The HERBA Study: A Retrospective Multi-Institutional Italian Study on Patients With Brain Metastases From HER2-Positive Breast Cancer

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Abstract

In this retrospective, multi-institutional study, we collected data of 154 HER2-positive breast cancer patients diagnosed with brain metastases from 2005 to 2014 with the aim to assess the impact of local and systemic treatments on the outcome. We report better survival for patients receiving surgery or stereotactic radiosurgery as local treatment and for those receiving HER2-targeted therapy as systemic treatment.

Background: There is no sufficient evidence to establish a standard of care for patients with brain metastases (BM) from HER2$^+$ breast cancer (BC). The aim of this study was to assess the impact of local and systemic treatments on the outcome of patients diagnosed with BM from HER2$^+$ BC over a period of 10 years, from 2005 to 2014. **Patients and Methods:** Data of 154 patients were retrospectively collected at 14 Italian institutions through a specifically designed database. **Results:** Median overall survival (OS) was 24.5 months. Patients receiving surgery/stereotactic radiosurgery experienced longer OS compared to those receiving whole-brain radiotherapy or no treatment (33.5 vs. 11.4 months; hazard ratio = 0.34; 95% confidence interval, 0.22-0.52; $P < .001$). Interestingly, whole-brain radiotherapy did not improve OS compared to no treatment (11.4 vs. 9.8 months; hazard ratio = 0.99; 95% confidence interval, 0.62-1.62; $P = .99$). HER2-targeted therapy was associated with better OS compared to systemic therapy without HER2-targeted therapy or no systemic therapy (27.5 vs. 5.4 months; hazard ratio = 0.26; 95% confidence interval, 0.17-0.41; $P < .001$). At multivariate analysis stratified by local treatments, systemic therapy, Karnofsky performance status, and neurologic symptoms significantly affected OS. Age, number of BM, steroid therapy, number of previous lines of systemic therapy, status of extracranial disease, and period of diagnosis had no significant impact on OS. **Conclusion:** Patients with BM from HER2$^+$ BC treated with surgery/stereotactic radiosurgery as local

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treatment and HER2-targeted therapy as systemic treatment experienced the best outcomes. Patients with low Karnofsky performance status and neurologic symptoms had poor survival.

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Introduction

HER2-positive breast cancer (BC) has a higher propensity to metastasize to the brain compared to other intrinsic subtypes.[1] It is estimated that 35% to 55% of patients with HER2$^+$ BC will develop brain metastases (BM) during the course of their disease.[2,3] Historically, the prognosis of patients with BM from BC unselected for HER2 status is poor, with a median overall survival (OS) of about 4 to 6 months.[4,5]

The advent of HER2-targeted therapies has prolonged the survival of patients with HER2$^+$ BC, including those with BM, whose median OS has been estimated at approximately 12 to 24 months.[2,6-10] Retrospective studies showed that the administration of trastuzumab-based therapy after the diagnosis of BM improves OS, although such improvement seems to be due to a prolonged control of extracranial disease (ECD) rather than activity against BM.[10-13] Conversely, the combination of lapatinib and capecitabine demonstrated direct activity against BM, with an objective partial intracranial response of 65.9%, a median time to intracranial progression of 5.5 months, and a median OS of 17 months, as reported by the phase 2 LANDSCAPE study.[14] More recently, the armamentarium for the treatment of metastatic HER2$^+$ BC has been further expanded by the introduction of pertuzumab and trastuzumab/emtansine (T-DM1). Pertuzumab, provided in combination with trastuzumab and docetaxel in the phase 3 CLEOPATRA study, translated into a delay in the onset of BM and a trend toward an increased OS after diagnosis of BM.[15] There is accumulating evidence that T-DM1 has activity against BM,[16] and an exploratory retrospective analysis of the EMILIA trial showed a survival benefit for patients with BM treated with T-DM1 compared to patients treated with lapatinib and capecitabine.[17]

At the same time, local treatment for BM has undergone remarkable progress. Particularly in the last 5 to 10 years, stereotactic radiosurgery (SRS) has been increasingly used as adjuvant treatment in the postoperative setting[18] or as a noninvasive alternative to surgical resection, and improvements in radiotherapy techniques now permit the treatment of patients with multiple BM using SRS.[19,20]

However, there is currently no sufficient high-level evidence to establish a standard of care for patients with BM from HER2$^+$ BC, and current recommendations suggest that treatment should be chosen on an individual basis.[21] Because data from randomized trials are lacking, observational studies may provide relevant information about the impact of different therapeutic strategies and prognostic factors in the era of modern treatments.[6-10]

We performed a multi-institutional retrospective study to assess the impact of local and systemic treatments on the outcome of a real-life population of patients diagnosed with BM from HER2$^+$ BC over a period of 10 years, from 2005 to 2014.

Patients and Methods

The HERBA study ("a study on HER2$^+$ metastatic BC patients with BrAin metastases") was a retrospective study conducted in 14 centers in Italy. Patients were included if they had histologically proven BC with HER2-positive status tested with immunohistochemistry and/or fluorescence in-situ hybridization according to period-appropriated guidelines,[22,23] and if they had first occurrence of BM documented by computed tomography or magnetic resonance imaging from January 1, 2005, to December 31, 2014. The study protocol was approved by the ethics committee of the Verona and Rovigo area, and by the institutional review board at each participating center.

Data Collection

Data obtained through a retrospective chart review at each participating institution were collected on a specifically designed database and included the following information: Ki-67, estrogen receptor (ER), and progesterone receptor (PgR) status, date of initial diagnosis of BC, date of diagnosis of metastatic disease, date of diagnosis of BM, number of BM, Karnofsky performance status (KPS), presence of neurologic symptoms, administration of steroids, status of ECD at the diagnosis of BM, type of first-line local treatment and first-line systemic treatment for BM, date of intracranial and ECD progression, type of local and systemic treatment received at the time of first intracranial disease progression, and date of death or last follow-up for patients who were alive at the time of data cutoff. The class of breast-specific graded prognostic assessment (breast-GPA) was determined for each patient on the basis of the reported information about age and KPS at the time of BM diagnosis, and ER/PgR status of the primary tumor.[24]

Statistical Analysis

Patients were divided in two cohorts according to the period of BM diagnosis: period A (2005-2009) and period B (2010-2014). These cohort time intervals were selected because lapatinib was approved by Italian Medicines Agency in May 2009, and from 2010 it became widely available in routine clinical practice in Italy. Descriptive statistics were used to describe clinicopathologic characteristics. Associations among variables were evaluated by the chi-square test or the Fisher exact test when appropriate for categorical variables, and the Mann-Whitney test for continuous variables. Time to occurrence of BM was defined as the time from BC diagnosis to the first evidence of BM. Intracranial progression-free survival (iPFS) was defined as the time from BM diagnosis to intracranial disease progression, defined according to Response Evaluation Criteria in Solid Tumors v1.1 or death for any cause, whichever occurred first. OS was defined as the time from BM diagnosis to death due to any cause. The Kaplan-Meier method and

log-rank test were used to estimate and compare survival times. Median follow-up time was estimated according to the reverse Kaplan-Meier method. Univariate Cox proportional hazards regression modeling and multivariate analysis were used to evaluate associations of clinicopathologic variables with OS.

All analyses were carried out from a data cutoff of April 30, 2016, using STATA/SE 14.2 software (StataCorp, College Station, TX). $P < .05$ was considered statistically significant.

Results

Patient Characteristics

A total of 154 patients with BM from HER2$^+$ BC were included in the study, 63 (41%) with BM diagnosed in period A (2005-2009) and 91 (59%) with BM diagnosed in period B (2010-2014). The main patient characteristics are summarized in Table 1. There was no significant difference in terms of patient characteristics between the two periods, except for median KPS, which was 100 for patients in period A and 80 for patients in period B ($P = .0011$).

Initial Treatment of BM and iPFS

Pattern of initial treatment for BM is listed in Table 2. In the overall population, 81% of patients received local treatment and 80% of patients received systemic therapy at the time of BM diagnosis. There was no difference between the two periods in terms of distribution of local treatments. As anticipated, regarding systemic therapy, there was an increased use of lapatinib (26% vs. 17%) and other HER2-targeted agents (9% vs. 0%), with a consequent reduced use of trastuzumab (34% vs. 44%) in period B compared to period A, although this difference was not statistically significant ($P = .084$). The percentage of patients who received lapatinib in first-line or subsequent lines of therapy was the same (42%) in both periods (data not shown).

Median iPFS was 8.68 months in the overall population, without a significant difference between periods A and B (9.86 vs. 7.50 months; hazard ratio [HR] = 1.16; 95% confidence interval [CI], 0.83-1.64; $P = .368$). Patients treated with surgery/SRS had longer median iPFS compared to those who received whole-brain radiotherapy (WBRT) or no local treatment (13.52 vs. 6.18 months; HR = 0.54; 95% CI, 0.38-0.76; $P = .001$).

Interestingly, median iPFS was significantly longer for patients receiving trastuzumab-based therapy or other HER2-targeted therapy compared to patients who did not receive HER2-targeted therapy (10.4 vs. 9.8 vs. 3.5 months, respectively; HR for trastuzumab vs. no HER2-targeted therapy: 0.41; 95% CI, 0.27-0.64; HR for other HER2-targeted therapy vs. no HER2-targeted therapy: 0.42; 95% CI, 0.27-0.67; $P < .001$). Median iPFS was 7.04 months for patients who had received ≥ 3 lines of systemic therapy and 8.79 months for those who had received 0 to 2 lines of systemic therapy before the diagnosis of BM (HR = 1.18; 95% CI, 0.76-1.81; $P = .467$).

Treatment of BM at First Intracranial Progression

Among 93 patients who experienced intracranial disease progression, 45% received local treatment, and 76% received systemic therapy (Table 3). More patients diagnosed in period B received HER2-targeted agents after intracranial disease progression than those diagnosed in period A, although this difference was not statistically significant (74% vs. 60%; $P = .38$).

Overall Survival

At the time of data cutoff, 107 patients had died. After a median follow-up of 58 months (interquartile range, 22-87 months), the median OS since diagnosis of BM was 24.5 months, with no significant difference between the two periods (period B vs. period A: 25.9 vs. 21.5 months; HR = 1.18; 95% CI, 0.79-1.74; $P = .422$; Figure 1).

Patients who were treated with surgery and/or SRS as initial local treatment experienced a longer median OS than those receiving WBRT or no local treatment (33.5 vs. 11.4 months; HR = 0.34; 95% CI, 0.22-0.52; $P < .001$; Figure 2). No significant difference in median OS was observed between patients treated with surgery compared to those treated with SRS (35.8 vs. 32.5 months; HR = 0.95; 95% CI, 0.46-1.98; $P = .90$), and between patients treated with WBRT compared to those who did not receive local treatment (11.4 vs. 9.8 months; HR = 0.99; 95% CI, 0.62-1.62; $P = .99$).

Regarding systemic therapy, patients who received HER2-targeted agents at the diagnosis of BM experienced longer median OS than those receiving systemic therapy without HER2-targeted agents (27.5 vs. 13.8 months; HR = 0.44; 95% CI, 0.25-0.78; $P = .004$) or no systemic therapy (27.5 vs. 2.1 months; HR = 0.09; 95% CI, 0.05-0.16; $P < .001$; Figure 3), with no significant difference between patients treated with trastuzumab compared to those treated with lapatinib (28.2 vs. 24.5 months; HR = 0.78; 95% CI, 0.47-1.29; $P = .333$; Figure 4).

Treatment provided at the time of first intracranial progression had a significant impact on survival. Patients who received surgery and/or SRS at first progression compared to those who received WBRT or no local treatment had longer median OS (25.8 vs. 11.3 months, calculated from the first evidence of intracranial progression; HR = 0.35; 95% CI, 0.19-0.65; $P = .001$). Similarly, patients who received HER2-targeted agents at first progression experienced longer median OS than patients who received systemic therapy without HER2-targeted agents or who received no systemic therapy (19.2 vs. 1.7 months; HR = 0.23; 95% CI, 0.13-0.42; $P < .001$).

Univariate and Multivariate Analysis for OS

In univariate analysis, younger age (< 60 years), better KPS (> 70), a limited number of BM (≤ 3), absence of neurologic symptoms, no need for steroid therapy, and high breast-GPA score were significantly associated with better OS, whereas hormone receptor status and ECD status did not affect the outcome. However, it should be noted that in this study, only 4 of 154 patients had uncontrolled ECD at the time of BM diagnosis, and therefore no definitive conclusion can be drawn regarding the prognostic impact of ECD (Table 4).

In the multivariate analysis, breast-GPA was not included, but it was separated into its component items: age, KPS, and genetic subtypes (defined as follows: HER2 if tumor was ER and PgR negative; and luminal B if tumor was ER and/or PgR positive). The multivariate analysis with backward selection identified 4 variables that significantly affected OS: local treatment, systemic therapy, KPS, and neurologic symptoms. Because local treatment did not

Table 1 Patient Characteristics

Characteristic	All	Year of Diagnosis		*P*
		2005-2009	2010-2014	
Patients	154 (100%)	63 (41%)	91 (59%)	
Age (y) at diagnosis of brain metastases, median (range)	53 (29-79)	53 (29-71)	54 (30-79)	.237
IHC Subtype				.669
ER/PgR positive	60 (39%)	23 (37%)	37 (41%)	
ER/PgR negative	86 (56%)	36 (57%)	50 (55%)	
Missing data	8 (5%)	4 (6%)	4 (4%)	
No. of Brain Metastases				.150
Median (range)	3 (1-20)	3 (1-20)	3 (1-20)	
1	47 (30%)	30 (32%)	27 (30%)	
2-3	37 (24%)	12 (19%)	25 (27%)	
>3	66 (43%)	28 (44%)	38 (42%)	
Missing data	4 (3%)	3 (5%)	1 (1%)	
KPS				.0011
Median (range)	80 (30-100)	100 (40-100)	80 (40-100)	
≤50	12 (8%)	4 (6%)	8 (9%)	
60	8 (5%)	1 (2%)	7 (8%)	
70-80	58 (38%)	16 (25%)	42 (46%)	
90-100	74 (48%)	40 (64%)	34 (37%)	
Missing data	2 (1%)	2 (3%)	-	
Breast-GPA				.268
Group 1 (score 0-1.0)	0 (0%)	0 (0%)	0 (0%)	
Group 2 (score 1.5-2.0)	11 (7%)	3 (5%)	8 (9%)	
Group 3 (score 2.5-3.0)	53 (35%)	18 (29%)	35 (38%)	
Group 4 (score 3.5-4.0)	88 (57%)	40 (63%)	48 (53%)	
Missing data	2 (1%)	2 (3%)	0 (0%)	
Neurologic Symptoms				.145
Present	86 (56%)	30 (48%)	56 (62%)	
Absent	62 (40%)	29 (46%)	33 (36%)	
Missing data	6 (4%)	4 (6%)	2 (2%)	
Steroid Therapy				.168
Yes	110 (71%)	41 (65%)	69 (76%)	
No	38 (25%)	19 (30%)	19 (21%)	
Missing data	6 (4%)	3 (5%)	3 (3%)	
No. of Lines of Systemic Therapy Received Before Brain Metastases				.502
Median (range)	1 (0-8)	1 (0-8)	1 (0-8)	
0-2	114 (74%)	45 (71%)	69 (76%)	
≥3	28 (18%)	13 (21%)	15 (16%)	
Missing data	12 (8%)	5 (8%)	7 (8%)	
Time From Diagnosis of BC to Brain Metastases				.111
Median (IQR), mo	39.1 (20.3-62.4)	45.7 (29.1-62.1)	34.9 (16.6-63.0)	
Time From Diagnosis of Metastatic Disease to Brain Metastases				.772
Median (IQR), mo	12.5 (2.0-24.0)	13.0 (0.9-25.8)	12.3 (3.1-22.3)	
Status of Extracranial Disease				.750
No evidence of extracranial disease	18 (12%)	6 (10%)	12 (13%)	
Controlled extracranial disease	128 (83%)	53 (84%)	75 (82%)	
Uncontrolled extracranial disease	4 (2.5%)	2 (3%)	2 (2%)	
Missing data	4 (2.5%)	2 (3%)	2 (2%)	

Data are presented as n (%) unless otherwise indicated.
Abbreviations: BC = breast cancer; breast-GPA = breast-specific graded prognostic assessment; ER = estrogen receptor; IQR = interquartile range; KPS = Karnofsky performance status; PgR = progesterone receptor.

Table 2 Initial Treatment for Brain Metastases From HER2-Positive Breast Cancer

Treatment	All	Year of Diagnosis		*P*
		2005-2009	2010-2014	
No. of patients	154	63	91	
Local Treatment				
Surgery	26 (17%)	10 (16%)	16 (17%)	.952
Surgery alone	7 (5%)	4 (6%)	3 (3%)	
Surgery + WBRT	15 (10%)	5 (8%)	10 (11%)	
Surgery + SRS	4 (2%)	1 (2%)	3 (3%)	
SRS	33 (21%)	14 (22%)	19 (21%)	
SRS alone	32 (20%)	13 (20%)	19 (21%)	
SRS + WBRT	1 (1%)	1 (2%)	—	
WBRT alone	66 (43%)	26 (41%)	40 (44%)	
No local treatment	29 (19%)	13 (21%)	16 (18%)	
Systemic Therapy at Time of Brain Metastases Diagnosis				
HER2-targeted agents	102 (66%)	39 (61%)	63 (69%)	.084
Trastuzumab	59 (38%)	28 (44%)	31 (34%)	
Lapatinib	35 (23%)	11 (17%)	24 (26%)	
Other	8 (5%)	—	8 (9%)	
Chemotherapy/endocrine therapy alone	20 (13%)	10 (16%)	10 (11%)	
No systemic therapy	22 (14%)	9 (14%)	13 (14%)	
Missing data	10 (6%)	5 (8%)	5 (5%)	

Data are presented as n (%).
Abbreviations: SRS = stereotactic radiosurgery; WBRT = whole-brain radiotherapy.

meet the proportional hazards assumption, it was considered as a stratification factor in the final model (Table 5).

Discussion

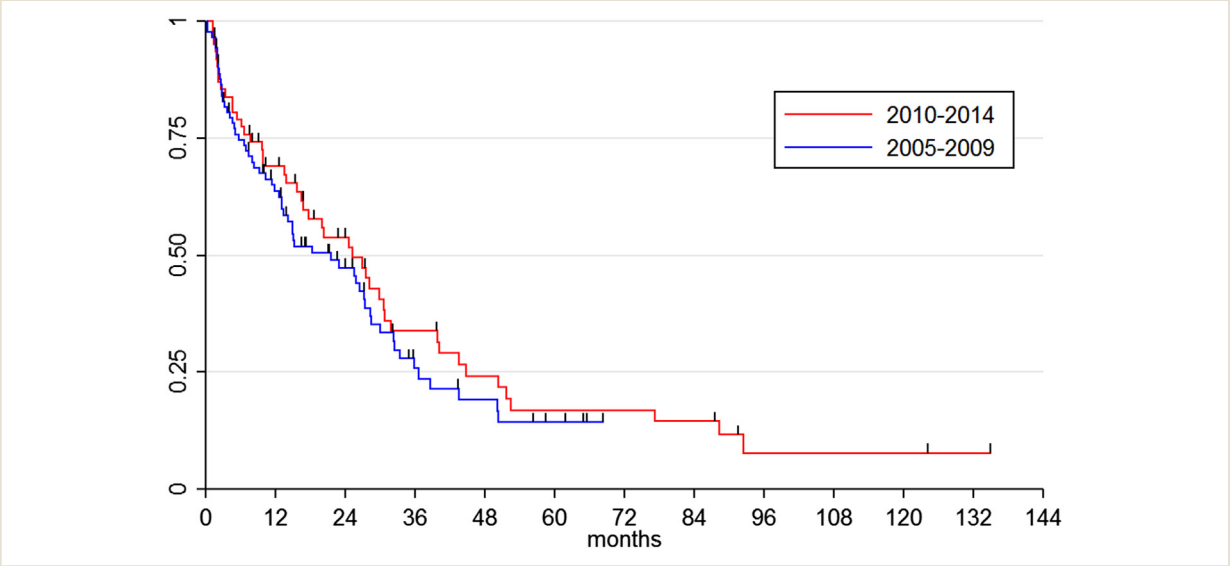
In the HERBA study, the median OS of patients diagnosed with BM from HER2$^+$ BC from 2005 to 2014 was approximately 24 months. This survival time is consistent with that reported across other series[2,6-10] and confirms an improvement in terms of life expectancy over time, going from few months in historical series of patients unselected for HER2 status[4,5] to 18 to 24 months in more recent series of patients with HER2$^+$ status in the era of modern multimodal treatments.

Table 3 Treatment for Brain Metastases at Time of First Intracranial Progression in Patients With HER2-Positive Breast Cancer

Treatment	All	Year of Diagnosis		*P*
		2005-2009	2010-2014	
Patients	93 (100%)	40 (43%)	53 (57%)	—
Local Treatment				
Surgery	5 (5%)	2 (5%)	3 (6%)	.310
SRS	21 (23%)	6 (15%)	15 (28%)	
WBRT alone	15 (16%)	9 (22%)	6 (11%)	
No local treatment	52 (56%)	23 (58%)	29 (55%)	
Systemic Therapy at Time of BM Diagnosis				
HER2-targeted agents	63 (67%)	24 (60%)	39 (74%)	.380
Trastuzumab	38 (41%)	11 (27%)	27 (51%)	
Lapatinib	19 (20%)	10 (25%)	9 (17%)	
Other	6 (6%)	3 (8%)	3 (6%)	
Chemotherapy/endocrine therapy alone	8 (9%)	6 (15%)	2 (4%)	
No systemic therapy	14 (15%)	8 (20%)	6 (11%)	
Missing data	8 (9%)	2 (5%)	6 (11%)	

Data are presented as n (%).
Abbreviations: BM = brain metastases; SRS = stereotactic radiosurgery; WBRT = whole-brain radiotherapy.

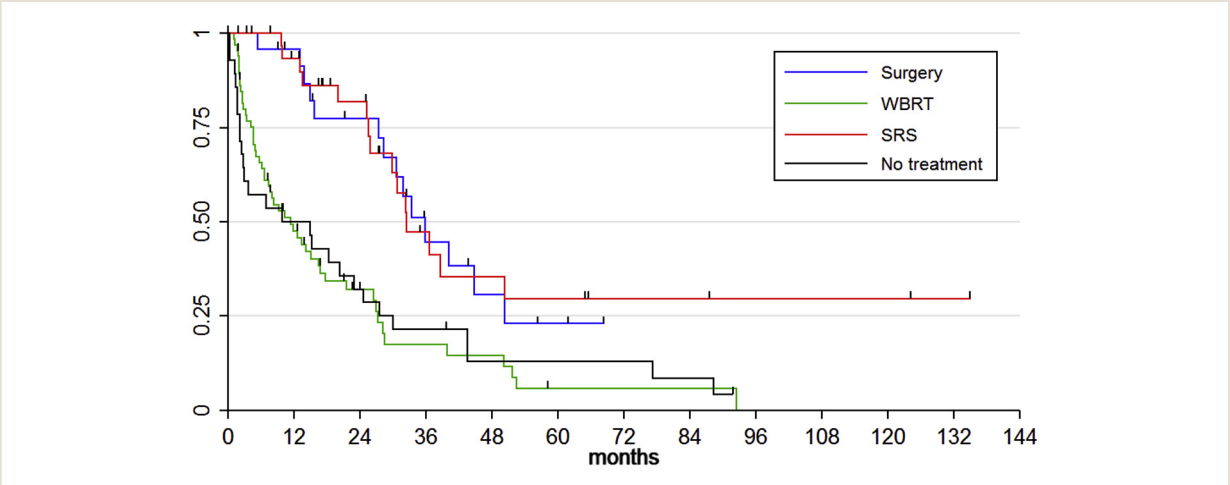
Figure 1 Kaplan-Meier OS Curves According to Period of Brain Metastases Diagnosis. For Period B (2005-2009) versus Period A (2010-2014), Median OS Was 25.9 Versus 21.5 Months; HR Was 1.18 (95% CI, 0.79-1.74; $P = .422$)



Abbreviations: CI = confidence interval; OS = overall survival.

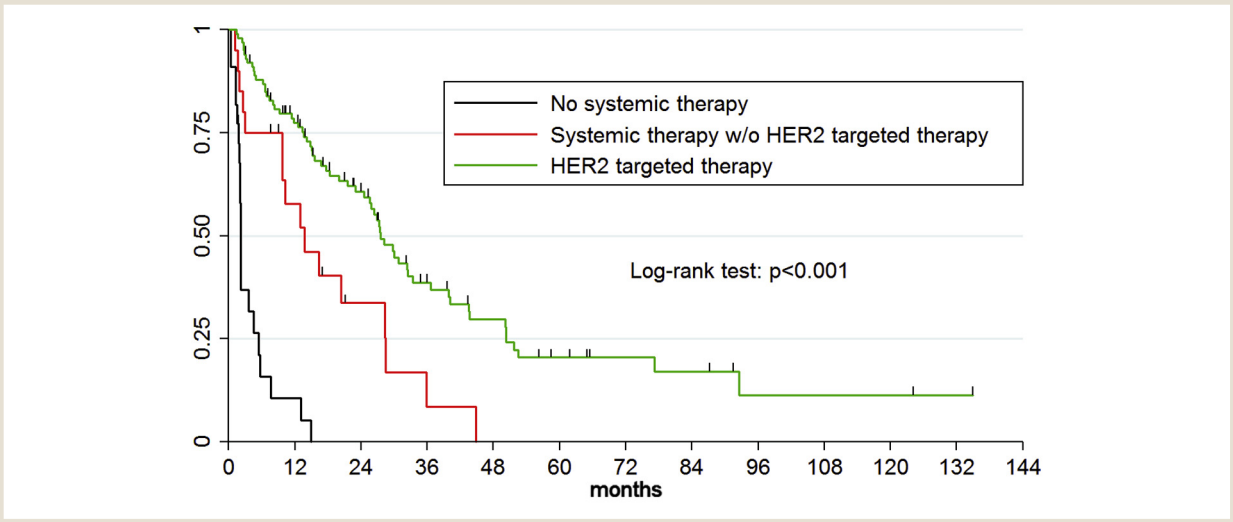
However, there is no meaningful difference in terms of survival when comparing data of patients diagnosed in the early 2000s[2] with those of patients diagnosed more recently,[7-9] including patients enrolled onto the present study. This observation suggests that median OS may have reached a plateau, despite the introduction of novel HER2-targeted therapy beyond trastuzumab, such as lapatinib, and more recently pertuzumab and T-DM1. In fact, a retrospective study of 123 patients conducted at the University of North Carolina,[9] which compared 3 cohorts of patients defined on the basis of year of HER2-targeted therapy approval by the US Food and Drug Administration (1998-2007 for trastuzumab, 2008-2012 for lapatinib, and 2013-2015 for pertuzumab and T-DM1), did not show any significant difference in terms of OS among the 3 cohorts. Similarly, among 100 consecutive patients with BM from $HER2^{+}$

Figure 2 Kaplan-Meier OS Curves According to Local Treatment. Median OS Was 35.8 Months for Surgery, 32.5 Months for SRS, 11.4 Months for WBRT, and 9.8 Months for No Local Treatment. HR for Surgery versus No Treatment Was 0.38 (95% CI, 0.20-0.75; $P = .005$); for SRS Versus No Treatment Was 0.33 (95% CI, 0.18-0.63; $P = .001$); and for WBRT Versus No Treatment Was 0.99 (95% CI, 0.62-1.62; $P = .99$)



Abbreviations: CI = confidence interval; HR = hazard ratio; OS = overall survival; SRS = stereotactic radiosurgery; WBRT = whole-brain radiotherapy.

Figure 3 Kaplan-Meier OS Curves According to Systemic Therapy. Median OS Was 2.1 Months for No Systemic Therapy (HR = 1.00), 13.8 Months for Systemic Therapy Without HER2-Targeted Agents (HR = 0.20; 95% CI, 0.10-0.40; $P < .001$), and 27.5 Months for Systemic Therapy With HER2-Targeted Agents (HR = 0.09; 95% CI, 0.05-0.16; $P < .001$)

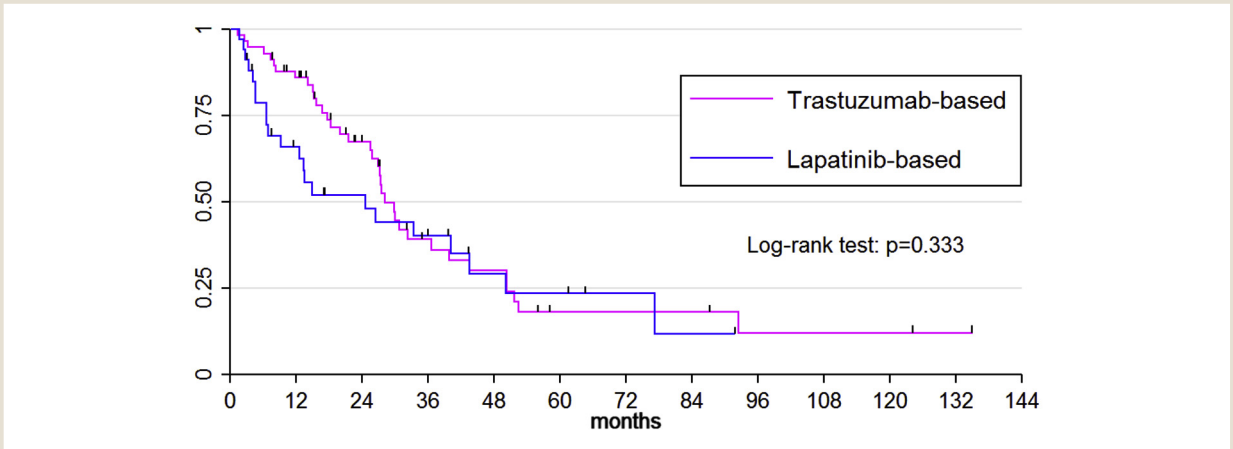


Abbreviations: CI = confidence interval; HR = hazard ratio; OS = overall survival.

BC treated at the Memorial Sloan Kettering Cancer Center (MSKCC) from 2001 to 2011,[8] lapatinib was not associated with a clear survival advantage because at multivariate analysis, the HR for survival was similar for patients who received lapatinib and for those who received nonlapatinib HER2-targeted therapy compared to patients who did not continue HER2-targeted therapy.

Consistent with these data, we did not observe a significant survival difference between patients diagnosed in 2005-2009 (period A) and those diagnosed in 2010-2014 (period B). This might be explained by the fact that there was actually no significant difference in terms of treatment between the two periods. Although there was a trend toward a more frequent use of frontline lapatinib for patients diagnosed in period B, the percentage of patients receiving lapatinib at some point during the course of their disease was the same for both periods. Patients in period B had a significantly worse median KPS than patients in period A, and this imbalance might have potentially hidden a positive impact of frontline lapatinib on survival. Therefore, on the basis of these observations, no definitive conclusion can be drawn about the impact of lapatinib on the OS of patients with BM from $HER2^{+}$ BC.

Figure 4 Kaplan-Meier OS Curves for Patients Treated With HER2-Targeted Trastuzumab-and Lapatinib-Based Systemic Therapy. Median OS was 28.2 and 24.5 Months for Trastuzumab- and Lapatinib-based Therapy, Respectively (HR = 0.78; 95% CI, 0.47-1.29; $P = .333$)



Abbreviations: CI = confidence interval; HR = hazard ratio; OS = overall survival.

Table 4 Univariate Analysis for OS

Variable	Median OS (Months)	HR (95% CI)	*P*
Age at Diagnosis of Brain Metastases			.004
≥60 y	13.0	1.00	
<60 y	27.3	0.55 (0.36-0.82)	
HR Status			.470
ER and PgR negative	20.0	1.00	
ER and/or PgR positive	23.0	0.86 (0.58-1.29)	
No. of Brain Metastases			.030
>3	14.1	1.00	
1-3	27.4	0.64 (0.43-0.96)	
KPS at Diagnosis of Brain Metastases			<.001
≤70	7.6	1.00	
>70	27.3	0.34 (0.22-0.54)	
Neurologic Symptoms			<.001
Present	13.8	1.00	
Absent	27.5	0.39 (0.26-0.61)	
Steroid Therapy			.001
Yes	16.4	1.00	
No	38.6	0.44 (0.27-0.73)	
No. of Lines of Previous Systemic Therapy			.6
≥3	13.6	1.00	
0-2	20.33	0.88 (0.53-1.45)	
Extracranial Disease			.75
Uncontrolled	28.4	1.00	
Absent/controlled	23.0	1.19 (0.38-3.79)	
Breast-GPA			<.001
Groups 1-3	12.6	1	
Group 4	27.4	0.48 (0.32-0.72)	
Period of Diagnosis			.422
Period A (2005-2009)	25.9	1.00	
Period B (2010-2014)	21.5	1.18 (0.79-1.74)	
Local Treatment			<.001
WBRT/No treatment	11.4	1.00	
Surgery/SRS[a]	33.5	0.34 (0.22-0.52)	
Systemic Treatment			<.001
No HER2-targeted therapy/no therapy	5.4	1.00	
HER2-targeted therapy	27.5	0.26 (0.17-0.41)	

Abbreviations: CI = confidence interval; ER = estrogen receptor; breast-GPA = breast-specific graded prognostic assessment; HR = hormone receptors; HR = hazard ratio; KPS = Karnofsky performance status; OS = overall survival; PgR = progesterone receptor; SRS = stereotactic radiosurgery; WBRT = whole-brain radiotherapy.
[a]Surgery includes surgery alone or surgery followed either by SRS or WBRT; SRS includes SRS alone or SRS followed by WBRT.

Although in the HERBA study it was not possible to assess the impact of each HER2-targeted agent, in general, the administration of HER2-targeted therapy significantly extended median OS (27.5 months) compared to no HER2-targeted therapy (13.8 months) or no systemic therapy (2.1 months); the positive impact of HER2-targeted therapy on OS was also confirmed at multivariate analysis (HR = 0.30). The association of HER2-targeted therapy with better OS is consistent with data already reported by other authors.[6-8] Interestingly, in this study, HER2-targeted therapy was also associated with a better iPFS, suggesting that the positive impact on OS may be due not only to an effective control of ECD but also to a possible role in delaying intracranial progression.

In terms of local treatment, surgery/SRS was associated with significantly longer OS (35 months) compared to WBRT (11.4 months) or no local treatment (9.8 months). Clearly, these data should be interpreted cautiously, given that the choice of local treatment is generally based on the prognostic assessment of the patient and on the extent of intracranial disease. Generally, surgery/SRS is offered in case of good prognosis and limited intracranial disease (1-3 BM), whereas WBRT is provided in cases of multiple BM. Therefore, the difference in OS between surgery/SRS and WBRT or no treatment observed in the present study may possibly reflect a different distribution of prognostic factors or number of BM among patients receiving different local treatments, rather than

Table 5 Multivariate Analysis for OS

Cox Model	HR (95% CI)	*P*
Initial Cox Model With All Covariates		
Local Treatment		<.001
WBRT/no treatment	1.00	
Surgery/SRS	0.26 (0.15-0.46)	
Systemic Treatment		<.001
No HER2-targeted therapy/no therapy	1.00	
HER2-targeted therapy	0.33 (0.20-0.52)	
Age at Diagnosis of Brain Metastases		.254
≥60 y	1.00	
<60 y	0.76 (0.47-1.22)	
KPS at Diagnosis of Brain Metastases		.077
≤70	1.00	
>70	0.63 (0.38-1.05)	
No. of Brain Metastases		.875
>3	1.00	
1-3	0.96 (0.59-1.56)	
Neurologic Symptoms		.073
Present	1.00	
Absent	0.58 (0.31-1.05)	
Steroid Therapy		.465
Yes	1.00	
No	0.75 (0.35-1.61)	
Final Cox Model[a]		
Systemic Treatment		<.001
No HER2-targeted therapy/no therapy	1.00	
HER2-targeted therapy	0.30 (0.19-0.47)	
KPS at Diagnosis of Brain Metastases		.026
≤70	1.00	
>70	0.58 (0.36-0.94)	
Neurologic Symptoms		.005
Present	1.00	
Absent	0.50 (0.31-0.81)	

Abbreviations: CI = confidence interval; HR = hazard ratio; KPS = Karnofsky performance status; OS = overall survival; SRS = stereotactic radiosurgery; WBRT = whole-brain radiotherapy.
[a]Cox model after backward selection, stratified by local treatment because this variable did not meet proportional hazards assumption.

a different efficacy of local treatments. Regarding the number of BM, however, in this study, it was not associated with OS at multivariate analysis. In fact, the prognostic role of the number of BM in BC is still controversial, and the breast-GPA index does not include number of BM in the prognostic assessment.[25] Accumulating evidence suggests that patient outcome, especially in patients treated with SRS, may be affected more by the cumulative intracranial tumor volume than by the number of BM.[20,26,27] Unfortunately, data about the cumulative intracranial tumor volume were not collected in this retrospective study.

Interestingly, we observed no significant difference in terms of OS between WBRT (11.4 months) and no treatment (9.8 months). These data are consistent with the results of the QUARTZ trial, a noninferiority phase 3 study comparing best supportive care plus WBRT with best supportive care alone in 538 patients with non–small-cell lung cancer and BM in patients with disease unsuitable for surgery or SRS, and with uncertainty by the physician or the patients about the potential benefit of WBRT. This trial showed no difference in OS between the two arms, although in a subgroup analysis, a potential benefit from radiotherapy was observed in younger patients, those with a good KPS, and those with no ECD.[26] These data suggest that when surgery/SRS is not feasible, the administration of WBRT may be questionable for patients with $HER2^+$ BC and BM.

Local and systemic treatments provided at the time of first intracranial progression were significantly associated with outcome. Again, even when provided as salvage therapy, surgery/SRS and HER2-targeted therapy were associated with the longest survival. On the basis of these data, we can speculate that in the era of modern multimodal treatment for BM, a frontline approach is important, but it should be integrated into a comprehensive therapeutic strategy involving multiple local and systemic treatments, provided sequentially at each disease progression.

In the HERBA study, we also explored the role of prognostic factors. Although older age (> 60 years), low KPS (≤ 70), multiple BM (> 3), presence of neurologic symptoms, need for steroid therapy, and lower breast-GPA score (groups 1-3) were associated with shorter survival at univariate analysis, only KPS and neurologic symptoms maintained a prognostic role at multivariate analysis. This may suggest that breast-GPA is not an optimal prognostic tool in the specific setting of patients with BM from $HER2^+$ BC, and that other important factors, such as HER2-targeted therapy, should be incorporated, as suggested by other authors.[12] In particular, a possible prognostic role of neurologic symptoms was recently observed in the MSKCC series.[8] The authors concluded that although routine screening for BM in asymptomatic patients with $HER2^+$ metastatic BC is not currently recommended,[21] this finding represents an argument for early detection of BM.[8]

We recognize that the HERBA study has several limitations. First, it is a retrospective study; therefore, results should be interpreted cautiously, especially because of potential selection bias. However, because data from randomized trials are lacking in this setting, we believe that retrospective studies may still provide relevant information. Second, a central review of central nervous system imaging was not planned, and this could have affected the response assessment and the evaluation of iPFS. However, the lack of central review has no impact on OS analysis, given the objective nature of this end point. Third, because only patients diagnosed from 2005 to 2014 were enrolled onto the study, the majority of patients received trastuzumab and/or lapatinib as HER2-targeted therapy, and no conclusions can be drawn about the role of novel HER2-targeted agents, such as pertuzumab and T-DM1. In this regard, a prospective observational study of patients with $HER2^+$ BC and BM diagnosed from 2016 to 2018, the Pro-HERBA study, is currently ongoing at the same institutions that participated to the retrospective HERBA study.

Conclusion

The HERBA study reported a median OS of approximately 24 months in patients with BM from $HER2^+$ BC. We did not observe a survival difference between patients diagnosed in 2005-2009 and

those diagnosed in 2010-2014. Surgery/SRS and HER2-targeted agents, provided as both up-front and as salvage treatment, were associated with better outcomes, with median OS exceeding 2.5 years in selected patients. When interpreting these data, it must be kept in mind that candidates for surgery/SRS or active systemic treatments, including HER2-targeted agents, generally have more favorable prognostic features than patients treated with WBRT or best supportive care alone. Notwithstanding these limitations, our results suggest that when feasible, surgery/SRS and HER2-targeted therapy should be considered as the preferred therapeutic approach.

Breast-GPA may not be the best tool to assess the prognosis of patients with $HER2^{+}$ BM from BC. KPS and the presence of neurologic symptoms are relevant prognostic factors and should be considered when planning the therapeutic strategy, whereas age, number of metastases, steroid therapy, and number of previous lines of systemic therapy should play only a secondary role in the choice of treatment.

Clinical Practice Points

- There is no high-level evidence from randomized studies on the best therapeutic approach for patients with HER2-positive BC with BM.
- In this retrospective study, among local treatments, surgery or SRS was associated with better OS compared to WBRT or no local treatment.
- Regarding systemic therapy, HER2-targeted agents provided longer survival compared to systemic therapy without HER2-targeted agents or no systemic therapy. No differences were observed between trastuzumab and lapatinib.
- At multivariate analysis, KPS and neurologic symptoms represented relevant prognostic factors.

Disclosure

The authors have stated that they have no conflict of interest.

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