(1):57–62. doi:10.1007/s11060-007-9340-4
11. Berg SL, Chamberlain MC (2003) Systemic chemotherapy, intrathecal chemotherapy, and symptom management in the treatment of leptomeningeal metastasis. Curr Oncol Rep 5(1):29–40
12. Norris LK, Grossman SA, Olivi A (1997) Neoplastic meningitis following surgical resection of isolated cerebellar metastasis: a potentially preventable complication. J Neurooncol 32(3):215–223
13. Cokgor I, Friedman AH, Friedman HS (2002) Current options for the treatment of neoplastic meningitis. J Neurooncol 60(1):79–88
14. Chang EL, Maor MH (2003) Standard and novel radiotherapeutic approaches to neoplastic meningitis. Curr Oncol Rep 5(1):24–28
15. Boogerd W, van den Bent MJ, Koehler PJ, Heimans JJ, van der Sande JJ, Aaronson NK et al (2004) The relevance of intraventricular chemotherapy for leptomeningeal metastasis in breast cancer: a randomised study. Eur J Cancer 40(18):2726–2733. doi:S0959-8049(04)00677-X
16. Recht L, Phuphanich S (2004) Treatment of neoplastic meningitis: what is the standard of care? Expert Rev Neurother 4(4 Suppl):S11–S17. doi:10.1586/14737175.4.4.S11
17. Clatot F, Philippin-Lauridant G, Ouvrier MJ, Nakry T, Laberge-Le-Couteulx S, Guillemet C et al (2009) Clinical improvement and survival in breast cancer leptomeningeal metastasis correlate with the cytologic response to intrathecal chemotherapy. J Neurooncol 95(3):421–426. doi:10.1007/s11060-009-9940-2
18. Chamberlain MC (2008) Neoplastic meningitis. Oncologist 13(9):967–977. doi:theoncologist.2008-0138
19. Chamberlain MC, Glantz M (2006) Ventriculoperitoneal shunt in patients with leptomeningeal metastasis. Neurology 66(5):783
20. Lin NU, Winer EP (2007) Brain metastases: the HER2 paradigm. Clin Cancer Res 13(6):1648–1655. doi:13/6/1648
21. Lin NU, Claus E, Sohl J, Razzak AR, Arnaout A, Winer EP (2008) Sites of distant recurrence and clinical outcomes in patients with metastatic triple-negative breast cancer: high incidence of central nervous system metastases. Cancer 113(10):2638–2645. doi:10.1002/cncr.23930
22. Vincent T, Devita J (eds) (2011). Cancer principles & practice of oncology, 9th edn. Lippincott Williams & Wilkins, Philadelphia
23. Kokkoris CP (1983) Leptomeningeal carcinomatosis. How does cancer reach the pia-arachnoid? Cancer 51(1):154–160
24. Dawood S, Broglio K, Esteva FJ, Ibrahim NK, Kau SW, Islam R et al (2008) Defining prognosis for women with breast cancer and CNS metastases by HER2 status. Ann Oncol 19(7):1242–1248. doi:mdn036
25. Bartsch R, Rottenfusser A, Wenzel C, Dieckmann K, Pluschnig U, Altorjai G et al (2007) Trastuzumab prolongs overall survival in patients with brain metastases from Her2 positive breast cancer. J Neurooncol 85(3):311–317. doi:10.1007/s11060-007-9420-5