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ORIGINAL ARTICLE

Clinical features and outcome of leptomeningeal metastasis in patients with breast cancer: a single center experience

Jae-Cheol Jo · Myoung Joo Kang · Jeong Eun Kim · Jin-Hee Ahn · Kyung Hae Jung · Gyungyub Gong · Hak Hee Kim · Seung Do Ahn · Su Ssan Kim · Byung Ho Son · Sei Hyun Ahn · Sung-Bae Kim

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Abstract
Background Leptomeningeal metastasis (LM) is one of the major problems in the management of metastatic breast cancer; typically, LM has a devastating prognosis and often represents a terminal event. The present study analyzed the clinical features and outcome of LM in patients with breast cancer.
Methods The medical records of patients diagnosed with LM from breast cancer at Asan Medical Center, between 2002 and 2012, were reviewed retrospectively.
Results Of 95 LM patients, 38 (40 %) had an ECOG performance status (PS) ≤ 2, and the median age was 47 years (range 26–72 years). At the time of LM diagnosis, 46 patients (48.4 %) presented with coincidental failure of systemic disease control. Seventy-eight patients (82.1 %) underwent intrathecal (IT) chemotherapy, resulting in cytologic negative conversion in 26 patients, and 46 patients (48.4 %) received systemic chemotherapy. The median overall survival (OS) time was 3.3 months, and 7.8 % of the patients survived for more than 1 year. OS tended to be higher in patients who achieved cytologic negative conversion from IT chemotherapy than in those who did not (4.5 vs. 2.4 months, $P = 0.088$). Multivariate analysis demonstrated that ECOG PS ≤ 2, controlled extracranial disease at the time of LM diagnosis, and systemic chemotherapy after LM diagnosis were independent factors associated with survival.
Conclusions The prognosis of patients with LM from breast cancer is poor. Systemic chemotherapy, in addition to intrathecal chemotherapy, might confer a survival benefit, even after the detection of LM.

Keywords Leptomeningeal metastasis · Prognosis · Chemotherapy · Breast cancer

J.-C. Jo · M. J. Kang · J. E. Kim · J.-H. Ahn · K. H. Jung · S.-B. Kim (✉)
Departments of Oncology, Asan Medical Center, University of Ulsan College of Medicine, 88, Olympic-ro 43-gil, Songpa-gu, Seoul 138-736, Korea
e-mail: sbkim3@amc.seoul.kr

G. Gong
Departments of Pathology, Asan Medical Center, University of Ulsan College of Medicine, 88, Olympic-ro 43-gil, Songpa-gu, Seoul 138-736, Korea

H. H. Kim
Departments of Radiology, Asan Medical Center, University of Ulsan College of Medicine, 88, Olympic-ro 43-gil, Songpa-gu, Seoul 138-736, Korea

S. D. Ahn · S. S. Kim
Departments of Radiation Oncology, Asan Medical Center, University of Ulsan College of Medicine, 88, Olympic-ro 43-gil, Songpa-gu, Seoul 138-736, Korea

B. H. Son · S. H. Ahn
Departments of Surgery, Asan Medical Center, University of Ulsan College of Medicine, 88, Olympic-ro 43-gil, Songpa-gu, Seoul 138-736, Korea

Introduction

Leptomeningeal metastasis (LM) is a devastating neurologic complication of cancer occurring in 3–15 % of all patients with solid cancers [1, 2]. Improved systemic therapy for a cancer and prolonged survival has increased the frequency of central nervous system (CNS) involvement, including LM, especially in breast cancer [3, 4]. Once established, LM has a poor prognosis and is often a terminal event. In this context, LM has become a matter of concern for medical oncologists.

The administration of trastuzumab in HER2-positive breast cancer, a recent therapeutic development, prolongs survival, even after development of CNS metastasis [4, 5]. Additionally, new HER2-targeted drugs, such as lapatinib, that may cross the blood–brain barrier, can be expected to efficiently control brain metastasis [6]. Indeed, lapatinib showed some efficacy in selected subgroups of patients with LM from breast cancer. Moreover, until now, standard treatment guidelines and optimal therapies for LM have not been determined, and well-defined prognostic factors are needed to help physicians decide whether to elect treatment or spare patients from intensive therapy if they would not benefit from it.

This study was performed to understand the natural history of LM in breast cancer and to describe the clinical outcome of LM based on clinical factors and treatment modalities.

Patients and methods

Patients

Of the 7,723 patients histologically diagnosed with breast cancer at the Asan Medical Center between April 2002 and February 2012, 95 patients who were diagnosed with LM from breast cancer were included in this retrospective study. All 95 patients presented histologically confirmed adenocarcinoma of the breast. The diagnosis of LM from breast cancer was based on signs and symptoms, detection of malignant cells in cerebrospinal fluid (CSF), and the typical findings of subarachnoid tumor enhancement on brain and/or spine magnetic resonance imaging (MRI), or both. If cytological results were negative yet clinical and/or radiological data suggested the presence of tumor, lumbar punctures were repeated 2–3 times to confirm LM by CSF cytology. Brain and/or whole-spine MRI with gadolinium enhancement was examined in all patients. Receptor status was assessed by immunohistochemical staining (estrogen receptor (ER), progesterone receptor (PgR), and HER2) and included in the retrospective analysis. HER2 fluorescence in situ hybridization (FISH) was performed to confirm HER2 amplification if the HER2 score by immunohistochemistry (IHC) was 2+. The hormone receptor-positive (HR+) subtype was defined as breast cancer with positive IHC staining for ER and/or PgR, regardless of HER2 status. The triple negative (TN) subtype was defined as breast cancer with negative IHC staining for ER, PR, and HER2. Specimens positive for HER2 but negative for hormone receptor (ER and PR) were classified in the HER2+ subtype.

Intrathecal (IT) treatment

The treatment regimen for first-line IT chemotherapy was fixed dose of 12 mg methotrexate (MTX) with or without 50–100 mg hydrocortisone [7]. IT administration of MTX was repeated two or three times a week. The response of LM to IT chemotherapy was evaluated by CSF cytology and CSF cytospin; response was assessed by complete clearing of all malignant cells from the CSF. The responders, in whom the CSF showed no malignant cells or no atypical cells, received weekly maintenance therapy with the same regimen as with the previous regimen, while the response persisted. In the absence of response or when disease progressed after initial response, IT administration was changed to 15 (or 10) mg thiotepa with or without hydrocortisone, if the patient could be conditioned [8]. The schedule of IT thiotepa administration was the same as that of IT methotrexate.

Statistical analysis

The date of LM diagnosis was defined as the date on which LM was confirmed via imaging or cytological study. The time to LM was defined as the interval between the date of diagnosis of distant metastasis and the date of LM diagnosis. Overall survival (OS) was measured from the time of initial LM diagnosis until death (event) or last follow-up (censored) and was estimated using the Kaplan–Meier method. The comparison of survival between groups was conducted using the log-rank test. Multivariate analysis was performed using the Cox proportional hazard regression model. $P < 0.05$ was considered to indicate statistical significance. All statistical analyses were performed with the Statistical Software Package for the Social Sciences (SPSS version 18.0 for Windows; SPSS, Chicago, IL, USA).

Results

Patient characteristics

The characteristics of the 95 breast cancer patients with LM are listed in Table 1. The median age at diagnosis of LM was 47 years (range 26–72 years), and 38 patients (40.0 %) had an ECOG performance status (PS) of 1 or 2. The most common subtype of breast cancer was the TN subtype (53.7 %). LM was present in two patients at the time of initial diagnosis. Twenty-three patients (24.2 %) had isolated CNS metastasis, and six patients (6.3 %) had LM without any other detectable metastatic site. The most common additional metastatic site at the time of LM diagnosis was bone (55.8 %). Brain parenchymal metastasis was not detected in 34 patients (35.8 %) during the follow-up period. The median time to diagnosis of LM was 10.3 months (95 % CI, 5.5–15.0 months) from the time of diagnosis of metastatic breast cancer. The median number

Table 1 Demographic and clinical characteristics of patients ($n = 95$)

Characteristics	No. of patients (%)
Median age at the time of LM diagnosis, years (range)	47 (26–72)
ECOG performance status at LM diagnosis	
1–2	38 (40)
3–4	57 (60)
Subtype of tumor	
ER+ and/or PgR+ regardless of HER2 status	24 (25.3)
HER2 +/ER−/PgR−	15 (15.8)
ER−/PgR−/HER2− (triple negative)	51 (53.7)
Unknown	5 (5.3)
Initial TNM stage	
1	14 (14.7)
2	16 (16.8)
3	41 (43.2)
4	20 (21.1)
Unknown	4 (4.2)
Metastatic sites	
Bone	53 (55.8)
Distant lymph nodes	38 (40)
Lung	25 (26.3)
Liver	19 (20)
Presence of brain metastasis	
None	34 (35.8)
Before presentation of LM	37 (38.9)
Concurrent LM	24 (25.3)
Previous line of chemotherapy	
0	19 (20.0)
1	28 (29.5)
2	23 (24.2)
≥3	25 (26.3)
Extracranial systemic control at LM	
Not PD	49 (51.6)
PD	46 (48.4)

LM leptomeningeal metastasis, *ER* estrogen receptor, *PgR* progesterone receptor, *CNS* central nervous system, *PD* progressive disease

of chemotherapy regimens before diagnosis of LM was 2 (range 0–7), and 48 patients (50.5 %) received ≥2 lines of chemotherapy. Coincidental failure of extracranial disease control at the time of diagnosis of LM was noted in 46 patients (48.4 %).

Treatment for LM

Seventy-eight patients (82.1 %) received IT chemotherapy via lumbar puncture or Ommaya reservoir (45.3 %). Due to patient refusal of IT chemotherapy or poor PS, 17 patients did not undergo IT chemotherapy. The median length of IT MTX cycles, received by 67 patients, was 7, and 11 patients were administered thiotepa as a second-line regimen after progression post-IT MTX. Of the 78 patients, complete cytological resolution of CSF was achieved in 26 patients, reaching a response rate of 33.3 %. The median session of IT treatment required to achieve negative conversion was 5 (range 1–14). Treatments and clinical outcomes of IT chemotherapy are summarized in Table 2.

Table 2 Treatments and clinical outcomes

Characteristics	No. of patients (%)
Median overall survival	3.3 months (95 % CI, 2.5–4.2)
Survival at 6 months	26.7 %
Survival at 12 months	7.8 %
Ommaya reservoir insertion	
Yes	43 (45.3)
No	52 (54.7)
Detection of malignant cells in CSF	
Yes	81 (85.3)
No	14 (14.7)
Intrathecal chemotherapy	78 (82.1)
MTX alone	67
Median number of cycles of MTX	7 (range, 2–21)
MTX alone → thiotepa alone	11
Median number of cycles of MTX	11 (range, 4–31)
Median number of cycles of thiotepa	7 (range, 1–25)
Cytologic response	
Complete cytologic resolution of CSF	26/78 (33.3)
Radiation therapy	
None	45 (47.4)
Yes	50 (52.6)
Before LM presentation	38 (40.0)
After LM presentation	12 (12.6)
Systemic chemotherapy after diagnosis of LM	
Yes	46 (48.4)
No	49 (51.6)

LM leptomeningeal metastasis, *CSF* cerebrospinal fluid, *MTX* methotrexate

Either concomitantly or subsequently, systemic therapy was administered to 46 patients (48.4 %). Of these 46 patients, 34 received cytotoxic chemotherapy only, 7 received antihormone therapy only, 4 received lapatinib plus capecitabine, and 1 received trastuzumab. Further cytotoxic chemotherapy regimens were capecitabine alone ($n = 12$), taxane alone ($n = 7$), capecitabine plus other cytotoxic agents ($n = 4$), adriamycin plus cyclophosphamide ($n = 3$), taxane plus platinum ($n = 3$), and other cytotoxic agents ($n = 5$). Four patients with HER2+ disease, who were treated with lapatinib plus capecitabine,

received the median three cycles (range 2–5) and survived for 3.3, 4.0, 5.8, and 7.4 months, respectively. Only one patient received trastuzumab (1 cycle) and died of LM within 2 months. The median OS of five HER2+ patients who were treated with HER2-targeted agents was 4.0 months (range 2.0–7.4 months).

Survival and prognostic factors

For all 95 cases, the median OS after diagnosis of LM was 3.3 months (95 % CI, 2.5–4.2, Fig. 1). The median OS was 4.5 months among cytological responders and 2.4 months among non-responders with borderline significance ($P = 0.088$). There was no survival difference between patients who achieved cytological response before five sessions of IT treatment vs. after five sessions (median 4.5 vs. 4.5 months, $P = 0.692$). The median OS was not different between subtypes (2.9, 3.5, and 3.2 months for HR+, HER2+, and TN, respectively, $P = 0.853$). Patients with ECOG PS 1–2 had prolonged survival compared with patients who had poor ECOG PS 3–4 (4.5 vs. 2.6 months, $P = 0.001$; Fig. 2a). Controlled systemic metastasis at LM diagnosis was an independent good prognostic factor for OS (Fig. 2b), and the median OS in patients with systemic therapy after LM diagnosis was significantly longer than in those who did not receive therapy (Fig. 2c). The results of univariate and multivariate analyses are shown in Table 3. The significant prognostic factors by multivariate analysis were ECOG PS, disease status of extracranial metastatic lesions, and systemic therapy after LM diagnosis.

Characteristics of patients who survived more than 1 year

A total of seven patients (7.8 %) with LM from breast cancer were managed over 1 year at our center (Table 4). All seven patients not only had controlled extracranial disease, but also received systemic therapy that included cytotoxic chemotherapy and antihormone therapy. Of the seven patients, all had good PS, and four were hormone receptor-positive. The median number of sessions of IT treatment was 21 (range 3–56); however, all patients eventually died of uncontrolled LM from breast cancer.

Discussion

In this study, the prognosis of patients with LM from breast cancer was poor, with a median OS of only 3.3 months. Good PS and controlled extracranial disease were associated with better prognosis in the overall cohort. Prolonged survival was observed in patients treated with systemic therapy after LM diagnosis. To the best of our knowledge,

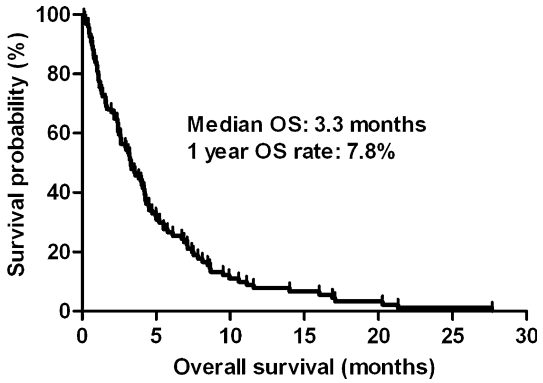

Fig. 1 Kaplan–Meier curve for overall survival

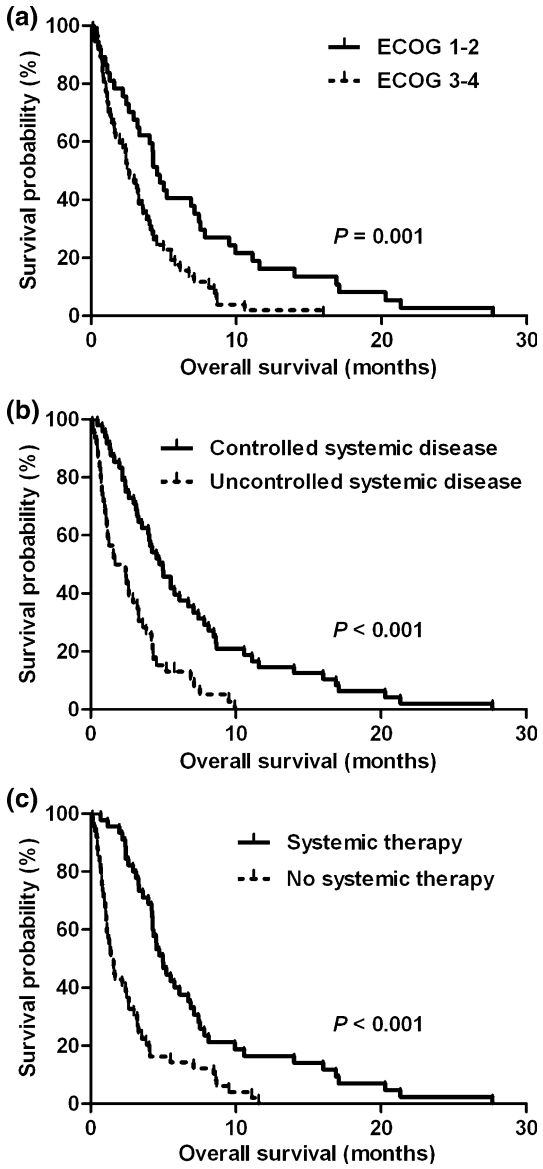

Fig. 2 Overall survival curve according to ECOG PS (**a**) extracranial disease control (**b**) and systemic therapy (**c**)

Table 3 Univariate and multivariate analyses of factors associated with overall survival in all 95 patients

Variables	Univariate		Multivariate	
	HR (95 % CI)	*P*	HR (95 % CI)	*P*
Age at the time of LM diagnosis		0.333		
≤45 years	0.82 (0.54–1.23)			
>45 years	1			
ECOG performance status at LM diagnosis		0.001		0.006
1–2	0.48 (0.31–0.75)		0.51 (0.31–0.82)	
3–4	1		1	
Subtype of tumor		0.854		
ER+ and/or PgR+ regardless of HER2 status	1.02 (0.56–1.86)			
HER2+/ER−/PgR−	0.87 (0.53–1.45)			
ER−/PgR−/HER2− (triple negative)	1			
Coexisting brain metastasis		0.131		
Yes	1.40 (0.90–2.18)			
No	1			
Isolated CNS metastasis		0.156		
Yes	0.71 (0.44–1.14)			
No	1			
Controlled extracranial disease		<0.001		<0.001
Yes	0.39 (0.25–0.60)		0.33 (0.21–0.52)	
No	1		1	
Cytology negative conversion		0.082		
Yes	0.66 (0.42–1.05)			
No	1			
Systemic chemotherapy after diagnosis of LM		<0.001		<0.001
Yes	0.37 (0.24–0.57)		0.41 (0.26–0.64)	
No	1		1	

HR hazard ratio, *CI* confidence interval, *LM* leptomeningeal metastasis, *ER* estrogen receptor, *PgR* progesterone receptor, *CNS* central nervous system

Table 4 Treatment modalities in patients who survived longer than 12 months after LM diagnosis

Patient	Age	ECOG PS	Subtype of tumor[a]	Coexisting CNS metastasis	Status of extracranial disease	Intrathecal chemotherapy	CSF cytology negative conversion	Systemic chemotherapy after LM diagnosis	Survival after LM diagnosis (months)
#1	48	2	HR	No	Not PD	MTX#17 → Thiotepa#24	No	Capecitabine/ vinorelbine	16.0
#2	32	2	TN	Yes	Not PD	MTX#11 → Thiotepa#6	Yes	Capecitabine	20.3
#3	47	2	HR	Yes	Not PD	MTX#3	No	EAP	27.7
#4	43	1	HR	No	Not PD	MTX#13	No	Paclitaxel	21.3
#5	37	1	TN	No	Not PD	MTX#21	Yes	Capecitabine/ vinblastine	17.1
#6	60	1	HR	No	Not PD	MTX#8	Yes	Exemestane	14.0
#7	41	2	TN	No	Not PD	MTX#31 → Thiotepa#25	No	Capecitabine	16.9

LM leptomeningeal metastasis, *PS* performance status, *CNS* central nervous system, *CSF* cerebrospinal fluid, *PD* progressive disease, *ER* estrogen receptor, *PgR* progesterone receptor, *MTX* methotrexate, *EAP* etoposide/adriamycin/cisplatin

[a] HR; ER+ and/or PgR+ regardless of HER2 status, *TN* triple negative

this is the largest study describing clinical features and survival outcome in breast cancer with LM.

Previous studies have demonstrated that PS is one of the most important prognostic factors in patients with LM from breast, lung, and others cancer [9–12]. As with previous studies, a good ECOG PS was also a significant prognostic factor in our cohort. Additionally, in the present study, all patients who lived beyond 12 months were those with an ECOG PS ≤ 2. In our multivariate analysis, the administration of systemic chemotherapy was a prognostic factor for survival time. The physician's decision to administer systemic chemotherapy might have been influenced by the patient's PS leading to a selection bias in this variable; however, the blood–brain barrier may be partially damaged by leptomeningeal lesions, allowing cytotoxic chemotherapeutic agents to penetrate into the CSF [13–15]. Agents such as cyclophosphamide, fluorouracil, methotrexate, and adriamycin have shown activity against intracranial metastases, likely as a result of increased tumor vessel permeability [16, 17]. Moreover, systemic chemotherapy has antitumor efficacy in other extracranial or systemic lesions in addition to LM, which is consistent with the significant impact of systemic chemotherapy on prognosis observed in the present study. Therefore, patients with good PS may be suitable candidates for more aggressive treatment, although LM treatment would be palliative.

In the literature, systemic chemotherapy has been suggested to improve survival in patients with LM as well as brain parenchymal lesions mainly from chemo-responsive tumors, such as breast cancer, lung cancer, and hematologic malignancies [15, 18–20]. Although prolonged survival in cancer patients has been achieved with the development of various anti-cancer agents, no effective therapy for LM has yet been established. Some reports on LM from lung cancer indicate that epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs), such as gefitinib and erlotinib, may be valuable, especially in patients with EGFR mutations inducing sensitivity to these agents or in patients with predictors of EGFR TKI responsiveness [11, 19]. Although no clinical data exist on LM from breast cancer, several trials support a role for lapatinib plus capecitabine in the treatment of women with recurrent brain metastases from HER2+ breast cancer [21–23]. Several reports showed that continuation of the treatment with trastuzumab beyond progression of CNS metastasis appears to prolong survival in patients with breast cancer brain metastasis by controlling both systemic disease and brain metastases [24, 25]. Although trastuzumab could be a treatment option in this situation, it was difficult to continue trastuzumab treatment in patients for whom brain metastatic lesions had progressed, as trastuzumab beyond progression in CNS is not covered by health insurance in Korea. Although only five patients out of 15 patients with HER2+ lesions who were treated with HER2-target agents were included in this cohort, survival data in these patients showed a trend toward longer survival (median 4.0 months) compared with the whole study population (median 3.3 months). Further investigation of HER2-targeted therapy in HER2+ subtype breast cancer patients confined to LM is warranted.

In contrast to systemic chemotherapy, the effectiveness of IT chemotherapy in the treatment of LM may be limited. Summarizing the current evidence, IT chemotherapy in solid cancers seems to have no effect on survival compared with other treatment modalities and is even associated with an increased rate of therapy-associated complications [8, 13, 26]. However, in our data, cytologic conversion and prolonged survival were observed in response to IT treatment (4.5 vs. 2.4 months, $P = 0.088$), which is consistent with previous reports [10, 14]. Currently, using liposomal cytarabine, a therapeutic concentration of cytarabine can be maintained in the CSF for up to 28 days in contrast to the conventional formulation of cytarabine that has a half-life of less than 4 h in the CSF [27]. In a trial, where 61 patients with solid tumors were randomly assigned to liposomal cytarabine or IT MTX, there was a statistically significant delay in time to neurologic progression (58 vs. 30 days with IT MTX), and there was a non-significant trend toward increased median survival (105 vs. 78 days) [28]. The reduced frequency of liposomal cytarabine administration is an important advantage, but further investigation of the efficacy of IT chemotherapy is needed.

Our study has several limitations. First, patients were not treated homogenously, that is, received various lines of chemotherapy or chemotherapy regimens, which was inevitable considering that this is a retrospective analysis. Second, even though a multivariate analysis was performed to adjust for such heterogeneity, patient characteristics might not be identical between the subgroups. The other limitations are a relatively small sample size and a single center. Therefore, our conclusions should be cautiously interpreted, and further evaluation of our findings is warranted.

In conclusion, the prognosis of patients with LM from breast cancer remains poor. We suggest that clinicians consider systemic chemotherapy in patients with LM from breast cancer, especially in patients with good PS and controlled extracranial disease.

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Conflict of interest The authors declare no conflict of interest.

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