Clinical characteristics and prognostic factors in patients with breast cancer and leptomeningeal metastases: a subanalysis of the German Brain metastases in Breast Cancer registry (BMBC)

#767

Elena Laakmann[1], Elisa Agostinetto[2], Mette van Ramshorst[3], Francesco Schettini[4], Mario Fontes Sousa[5], Leonor Matos[6], Amanda Fitzpatrick[7], Marta Vaz Batista[8], Fanny Le Du[9], Kerstin Riecke[1], Marcus Schmidt[10], Tanja Neunhöffer[11], Rudolf Weide[12], Tjoung-Won Park-Simon[13], Carsten Denkert[14], Isabell Witzel[15], Julia Rey[16], Sibylle Loibl[16], Volkmar Müller[1]

[1]University Medical Center Hamburg-Eppendorf, Germany [2]Institut Jules Bordet, Brussel, [3]Netherlands Cancer Institute, Amsterdam, the Netherlands, [4]Department of Medical Oncology, Hospital Clinic of Barcelona and Translational Genomics and Targeted Therapies in Solid Tumors Group, IDIBAPS, Barcelona, Spain, [5]CUF - Hospitais e Clínicas, Lisboa, Portugal, [6]Breast Cancer Unit, Champalimaud Foundation, Lisboa, Portugal, [7]Kings College London, UK, [8]Hospital Professor Doutor Fernando Fonseca EPE, Amadora, Portugal, [9]Centre Eugène Marquis, France, [10]University Medical Center Mainz, Germany, [11]Frauenärzte am Dom, Mainz; HELIOS Dr. Horst Schmidt Kliniken Wiesbaden, [12]Institut für Versorgungsforschung in der Onkologie, Koblenz, Germany, [13]Hannover Medical School, Abteilung Gynäkologie, Germany [14]University of Marburg, Institute of Pathology, Marburg, Germany [15]University Hospital, Zürich, Switzerland, [16]German Breast Group, Neu-Isenburg, Germany

Background

- Leptomeningeal metastases (LM) in patients with breast cancer (BC) is rare and associated with poor prognosis.
- About 5% of patients with BC develop LM during the disease[1].
- Specific factors associated with prognosis of patients with LM have not been characterized in a large patient cohort.
- **The aim of this evaluation was to characterize the cohort of patients with brain metastases (BM) and LM and to perform a survival analysis for LM along with factors associated with prognosis for this cohort of patients.**

Patients and Methods

Clinical data of 3857 patients from the German Brain Metastases in Breast Cancer Registry (BMBC) was available for the analysis. Patients registered before 07.01.2023 were considered.

Objectives:

1. To characterize descriptively the patient cohort with LM, and to compare the clinical characteristics of this cohort with patients without LM.
2. Estimation and comparison of the overall survival (OS) and progression-free survival (PFS) between patients with vs. without LM.
3. Characterization of OS and PFS in patients with LM regarding the clinical variables.

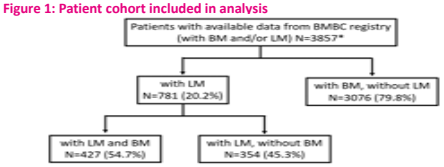
Baseline characteristics were assessed by Wilcoxon test, Fisher's exact test resp. Pearson χ^2-test between patients with vs without LM. OS was defined as the time from first diagnosis of central nervous system (CNS) metastases to death from any cause. PFS was defined as the time from first diagnosis of CNS metastases to progression in CNS, extracranial metastases, or death.

Differences in OS and PFS were shown by Kaplan-Meier curves and tested by the log-rank test. Univariate and multivariate Cox proportional hazards models were performed to report hazard ratios with the corresponding 95% confidence intervals (CI) and to adjust for the covariates.

All reported p-values were two-sided, the significance level was set to 0.05. The data was analyzed using SAS® (Statistical Analysis Software) version 9.4 with SAS Enterprise Guide Version 8.3 on Microsoft Windows 10 Enterprise.

Results

Figure 1: Patient cohort included in analysis



*in comparison to the abstract one patient excluded from analysis due to non-existence of BM or LM after data cleaning.

Table 1. Baseline characteristics

Parameter at diagnosis	Category	Patients without LM N=3076 (%)	Patients with LM N=781 (%)	p-value
Age at first BC diagnosis, years	Median (range)	52.0 (10.0-98.0)	51.0 (24.0-85.0)	0.595
Age at first BM/LM diagnosis, years	Median (range)	57.0 (13.0-99.0)	58.0 (25.0-86.0)	0.355
ECOG	ECOG 0-1	882 (62.8)	189 (51.1)	<0.001
	ECOG 2-4	522 (37.2)	181 (48.9)	
Biological subtype*	HR+/HER2+	818 (29.2)	154 (21.8)	<0.001
	HR-/HER2+	464 (16.5)	80 (11.3)	
	Luminal A/B like	873 (31.1)	325 (46.1)	
	TNBC	650 (23.2)	146 (20.7)	
pT	pT0	7 (0.4)	4 (0.8)	0.463
	pTis	21 (1.2)	7 (1.5)	
	pT1	554 (30.4)	133 (27.7)	
	pT2	867 (47.6)	234 (48.8)	
	pT3	168 (9.2)	40 (8.3)	
	pT4a-d	203 (11.1)	62 (12.9)	
ypT after NACT	ypT0	172 (17.9)	41 (17.7)	0.197
	ypTis	61 (6.3)	7 (3.0)	
	ypT1	285 (29.6)	73 (31.6)	
	ypT2	271 (28.2)	62 (26.8)	
	ypT3	88 (9.1)	29 (12.6)	
	ypT4a-d	85 (8.9)	19 (8.2)	
Tumor grading	G1	58 (2.1)	10 (1.4)	0.001
	G2	1095 (39.9)	334 (47.3)	
	G3	1589 (58.0)	362 (51.3)	
Histological tumor type	Ductal or ductal-lobular invasive	2303 (75.7)	516 (66.6)	<0.001
	Lobular invasive	199 (6.5)	102 (13.2)	
	Other	541 (17.8)	157 (20.3)	
Number of BM	1	888 (30.5)	219 (36.7)	0.011
	2-3	785 (26.9)	145 (24.3)	
	≥ 4	1241 (42.6)	232 (38.9)	
Neurological symptoms**	no	715 (23.2)	138 (17.7)	<0.001
	yes	2361 (76.8)	643 (82.3)	
ECM**	no	610 (19.9)	140 (17.9)	0.244
	yes	2462 (80.1)	641 (82.1)	
ECM in further course of disease	No	2952 (96.1)	764 (97.8)	0.017
	Yes	120 (3.9)	17 (2.2)	

* If HER2-Status at diagnosis of BC was unknown, but Anti-HER2-targeted therapy was given, the subtype was set to HR+/HER2+ resp. HR-/HER2+ (if information about HR-status was given, too); **at diagnosis of BM

Table 2. Distribution of BC treatment after the diagnosis of BM

Parameter	Category	Patients without LM N=3076 N(%)	Patients with LM N=781 N(%)	Overall N=3857 N(%)	p-value
Chemotherapy	no	1996 (64.9)	501 (64.1)	2497 (64.7)	0.706
	yes	1080 (35.1)	280 (35.9)	1360 (35.3)	
Hormone therapy*	no	2657 (86.4)	668 (85.5)	3325 (86.2)	0.561
	yes	419 (13.6)	113 (14.5)	532 (13.8)	
HER2-targeted therapy*	no	2485 (80.8)	697 (89.2)	3182 (82.5)	<0.001
	yes	591 (19.2)	84 (10.8)	675 (17.5)	

*these parameters were set to 'no' in HR-negative patients resp. HER2-negative patients

Figure 1: Kaplan-Meier curves for the time from diagnosis of BM/LM to death between patients with vs. without LM

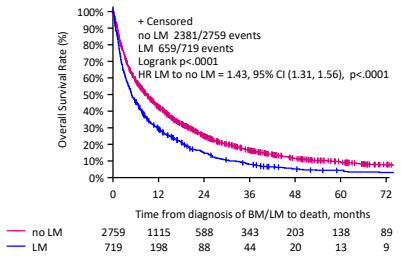
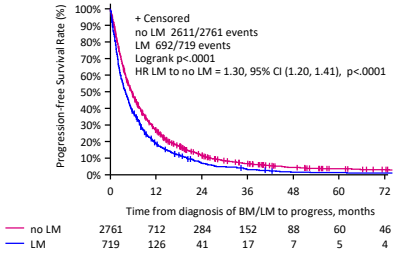


Figure 2: Kaplan-Meier curves for the time from diagnosis of BM/LM to progress (BM, ECM or death) between patients with vs. without LM



Compared to patients without LM, patients with LM had:

- Significantly more often luminal–like (46.1 vs. 31.1%) tumor biology, and significantly less common HR-negative/HER2-positive (11.3 vs. 16.5%), triple-positive (21.8 vs. 29.2%), and triple-negative (20.7 vs. 23.2%) tumor biology
- Significantly more often grade 2 tumor biology (47.3 vs. 39.9%)
- Significantly more often lobular subtype of the primary BC (13.2 vs. 6.5%)
- Significantly more often neurological symptoms at diagnosis of CNS metastases (82.3 vs. 76.8%)
- A significantly worse ECOG status at diagnosis of CNS metastases (ECOG 2-4 48.9 vs 37.2%)
- Significantly more often bone metastases (52.8 vs. 37.9%) and significantly less often lung and liver metastases (19.7 vs. 34.0%, and 20.1 vs. 26.5%, respectively)
- Significantly less often extracranial metastases in course of disease (2.2 vs. 3.9%)
- Significantly lower number of brain metastases (1 BM 36.7 vs. 30.5%)

Table 3 Univariate and multivariate Cox Regression of the time from BM/LM to death in patients with LM

Parameter	Category	Univariate analysis Hazard ratio (95% CI)	Univariate analysis p-value	Multivariate analysis Hazard ratio (95% CI)	Multivariate analysis p-value
Age*, years	≥ 60 vs. <60	1.44 (1.24, 1.68)	<0.001	1.94 (1.44, 2.61)	<0.001
ECOG*	ECOG 2-4 vs. 0-1	2.19 (1.73, 2.76)	<0.001	2.01 (1.51, 2.69)	<0.001
Biological subtype*	HR-/HER2+ vs. triple-positive	1.14 (0.84, 1.57)	0.401	0.84 (0.45, 1.56)	0.576
	Luminal A/B like vs. triple-positive	1.72 (1.39, 2.13)	<0.001	1.37 (0.93, 2.03)	0.113
	TNBC vs. triple-positive	2.32 (1.81, 2.97)	<0.001	2.06 (1.31, 3.23)	0.002
Number of BM	2-3 vs. 1	1.25 (0.99, 1.58)	0.065	1.51 (1.02, 2.23)	0.041
	≥ 4 vs. 1	1.37 (1.12, 1.69)	0.002	1.34 (0.95, 1.90)	0.095
Clinical Symptoms	yes vs. no	1.60 (1.30, 1.97)	<0.001	1.57 (1.01, 2.44)	0.043
ECM*	yes vs. no	1.28 (1.04, 1.57)	0.020	1.28 (0.84, 1.98)	0.255
Radiotherapy	WBRT only vs. no RT	0.62 (0.52, 0.73)	<0.001	0.64 (0.46, 0.90)	0.010
	Stereo RT only vs. no RT	0.40 (0.29, 0.56)	<0.001	0.83 (0.45, 1.54)	0.559
	WBRT and Stereo RT vs. no RT	0.38 (0.20, 0.71)	0.003	0.55 (0.21, 1.41)	0.212
	RT unknown vs. no RT	0.53 (0.26, 1.07)	0.075	3.23 (0.38, 27.3)	0.281
Chemotherapy**	yes vs. no	0.56 (0.48, 0.66)	<0.001	0.81 (0.60, 1.08)	0.153
Hormone therapy**/***	yes vs. no	0.46 (0.36, 0.57)	<0.001	0.38 (0.25, 0.58)	<0.001
HER2-targeted therapy**/***	yes vs. no	0.38 (0.29,0.49)	<0.001	0.49 (0.28, 0.86)	0.014

*at diagnosis of BM/LM; **after diagnosis of BM/LM; *** these parameters were set to 'no' in HR-negative patients resp. HER2-negative patients

Survival analysis

- mOS was 4.9 months in patients with LM (95%CI 4.3-5.7) and 8.8 months (95%CI 8.1-9.5) in patients without LM (HR 1,43, 95% 1.31-1.56, P<0.0001, Figure 1)
- mPFS (BM or extracranial) was 3.9 months (95%CI 3.4-4.5) in patients with LM and 5.6 months (95%CI 5.2, 5.9) in patients without LM (HR 1.3 95%CI 1.2-1.41, P <0.0001, Figure 2)

Factors associated with survival of patients with LM (multivariate Analysis)

Following factors were significantly associated with a **shorter survival** in the multivariate analysis:

- Older age (≥ 60 vs. <60 years, HR 1.94, 95%CI 1.44-2.61)
- Worse ECOG performance status (2-4 vs. 0-1 HR 2.01, 95% CI 1.51-2.69)
- Tumor subtype: Patients with luminal-like BC or TNBC had a shorter survival than patients with a triple-positive BC (HR 1.37, 95%CI 0.93-2.03; and HR 2.06, 95%CI 1.31-3.23, respectively)
- Clinical symptoms at time of diagnosis of CNS metastases (HR 1.57, 95%CI 1.01-2.44)

Following factors were significantly associated with a **longer survival** in the multivariate analysis:

- Endocrine treatment for HR+ BC (HR 0.38, 95%CI 0.25-0.58)
- HER2-targeted therapy for HER2-positive BC (HR 0.49, 95%CI 0.28-0.86)
- Whole brain radiotherapy (HR 0.64, 95%CI 0.46-0.90).

Conclusions

- Patients with LM have a short survival, which indicates an unmet clinical need of the optimization of the treatment of LM and development of prophylactic strategies for LM
- Analysis of this large cohort of patients shows that the prognosis of patients with BC and LM is significantly worse in comparison to patients with BC and brain metastases without LM
- The identified prognostic factors for patients with LM can support the clinicians to identify groups of patients with potential for better survival who could possibly benefit from a more intense treatment regimen.
- Further collaboration in the presented topic is planned in our international working group.

References

1. Franzoi et al. Leptomeningeal carcinomatosis in patients with breast cancer. Crit Rev Oncol Hematol. 2019 Mar;135:85-94

Presented at: ESMO Breast Cancer Congress 2023 (May 11-13), Berlin, Germany
We thank the patients and their families for thier contribution

Financial support for the management of BMBC Registry was provided by an unrestricted research grant from Daiichi-Sankyo to GBG.