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CLINICAL STUDY

Determinants of prolonged survival for breast cancer patient groups with leptomeningeal metastasis (LM)

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Abstract

The study aimed to assess factors affecting survival of breast cancer patients suffering leptomeningeal metastasis (LM) and to compare survivals in patients with LM as the first and only site of metastases at presentation to patients with LM and metastases in other organs, along with selecting a patient group which had the best survival outcomes. Subject groups consisted of 187 patients consecutively referred during 1999–2015. A Cox proportional hazards model was used to identify factors associated with prolonged survival from LM. The Cox prognostic index was created to identify the group of patients with the most favorable prognosis. Median survival for all patients and for those with LM as the first site of metastases at presentation was 17 weeks and 1 year-survival was 15 and 16%, respectively. Factors beneficially affecting survival were: KPS ≥ 70, older age, biological subtype ER/PR+HER2−, systemic treatment, intrathecal treatment and radiation therapy. Based on these factors, 4 prognostic groups were found, with the most favorable group being 24 LM patients with median survival of 9.6 months. In this group, all patients were treated systemically and all were irradiated, 88% had KPS ≥ 70, about 80% had luminal breast cancer, 75% were treated intrathecally and 58% were more than 53 years old. Out of 4 prognostic groups of patients with LM, the most favorable group was selected. The median survival of breast cancer patients with the leptomeninges as the only site of metastases was comparable to those who had metastases in the leptomeninges and in other organs.

Keywords Breast cancer · Carcinomatous meningitis · Leptomeningeal metastasis · Long-survivor · Intrathecal treatment

Introduction

Despite spectacular improvements made in the treatment of breast cancer, patient outcomes in those suffering from breast cancer and leptomeningeal metastasis (LM) remains unsatisfactory. Median survival of patients with breast cancer LM range from 7 weeks to 5 months [1–10] and the 1-year survival varies from 7 to 24% [1–8]. An analysis of 36 studies, with 851 breast cancer subjects demonstrates that median survival of breast cancer patients with LM was 15 weeks [11]. This is longer than that observed in patients with LM derived from other solid tumors (8 weeks), but is shorter than in patients with lymphoma LM (24 weeks) [11].

No definitive management paradigm exists for treating breast cancer LM patients because high quality evidence for optimal treatment of this disease is minimal. Of only four randomized controlled trials, one compared standard systemic therapy and involved field radiotherapy ± intrathecal therapy [12], while the other three compared different intrathecal chemotherapy regimens [13–17].

Disappointing treatment outcomes found in cases of LM breast cancer has prompted analyses of clinical characteristics, treatments and factors affecting survival in such patients in order to create a prognostic index and to select patient groups with prolonged survival. Such an index could thereby enable the physician to assess a given patient's prognosis whenever LM is detected.

The study aimed to:

– Assess factors affecting survival in 187 consecutive patients with breast cancer and LM; Group A.

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– Compare survival of patients with LM as the first and only site of metastases at presentation to those with LM and metastases in other organs; Group B.
– Selecting a patient group which had the best survival; Group C

Patients and methods

Between 1999 and 2015, 187 consecutive patients with breast cancer were treated for LM at Cancer Center in Warsaw, Poland. Observations on patients started at the time when LM was detected, and all data were collected prospectively into a database. In each case, treatment options were approved by a multidisciplinary team consisting of a neurologist, radiation oncologist (AN), medical oncologists and radiologists, where the chosen option was performed after patients had signed appropriate written consent forms. At every step of the treatment the decision regarding treatment continuation, modification, or cessation was made by the multidisciplinary team.

LM diagnosis was established by performing neurological examination, lumbar puncture and contrast enhanced magnetic resonance imaging (MRI) of the brain and of the symptomatic site of the spinal cord. In 181 patients, cancer cells were detected in cerebro-spinal fluid (CSF) thus confirming the diagnosis. Only in 6 patients was the diagnosis of LM confirmed by clinical/neurologic signs and symptoms and contrast-enhanced MRI, but without lumbar puncture.

Clinical characteristics of the entire 187 patient group (Group A) are presented in Table 1. Definitive treatment was administered to 178 patients (95%). Nine patients (5%) received only symptomatic treatment because of poor performance status. Whole brain radiation therapy (WBRT) and/or focal radiation therapy of spine was ordered in 105 (56%) patients with bulky disease or clinical/neurological symptoms. Of these, 65 received WBRT, in 15—only a part of the spinal cord was irradiated whilst in 24, both—WBRT and focal spinal irradiation was performed. In most of the patients with WBRT the total dose was 30 Gy delivered in 10 fractions; in 14 patients with KPS 30 and 40 was a dose given of 20 Gy in 5 fractions. The dose of focal irradiation to the spinal cord was 20 Gy/t in 5 fractions. Intra-CSF therapy was performed in 127 (68%) patients consisting of giving methotrexate or liposomal cytarabine. In patients treated with intrathecal methotrexate, a dose of 10 mg was given along with 4 mg of dexamethasone twice weekly for the first 2 weeks and then, after obtaining clinical improvement, once weekly until the total dose of 150 mg was achieved or until clinical and/or intra-CSF progression of the disease. Seven courses were administered (range 2–15 doses) on average. Liposomal cytarabine (DepoCyt, Mundipharma Inc.) as intrathecal treatment was introduced in 2008. The criteria for including intra-CSF treatment with liposomal cytarabine were the same as those used in the treatment with methotrexate. This was administered as 50 mg every 2 weeks for a total of five treatments and then once every 4 weeks until disease progression. Dexamethasone (4 mg twice daily for 5 days) was administered at the day of treatment and 4 days thereafter in order to minimize arachnoiditis as the main side-effect. A median of 5 liposomal cytarabine injections were given (range 1–7 doses). In 104 (56%) patients treated with systemic intravenous/oral chemotherapy, programs with vinorelbine, anthracyclines, capecitabine, platinum salts or taxanes were usually administered. Out of 33 patients with HER2-positive breast cancer, 7 were treated with trastuzumab and chemotherapy and 1 with lapatinib with chemotherapy.

Biologic subtypes of breast cancer were defined as being based on the expression of the estrogen receptor (ER), progesterone receptor (PR), and HER2 receptor. Patients were categorized into 3 biologic subsets based on immunohistochemistry (IHC): triple negative breast cancer (ER−, PR−, HER2−; TNBC), HER2 positive (HER2+, any ER/PR status) and luminal (ER+ or PR+, or both, and HER2−).

In 45 (24%) out of 187 patients, LM was the first and only site of dissemination at presentation, without metastases to other organs. Group B was a subgroup of Group A. Characteristics of Group B are presented in Table 1.

Statistical analysis

In the entire group of patients, the Cox proportional hazards model was used to identify factors associated with prolonged survival from LM. The following variables were included as potential predictors: age at diagnosis of LM (<53 vs. ≥ 53 years), Karnofsky performance status (KPS) (≤ 70 vs. >70), biological subtype of breast cancer (ER/PR+HER2− (luminal) vs. HER2+ vs. ER−, PR−, HER2− (triple-negative), LM as the first/only site of metastasis (yes vs. no), year of diagnosing LM (pre- and in 2005 vs. post-2005), systemic intravenous/oral treatment (yes vs. no), intrathecal treatment (yes vs. no) and radiation therapy (yes vs. no). All factors were analyzed as categorical variables (variable age was categorized into four equally numerous groups). The backward selection method was used for the modeling process with 0.1 and 0.05 thresholds adopted for respectively excluding and including variables.

The prognostic index was used to identify patients with the longest survival. The index was calculated based on the risk factors included in the final Cox prognostic model. In order to construct the prognostic index, the model coefficients were unified and then the index was normalized to a minimum value of one. Unification of coefficients was performed by assuming a mean value for coefficients whose values differ by less than the standard error.

Table 1 Characteristics of the whole group of patient with breast cancer and LM (Group A) and of subgroups of patients with LM as the first/only site of metastasis (Group B)

Feature	Entire group of patients with LM Group A	Patients with L as the first/only site of metastasis Group B
	Number of patients (%)	Number of patients (%)
Number of patients	187 (100)	45 (24)
Median age	49 years	48 years
Initial TNM stage of breast cancer		
I	11 (6)	2 (4)
II	68 (36)	16 (36)
III	76 (41)	24 (53)
IV	32 (17)	3 (7)
Histologic type		
Ductal carcinoma	104 (57)	27 (60)
Lobular carcinoma	48 (26)	10 (22)
Other types	8 (4)	2 (5)
Cancer cells without the assessment[a]	27 (14)	6 (13)
Biologic subtypes		
ER–PR–HER2−	64/172 (37)	17/41 (42)
HER2+ER/PR+	20/172 (12)	3/41 (7)
HER2+ER/PR−	13/172/(7)	3/41 (7)
ER/PR+HER2−	75/172 (44)	18/41 (44)
No data	15	4
KPS		
< 70	112 (60)	31 (69)
≥ 70	75 (40)	14 (31)
Leptomeninges as the first/ only site of metastases		
Yes	45 (24)	45 (100)
No	142 (76)	0
Localization of metastases[a]		
Lungs	57 (30)	N.A.
Liver	42 (22)	
Bones	79 (42)	
Brain (parenchyma)	68 (36)	
Local recurrence	55 (29)	
Other	34 (18)	
Intrathecal chemotherapy		
Yes	127 (68)	37 (82)
No	60 (32)	8 (18)
Type of intrathecal therapy		
Methotrexate	99 /127(78)	28/37 (76)
Depocyte	28/127 (22)	9/37 (24)
Radiotherapy of LM		
Yes	105 (56)	28 (62)
No	82 (44)	17 (38)
Type of radiotherapy		
Whole brain radiation therapy (WBRT) only	66 (63)	19 (68)
Focal spinal radiation therapy only	15 (14)	4 (14)
Both	24 (23)	5 (18)

Table 1 (continued)

Feature	Entire group of patients with LM Group A Number of patients (%)	Patients with L as the first/only site of metastasis Group B Number of patients (%)
Systemic therapy of LM		
Yes	104 (56)	26 (58)
No	83 (44)	18 (42)
Type of systemic therapy[b]		
Chemotherapy	90 (48)	26 (58)
Hormonal therapy	32 (17)	4 (9)
Targeted therapy	8 (4)	3 (7)
Intensity of treatment		
One method used (radiotherapy or systemic therapy or intrathecal therapy)	54 (29)	11 (24)
Two methods used	77 (41)	14 (31)
Three methods used	43 (23)	17 (38)
No treatment (symptomatic treatment only)	13 (7)	3 (7)

[a]Some patients had metastases at many locations

[b]Some patients received more than one type of systemic therapy

Survivals detected from the time of LM were estimated using the Kaplan–Meier method and were compared using the log-rank test. A probability of 0.05 was taken as being statistical significant.

Results

In Group A (whole group), median survival from the detection of LM was 17 weeks (4.2 months, range 0.1–47 months), the 6 month-survival was 34% and 1 year-survival was 15%.

In Group B (45 patients), median survival was the same as in Group A of 17 weeks (i.e. 4.2 months, range 0.3–37 months), the 6 month-survival was 30% and 1 year survival was 16%.

The results of the Cox proportional hazards model within the whole group of patients (Group A) are presented in Table 2. Six factors positively affecting survival were: KPS ≥ 70, older age (> 53 years), luminal biological subtype, systemic intravenous/oral treatment, intrathecal treatment and radiation therapy. Group B was included into the Cox model as being one of the variables (LM as the first and only site of metastasis). The analysis demonstrated that LM as the first/only site of metastasis and time of treatment (before and after 2005) were not associated with prolonged survival. The coefficients of the final Cox model are shown in Table 2.

Table 2 Cox multivariate analysis; factors affecting survival in 187 breast cancer patients with LM—final model

Feature	HR	p-value	95% CI
KPS ≥ 70 vs. < 70	0.613	0.008	0.427; 0.880
Age: < 53 years	1.633	0.003	0.180; 2.259
Biological type			
Luminal vs. others	0.640	0.007	0.461; 0.887
Systemic treatment	0.418	< 0.001	0.286; 0.611
Intrathecal treatment	0.683	0.029	0.486; 0.961
Radiotherapy	0.467	< 0.001	0.316; 0.689
LM as only site of metastases*		> 0.1**	
Treatment of LM before vs. after 2005		> 0.1**	

*(Group B), **Not significant

An adopted prognostic index was calculated based on the risk factors included in the final Cox prognostic model using the formula:

$$\text{INDEX} = 7 + (\text{Age} < 53) - (\text{KPS} \geqslant 70) - (\text{Luminal}) - (2 \times \text{RT}) - (\text{Intrathecal}) - (2 \times \text{Systemic})$$

The method for calculating the INDEX score is presented in Table 3. The formula shows that radiotherapy and systemic therapy are two factors counted double as 2 points.

Score 1 signifies the best prognosis, score 8—the worst. Median survivals of patients with scores 1, 2, 3, 4, 5, 6, 7 and 8 were respectively 9.6; 6.9; 3.9; 3.4; 1.6; 1; 1.4 and 0.3 months.

Table 3 The rules of calculation of the INDEX score

Feature	Abbreviation	1 point	0 (no point)
Age at LM diagnosis	Age < 53	< 53 years	≥ 53 years
Karnowsky performance status	KPS ≥ 70	≥ 70	< 70
Luminal biological type (ER/PR+HER2−)	Luminal	Yes	No
Radiotherapy	RT	Yes (2 points)	No
Intrathecal treatment	IT	Yes	No
Systemic treatment	SYST	Yes (2 points)	No

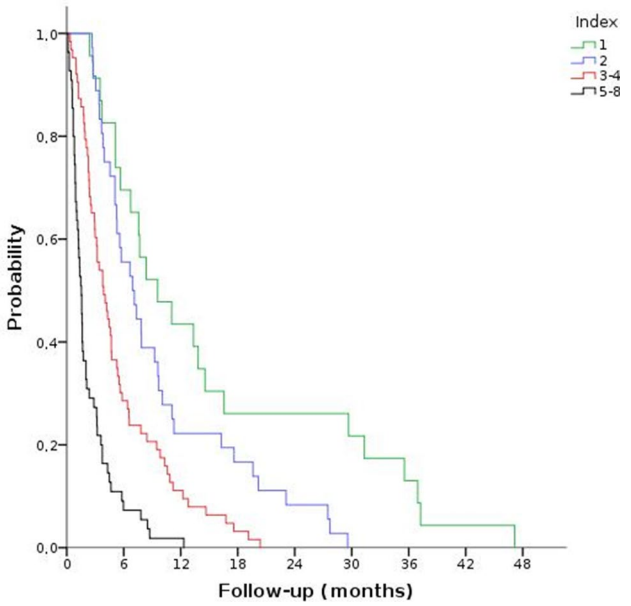

Fig. 1 The survival curves for the 4 prognostic groups based on prognostic index (median OS 9.6; 6.9, 3.9 and 1.5 months)

Based on the index, four prognostic groups with index values (score) of 1, 2, 3–4, 5–8 were respectively created. The survival curves for the prognostic groups are shown in Fig. 1 and the appropriate median values with 95% confidence intervals were respectively: 9.6 (4.3, 14.9), 6.9 (4.6, 9.3), 3.9 (2.7, 5.1), 1.5 (1.2, 1.9). The Cox prognostic index is presented in Fig. 1.

Twenty-four patients with an index level of 1 had the best prognosis (median OS 9.6 months) and this group was further analyzed (Group C). The breakdown of prognostic factors for the best prognostic group were as follow: systemic therapy in 100%, radiation therapy in 100%, KPS ≥ 70 in 88%, luminal subtype of breast cancer in 79%, intrathecal therapy in 75% and age ≥ 53 years in 58% of patients. The results are presented in Tables 4 and 5. Among these 24 patients two subgroups can be selected. The first consisted of 14 older women (53 years and more) treated with systemic therapy and radiation therapy. Most, but not all were in KPS ≥ 70, with luminal cancer and with intrathecal treatment. The second group consisted of 10 younger patients (< 53 years old) but with all the other favourable prognostic factors: KPS ≥ 70 and with luminal breast cancer, jointly together with radiotherapy treatment, intrathecal therapy and systemic therapy.

Discussion

In the presented study, we wanted to determine whether there has been any progress made in treating breast cancer LM compared to our previous studies from 2007 [4] 2013 [18] and 2015 [19]. Regrettably, only small, if any, improvements in outcomes were observed during these years. Our study from 2007, based on 67 patients with LM treated between 1999 and 2005, found that the median survival was 16 weeks and 1-year survival was only 7% [4]. In the present study, the median survival was almost the same (17 weeks), but the 1-year survival was a little

Table 4 The distribution of prognostic factors in the best prognosis group (Group C, 24 patients)

N (%) 24 (100)	Age < 53 yes = 1	KPS ≥ 70 yes = 1	Luminal subtype yes = 1	Radiotherapy[a] due to Neurological symptoms yes = 1	Intrathecal therapy due to result of cerebrospinal fluid test yes = 1	Systemic treatment[a] yes = 1
3 (12.5)	0	0	1	2	1	2
5 (20.8)	0	1	0	2	1	2
6 (25)	0	1	1	2	0	2
10 (41.7)	1	1	1	2	1	2

[a]In Cox index, radiotherapy and systemic treatment are two factors counted double as 2 points

Table 5 Distribution of prognostic factors in the best prognosis group (Group C, 24 patients)

Factor	Number of patients (%)
Systemic therapy	24/24 (100)
Radiation therapy	24/24 (100)
KPS ≥ 70	21/24 (88)
Luminal subtype of breast cancer	19/24 (79)
Intrathecal therapy	18/24 (75)
Age ≥ 53 years	14/24 (58)

better at 15%. However, the Cox multivariate analysis demonstrated that treatment outcomes before and after 31 December 2005 were the same i.e. survival of both groups was not significantly different ($p > 0.1$). We thus conclude that there have been no significant improvements in treatment since 1999.

Based on the literature, the median survival from LM observed in the present study was superior to that reported by some authors [3, 5, 20, 21] (7–14 weeks), it was comparable with some studies [1, 6–8, 22] (16–17 weeks) but inferior to the others [2, 23] (4.9–5.8 months). A 15% 1-year survival rate demonstrated in our study was higher to that reported by some authors [1, 3, 8] (7.8–11%), it was similar to some other studies [2, 5] (15%) but lower than in others [6, 7, 22] (20–25%).

The Cox multivariate analysis demonstrated 6 factors associated with prolonged survival. The role of performance status has been confirmed by many studies and its role in breast cancer patients with central nervous system involvement has also been established [3, 6, 7, 9, 19, 23–27]. Contrary to our previous studies [4, 18, 19], this present one, with more patient subjects, confirms a beneficial effect of luminal breast cancer on survival. These results were also comparable to those reported by Lee et al. [28] and Jo et al. [8].

Our study shows that patients aged 53 years or older have a chance to live longer. It seems that older breast cancer patients had luminal breast cancer which has the longest natural disease course, while young patients most often had the most deleterious triple-negative form of breast cancer.

The role of treatment methods in patients with breast cancer LM has been discussed by us in previous publications. In all, we confirmed the role of systemic therapy [4, 18, 19]. Contrary to our previous studies, we have now shown the beneficial role of each of the treatment methods (i.e. systemic therapy, intrathecal therapy and radiation therapy). Nevertheless, statistical analysis shows that the Cox model coefficients were different: systemic intravenous/oral therapy and radiation therapy were a twice times stronger factor associated with prolonging survival than was intrathecal therapy.

Based on the Cox analysis, a prognostic index was created and 4 prognostic groups were established. All patients belonging to the group with the best prognosis were treated with systemic therapy and radiation therapy. In most cases (88%), they were in a good performance status and about 80% had luminal breast cancer. More than half were also treated with intrathecal drugs. What is important in the younger patients, is that the likelihood of a long survival was high only on the condition of having a good performance status, luminal breast cancer and joint treatment with systemic therapy, radiation therapy and intrathecal therapy. In older patients all these conditions were not necessary, but they all received systemic therapy and radiation therapy.

The analysis of the best prognostic group confirms the highly beneficial role of intensive systemic therapy and radiotherapy. This can be explained as that systemic therapy consists of cytotoxic/ endocrine drugs precisely targeted to breast cancer cells and for this reason they are more efficacious than drugs usually ordered in intrathecal treatment. Patients with good performance status whenever LM is found should be treated intensively. If intrathecal treatment is ordered, it should not be used for a long time without adding other treatment methods. An early switch from intrathecal to systemic treatment has given the chance of prolonging survival. Patients with luminal breast cancer had the best survival because it has the best natural course among biological subtypes of breast cancer, and also of the many possibilities for endocrine and cytotoxic treatment.

In the literature, some of aforementioned prognostic factors, but not all, have been found to be significant. A study by Le Rhun et al. [24] suggest that patients with prolonged survival appeared to be those with good performance status, younger age, with ER positive breast cancer, with LM as the site of first metastasis, with minimal radiological abnormalities, with minimal signs and symptoms (without encephalopathy) and those who responded to combined modality therapy. A study by Jo et al. [8] confirm that ER positive breast cancer, good performance status, controlled extracranial disease and systemic treatment are factors associated with prolonged survival. Other studies confirm multiple-fixed neurological deficits [29], encephalopathy [20, 24], bulky disease [29], abnormalities in cerebrospinal flow (hydrocephalus in MRI) [29] and no response to systemic therapy [29] as being factors adversely associated with outcome.

We hope that the prognostic index presented in this study could enable the physician to assess a given patient's prognosis whenever LM is detected.

LM as the only site of metastasis

One of the aims of our study was to compare survival of patients in whom LM was detected as the first and only site

of metastasis and those with LM associated to distant metastasis in other sites. The outcomes of our analysis was disappointing. Unexpectedly, median survivals of both groups were similar and the Cox multivariate analysis of the entire 187 patient group revealed that LM as the first/only site of metastasis was not associated with prolonged survival. This result suggests that metastasis to the subarachnoid space is the most deleterious metastatic disease leading to death in the short term regardless of metastases in other organs.

There is limited data in the literature showing the frequency of LM as being the first presentation of relapse following breast cancer treatment. Only a few studies mention that patients with LM have this as the only site of metastases at presentation and all were considered in the first review article concerning this topic [29]. In these studies 8.6, 13.2 and 16.3% of patients were free of metastases in other locations at the time of presentation of LM [20, 21, 23]. In our study, 24% of patients were free of local recurrence or distant metastases at presentation of LM. This is more than the literature reports and almost identical to that previously published by ourselves based on a study on 118 patients [18]. The explanation of such patient numbers could be that in our clinic, in every case when breast cancer LM is newly diagnosed, restaging was performed in order to detect metastases in other organs. The second reason is that the oncology team providing healthcare to patients with breast cancer LM is very experienced in suspected cases and in the early detection of LM.

Strengths and limitations of the study

Strengths

Our study was performed on a relatively large group of 187 consecutive breast cancer patients with LM. Patients were treated at one institution, by a multidisciplinary team comprising a radiation oncologist (A.N.), neurologist and a small group of medical oncologists for all cases.

Limitations

This concerns the retrospective nature of the study.

Conclusions

1. For the entire LM patient group factors associated with prolonged survival were: older age, high KPS, luminal subtype of breast cancer, systemic treatment, radiotherapy and intrathecal treatment.
2. Based on these factors, 4 prognostic groups were found with the most favorable group being LM patients with median survival of 9.6 months.
3. The median survival of patients with LM as first /only site of metastases was similar to those with metastases in other organs.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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