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Original article

Implication of breast cancer phenotype for patients with leptomeningeal carcinomatosis

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ABSTRACT

Background: We aimed to study the implications of breast cancer (BC) subtypes for the development and prognosis of leptomeningeal carcinomatosis (LC).
Patients and methods: Data from the breast cancer patients diagnosed with LC between 2005 and 2010 were retrieved. Patients were classified in luminal A, B, HER2 positive and triple negative (TN) and their BC diagnosis, treatment, and outcome were analyzed according to each subtype. Pearson's chi-square and Fisher's exact test were used for categorical variables. Survival analyses were performed by Kaplan–Meier method and compared with the log-rank test.
Results: A total of 38 BC patients were identified, with a median age of 54.8 years (range 36–79). The proportion of luminal A, B, HER2 positive and TN was 18.4%, 31.6%, 26.3% and 23.7%, respectively. LC was the first evidence of metastatic disease in 5 BC patients. Twenty patients received the systemic chemotherapy, with 16 (80%) whole brain radiotherapy (WBRT). Nine patients received only WBRT. TN patients had the shorter interval between metastatic breast cancer diagnosis and the development of LC. Median survival after the diagnosis of LC (OSLC) was 2.6 months (range 1.2–6.4), and did not differ across breast cancer subtypes. In univariate analysis, performance status (ECOG = 0–2) and chemotherapy were prognostic for OSLC, but only the treatment stood as an independent prognostic factor in multivariate analysis.
Conclusions: Breast cancer subtype influences the timing of LC appearance, but not OSLC. Patients with LC from breast cancer should be offered systemic treatment, as it appears to associate with the improved outcome. New therapeutic strategy, including, targeted and intrathecal therapy are deserved for BC patients with LC.

Introduction

Leptomeningeal carcinomatosis (LC), the seeding of malignant cells to the leptomeninges and can occur either by hematogenous spread, direct extension or infiltration from vertebral metastases via Batson's plexus.[1]

Breast cancer is the solid tumor most commonly associated with LC. In autopsy series, its incidence reaches up to 16%,[2,3] but it becomes clinically evident in only about 5% of patients with metastatic breast cancer (MBC).[4,5] Although patients with LC from breast cancer fare better than the patients with LC from other solid tumors, their overall prognosis is poor: if left untreated, median overall survival ranges from 4 to 6 weeks,[6] reaching 3–4 months if systemic and/or intrathecal chemotherapy are given.[4,7]

Breast cancer subtypes are associated with the distinct patterns of metastatic spread, with notable differences in survival after relapse.[8] In several retrospective series evaluating LC from breast cancer, about two thirds of the patients were found to have hormonal receptor positive disease and around 20% to have triple negative (TN) tumors, while the frequency of HER2 disease varies across the studies.[4,7,9–12] However the incidence of LC and the prognostic implications according to the major four breast cancer subtypes –luminal A, luminal B, HER2 positive (hereinafter HER2+) and TN- is currently unknown.

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The aim of our study was therefore to characterize the implications of the different breast cancer subtypes for the development and prognosis of LC.

Patients and methods

This study was based on the data recorded at Vall d'Hebron University Hospital in Barcelona. The study period was 2005–2010. For the present analysis, we included all breast cancer patients diagnosed of LC by evocative contrast-enhanced magnetic resonance imaging (MRI) and/or by a lumbar puncture retrieving carcinoma cells in cerebro-spinal fluid (CSF) in the presence of suggestive symptoms. Diagnostic findings in brain MRI considered diagnostic of LC included diffuse leptomeningeal enhancement, meningeal thickening, multiple nodular deposits in the subarachnoid space, cerebellar or cortical surface and tumor masses, with or without hydrocephalus. Lumbar puncture was considered as a diagnostic of LC when retrieving the carcinoma cells in cerebrospinal fluid (CSF).

Medical charts of all patients were reviewed to confirm the accuracy of the variables recorded in the database. Patients' demographics, tumor characteristics (including pathological features and stage at diagnosis), characteristics of the metastatic disease (date of recurrence, number and localization of metastatic sites, treatment for metastatic disease), date of LC diagnosis, symptoms associated with LC, type of treatment to LC and vital status, including the date of death were recorded for each patient.

Patients were classified in 4 different groups according to the primary tumor's pathological characteristics and were classified in: (i) luminal A: Estrogen Receptor (ER) positive *and/or* Progesterone Receptor (PR) positive *and* Human Epidermal growth factor Receptor 2 (HER2) negative *and* Ki67 $< 14\%$; (ii) luminal B tumors: ER positive/HER2 negative, and grade 3 *or* Ki67 $\geq 14\%$ *or* PR negative; (iii) HER2+: HER2 positive (according to ACCP guidelines[13]) independently of ER/PR; (iv) TN: HER2 negative and ER and PR immunoperoxidase staining of tumor cell nuclei less than 5%.

Time to the development of LC (TTLC) was calculated from the date of breast cancer diagnosis until the date of LC diagnosis. Time to the development of LC after the diagnosis of MBC (TTLCMBC) was calculated from the date of MBC diagnosis (first distant recurrence after completion of loco-regional therapy) until the date of LC diagnosis. Overall survival (OS) was calculated from the date of diagnosis until the date of death. Overall survival from LC diagnosis (OSLC) was calculated from the date of LC diagnosis until the date of death. Patients who were alive at cutoff date were censored for the purposes of the OS and OSLC analysis.

Statistical analysis was done using SPSS for Windows v.15.0. Pearson's chi-square and Fisher's exact test were used for categorical variables to compare the patients' characteristics among the four subtypes of breast cancer. A Kruskal–Wallis test was performed to compare the median intervals among these four subgroups. Survival analyses were performed using the Kaplan–Meier method and compared by the log-rank test.

Results

Patients and tumor characteristics

The study included a total of 38 breast cancer patients diagnosed with LC according to the neuroimaging findings (37 patients) and/or lumbar puncture (9 performed, 6 patients diagnosed with). The median age was 54.8 years (range 35.9–79). Primary tumor's pathological features are shown in Table 1. Although Ki67 was unknown in half of the patients, date on grade and PR status allowed and accurate classification in all the population. Subtype classification was as follows: -luminal A: 7 (18.4%) patients: All with ER/PR positive, HER2 negative and Ki67 $< 14\%$. -Luminal B: 12 (31.6%): All with ER positive/HER2 negative, and grade 3 (8 patients) or Ki67 $\geq 14\%$ (4 patients) or PR negative (10 patients). -HER2+ (independently of ER/PR): 10 (26.3%) and -TN: 9 (23.7%) (Table 1).

Table 1
General clinical features.

	N (%)
Age (years)	
Median (range)	54.8 (35.9–79.0)
ER	
Positive	23 (60.5)
Negative	15 (39.5)
PR	
Positive	13 (34.2)
Negative	25 (65.8)
HER2	
Positive	10 (26.3)
Negative	28 (73.7)
Grade	
I	0 (0)
II	16 (42.1)
III	20 (52.6)
Unknown	2 (5.3)
Ki67	
$<14\%$	7 (18.4)
$\geq 14\%$	12 (31.6)
Unknown	19 (50)
Phenotype classification	
Luminal A	7 (18.4)
Luminal B	12 (31.6)
HER2 positive	10 (26.3)
TNBC	9 (23.7)

Table 2 shows the patients' characteristics according to breast cancer subtype. Thirty-three patients had other sites of metastases at the time of LC diagnosis. Bone metastases were more frequent in luminal tumors, whilst solid brain metastases were more frequent in HER2+ tumors. Two HER2+ patients and three TN patients had LC as the first evidence of metastatic disease. A total of 9 patients had received more than 3 lines of systemic chemotherapy before the diagnosis of LC, most of them in the HER2+ group (Table 2).

Headache was the most frequent symptom of LC, followed by nausea/vomiting, cerebellar signs and peripheral nerve deficiency (Table 3).

Treatment for leptomeningeal carcinomatosis

Twenty patients (52.6%) received systemic chemotherapy (CT), with 16 (80%) or without 4 (20%) whole brain radiotherapy (WBRT). WBRT with no CT was performed in 9 cases. Systemic regimens according to BC subtype were: - Anastrozole (1 patient luminal A) - Liposomal doxorubicin and cyclophosphamide (1 luminal A, 1 luminal B and 3 TN) - Liposomal doxorubicin and paclitaxel (1 Luminal B) - Paclitaxel (1 Luminal B) - Capecitabine (1 luminal A, 2 luminal B) - Capecitabine and lapatinib (1 HER2 case) - Combinations with trastuzumab in 9 HER2+ group: With paclitaxel: 5, docetaxel: 2 and vinorelbine: 2. - Combinations with bevacizumab: With paclitaxel (1 luminal B and 2 TN) and irinotecan (1 Luminal B). Of the 5 patients without extracranial disease, two received systemic chemotherapy.

Survival

Time to the development of LC significantly differed across the breast cancer subtypes, being longer in luminal A and shorter in TN

Table 2
Pathological and clinical features according to breast cancer phenotype.

$n = 38$	Phenotype classification n (%)				P
	Luminal A $n = 7$	Luminal B $n = 12$	HER2+ $n = 10$	TNBC $n = 9$	
Age at breast cancer dx median (range)	59.7 (38.6–72.8)	50.3 (32.9–63.1)	43.4 (30.3–70.1)	48.1 (33.6–77.6)	
Age (LC dx) median (range)	61.9(47.8–76.1)	57.5 (36.7–74.2)	51.0 (36.6–70.6)	58.9 (35.9–79.0)	
Menopausal status					
Premenopausal	1 (14.3)	3 (25)	6 (60)	4 (44.4)	0.188
Postmenopausal	6 (85.7)	9 (75)	4 (40)	5 (55.6)	
Histology					
Ductal carcinoma	6 (85.7)	11 (91.7)	10 (100)	78 (88.9)	0.466
Lobular carcinoma	1 (14.3)	1 (8.3)	0 (0)	0 (0)	
Other	0 (0)	0 (0)	0 (0)	1 (11.1)	
Stage at initial diagnosis					
I	1 (14.3)	0 (0)	1 (10)	1 (11.1)	0.389
II	3 (42.9)	6 (50)	1 (10)	4 (44.4)	
III	1 (14.3)	5 (41.7)	5 (50)	4 (44.4)	
IV	2 (28.6)	1 (8.3)	3 (30)	0 (0)	
ECOG					
0	0 (0)	0 (0)	0 (0)	0 (0)	0.104
1	3 (42.9)	3 (25)	3 (30)	3(33.3)	
2	1 (14.3)	7 (58.3)	7 (70)	6 (66.7)	
3	3 (42.9)	2 (16.7)	0 (0)	0 (0)	
4	0 (0)	0 (0)	0 (0)	0 (0)	
Number of metastatic sites (prior to LC diagnosis)					
0	0 (0)	0 (0)	2 (20)	3 (33.3)	0.090
<3	5 (71.4)	11 (91.7)	5 (50)	4 (44.4)	
≥3	2 (28.6)	1 (8.3)	3 (30)	2 (22.2)	
Metastatic sites					
Brain	2 (28.6)	1 (8.3)	6 (60)	3 (33.3)	0.079
Bone	7 (100)	11 (91.7)	6 (60)	4 (44.4)	0.024
Liver	4 (57.1)	3 (25)	6 (60)	2 (22.2)	0.183
Lung	4 (57.1)	3 (25)	2 (20)	4 (44.4)	0.333
Other	2 (28.6)	4 (33.3)	4 (40)	3 (33.3)	0.968
Previous chemotherapy lines					
≤3	5 (71.4)	11 (91.7)	5 (50)	8 (88.9)	0.099
>3	2 (28.6)	1 (8.3)	5 (50)	1 (11.1)	

patients, 96.2 months (range: 63–129) and 22.9 months (range: 11–35), respectively ($p = 0.035$) (Table 4). Median time to the development of LC after the diagnosis of metastatic disease also tended to differ across breast cancer subtypes though not in a significant way ($p = 0.055$) with TNBC patients presenting the shorter interval between MBC diagnosis and the onset of LC.

Table 3
Leptomeningeal carcinomatosis features.

	N (%)
Symptoms	
Headache	27 (71.1)
Nausea/vomiting	17 (44.7)
Cranial nerve deficiency	8 (21.1)
Peripheral nerve deficiency	10 (26.3)
Cerebellar signs	17 (44.7)
Seizures	6 (15.8)
Motor aphasia and dysarthria.	7 (18.4)
Methods of diagnosis	
CSF cytology	6 (15.8)
MRI	37 (97.4)
Treatment	
Chemotherapy ± Radiotherapy	20 (52.6)
Luminal A	3 (42.9)
Luminal B	7 (58.3)
HER2+	5 (50.0)
TNBC	5 (55.6)
Radiotherapy	9 (23.7)
Luminal A	3 (42.9)
Luminal B	3 (25)
HER2+	1 (10.0)
TNBC	2 (22.2)
Best supportive care	9 (23.7)
Luminal A	1 (14.3)
Luminal B	2 (16.7)
HER2+	4 (40)
TNBC	2 (22.2)

As of the time of writing, 34 patients (89%) had died. Median OSLC was not statistically different across breast cancer subtypes ($p = 0.296$), ranging from 1.3 months in luminal B tumors to 3.1 months in TN tumors (Table 4). Patients who had the first evidence of breast cancer recurrence in the form of LC tended to live shorter (OSLC) when compared to the group who had other sites of disease: 1.5 vs. 2.8 months, $p = 0.173$.

Table 5 depicts the prognostic factors for OSLC. In univariate analysis, ECOG performance status 0–2 ($p = 0.003$) and treatment with systemic chemotherapy ($p < 0.00001$) were associated with a better prognosis ($p = 0.482$ for interaction), but no differences were found according to breast cancer subtype, previous number of chemotherapy lines, ER status, number of metastatic sites or age. In multivariate analysis, however, only type of treatment for LC stood as an independent prognostic factors for OSLC ($p = 0.018$).

Discussion

The discovery that breast cancer is not a homogeneous disease but it is rather composed of several biological intrinsic subtypes has been a major breakthrough in the comprehension and in the consequent management of breast cancer patients. To our knowledge, this is the first attempt to study LC from breast cancer according to the four major different biological subtypes, with the specific purpose of evaluating their different prevalence and prognosis.

In the study, we found a high proportion of luminal B and HER2+ tumors (31.6% and 26.3%, respectively), followed by TN tumors (23.7%), while luminal A tumors were less likely to

Table 4
Time to disease and survival data, according to breast cancer phenotype.

Time (months)	Luminal A	Luminal B	HER2+	TNBC	*p*
TTLC median (95% CI)	96.2 (63.3–129.3)	66.3 (33.2–97.4)	43.0 (37.1–48.9)	22.9 (11.1–34.7)	0.035
TTLCMB median (95% CI)	26.0 (4.0–48.0)	23.0 (13.7–32.3)	19.7 (13.2–26.1)	4.9 (0.0–12.9)	0.055
OS median (95% CI)	112.0 (83.5–140.5)	66.4 (31.8–101.1)	59.6 (36.7–82.5)	26.6 (10.0–43.2)	0.024
OSLC median (95% CI)	2.7 (1.2–4.1)	1.3 (0.0–3.2)	3.0 (2.6–3.4)	3.1 (0.0–6.4)	0.296

TTLC: Time to leptomeningeal carcinomatosis. TTLCMB: Time to leptomeningeal carcinomatosis from diagnosis of metastatic breast cancer. OS: Overall Survival. OSLC: Overall survival from leptomeningeal carcinomatosis diagnosis.

metastasize to the leptomeninges (18.4%). No work has so far reported the proportion of luminal B tumors in a population of LC from breast cancer, and our study raises the possibility that this subtype may metastasize more often to the leptomeninges than the less aggressive hormonal receptor positive luminal A tumors. Although direct comparison with other works is difficult, our date are generally similar to what has been so far reported in HER2+ and TN tumors. At the 2011 Annual ASCO Meeting, Niwinska and colleagues analyzed a series of 118 patients with LC from breast cancer and found an incidence of HER2+, TN and luminal A tumors of 22%, 40.5% and 37.5%, respectively.[14] Of note, the criteria for luminal A tumors in this work were: ER/PR positive and HER2-negative, did not include Ki67 status nor histological grade, which impairs and accurate subtype classification. Gauthier et al., in turn, reviewed 91 patients with LC from breast cancer and found a proportion of HER2+ (3 + or FISH), TN tumors and ER/PR positive of 10%, 21% and 74% respectively.[7] In another work, De Azevedo and colleagues reported 15% of HER2+ tumors, 30% of TN tumors and 52% ER/PR positive in a cohort of 60 patients with LC from breast cancer.[11] In both studies no include classification of luminal group. A similar proportion of TN tumors (25%) was found by Kotecki and colleagues,[15] but these authors found a higher percentage of HER2+ tumors (26%), a number more in line with our own study.

The results of Gadolinium-enhanced MRI and analysis of CSF are complementary, and the use of both increases diagnostic accuracy in LC.[16] The study included a total of 38 breast cancer patients diagnosed of LC according to the neuroimaging findings (37 patients) and/or lumbar puncture (6 patients). In our hospital MRI is generally performed before lumbar puncture to avoid iatrogenic meningeal enhancement. Therefore, most of the patients were first unequivocally diagnosed by MRI and were spared of lumbar puncture thereafter. Although MRI probably is more sensitive (76–87%) than a single CSF specimen for cytology, it is less specific because false positive cytologies are rare. A total of 9 patients received LP, that resulted diagnostic in 6 out of these 9 cases (67%), according to the data from literature,[16–18] and the survival rates reported are consistent with the results expected with LC.

Table 5
Prognostic factors for OSLC.

	Median (95% CI) (months)	*P*
a)Univariate analysis		
Breast cancer phenotype		
Luminal A	2.7 (1.2–4.1)	0.296
Luminal B	1.3 (0.0–3.2)	
HER2 positive	3.0 (2.6–3.4)	
TNBC	3.1 (0.0–6.4)	
ECOG		
0–2	2.9 (1.8–4.0)	0.003
3–4	1.0 (0.6–1.3)	
Previous chemotherapy lines		
≤3	2.7 (1.8–3.6)	0.755
>3	2.1 (1.3–2.9)	
ER status		
Positive	2.2 (1.3–3.1)	0.486
Negative	3.0 (1.7–4.4)	
Number of metastatic sites		
None	1.5 (0.7–2.4)	0.173
≥1	2.8 (1.9–3.7)	
Age		
<Median age	2.9 (1.6–4.2)	0.453
>Median age	2.2 (1.0–3.3)	
LC treatment		
CT ± RT	5.9 (2.1–9.7)	<0.00001
RT	1.2 (0.9–1.6)	
BSC	1.4 (1.2–1.7)	
b) Multivariate analysis		
ECOG	2.4 (0.8–7.1)	0.126
LC treatment	1.7 (1.1–2.6)	0.018

According to our data, brain metastases were present in 31.6% of the overall population and were more frequent in HER2+ tumors, as reported by others.[19,20] In the past, several works have shown that HER2+ tumors relapse more often in brain, either in the presence or not of adjuvant trastuzumab.[21,22] From our own and other's data, it seems that this HER2+ tumors' CNS tropism also occurs in the form of LC. This is an important finding to take into consideration. Trastuzumab has prolonged the natural history of HER2+ metastatic breast cancer, but its high molecular weight precludes it from crossing the intact blood–brain and CSF-blood barriers,[23] making the CNS a sanctuary for HER2+ metastatic disease. Innovative ways of achieving therapeutic levels of trastuzumab in CSF should be studied in the future, in order to treat HER2+ CNS disease. One of these approaches is the direct application of trastuzumab via an intrathecal route, as it has already been successfully done and reported.[24–26]

In 5 patients (3 with TN and 2 with HER2+ tumors), LC was the first and only site of metastatic disease, and although not reaching statistical significance, these patients fared worse when compared to the patients with other sites of disease. This could suggest that there are some tumors with an early tropism to the central nervous system, and that this feature confers an intrinsic poor prognosis. This interesting finding may support additional studies to identify suitable populations to primary prophylaxis strategies.

A striking data is that the timing of LC appearance depends on breast cancer subtype, being an early event in the natural history of TN breast cancer. To our knowledge, no other work had so far established this correlation. Another interesting finding is that this also occurs within the natural history of metastatic TN breast cancer. This raises the question whether LC should be routinely screened in a patient with TN presenting with metastatic disease.

Overall, the prognosis of these patients is poor, with a median survival of 2.6 months –in line with other published studies[4,7,10,11,14,15,27] – and no differences in survival according to the different breast cancer subtypes could be demonstrated.

All patients treated with chemotherapy in our series received systemic treatment. Recently, the use of intrathecal chemotherapy has been reported to associate with improved survival in with patients LC from solid tumors. As there is no direct comparison between intrathecal and systemic treatment or best supportive care, a clinical trial is urgently warranted to provide unequivocal evidence of a survival advantage of treatment over best supportive care and on the best way to provide chemotherapy.[28–30]

Breast cancer subtype didn't impact in the decision of the type of treatment. Of note, 4 patients in the HER2+ group continued to receive systemic trastuzumab after the diagnosis of LC. It is possible that maintaining systemic trastuzumab in patients with LC from HER2+ breast cancer improves their prognosis, similarly to what happens with brain metastases from HER2+ tumors,[31–34] but the small numbers in our series preclude a definitive conclusion.

We found that ECOG performance status and treatment with systemic CT for LC are prognostic for survival, but not number of CT regimens prior of LC diagnosis, ER status, number of metastatic sites or age, as described in other works.[4,7,10–12,35] However, only the treatment with systemic chemotherapy stood as a prognostic factor in the multivariate model, clearly pointing to the fact that these patients do benefit from continuing systemic treatment despite of being diagnosed with LC. We recommend that, if medically fit, patients with LC from breast cancer should be treated as any other metastatic breast cancer patient with a similar disease burden and no LC.

In conclusion, this work provides a new data on the distribution of breast cancer subtypes in patients with LC from breast cancer, especially with respect to luminal B tumors, and suggests that HER2+ breast cancer's particular tropism to the CNS also occurs in the form of LC. The timing of LC appearance depends on breast cancer subtype, but breast cancer subtype per se doesn't influence prognosis once LC is diagnosed. The only factor associated with improved survival was treatment with CT, which stresses the fact that the diagnosis of LC must not preclude the maintenance of adequate systemic treatment in breast cancer patients. More efficient treatment strategies are needed, desirably taking the account of specific targeted and intrathecal therapy to the different breast cancer subtypes, to improve the prognosis of these patients.

Conflict of interest statement

The authors have declared no conflict of interests.

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