89

RegistHER: Patient Characteristics and Time Course of Central Nervous System Metastases in Patients with HER2-Positive Metastatic Breast Cancer

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UPDATED ABSTRACT

Background: registHER is a prospective, observational study of 1023 patients with newly diagnosed HER2-positive metastatic breast cancer (MBC). This report describes the subset of patients with central nervous system (CNS) metastases.

Methods: As of January 2, 2008, median follow-up from MBC diagnosis was 25 months. Baseline characteristics of patients with and without CNS metastases were compared; incidence, time to development, and survival after CNS metastases were assessed. Associations between treatment after CNS metastases and survival were evaluated.

Results: Of the 1009 treated patients included in this analysis, 337 (33.4%) developed CNS metastases. Median time to CNS progression among patients without CNS disease at initial MBC diagnosis was 12.8 months. Compared with patients without CNS metastases, patients with CNS metastases were younger, more likely to have had hormone receptor–negative disease, and had higher disease burden. For patients receiving trastuzumab following diagnosis of CNS disease, median survival was 17.5 months, compared with 5.5 months for patients who did not receive trastuzumab. In a multivariable model, after adjusting for clinical and tumor characteristics, patients who received trastuzumab following CNS diagnosis had a decreased hazard of death (HR=0.49; 95% CI: 0.36, 0.66) compared with those who did not.

Conclusions: Approximately one third of HER2+MBC patients in this registry developed CNS metastases; median time to diagnosis was approximately one year after metastatic diagnosis. Use of trastuzumab, chemotherapy, and surgery following CNS metastases was associated with longer survival.

BACKGROUND

- Clinically evident CNS metastases are reported in 2.5–13.4% of women with breast cancer and studies of autopsy results show that brain metastases are found in up to 30% of patients with advanced MBC.[1-3]
- Data from retrospective reviews of trastuzumab trials and single-institution experiences suggests that patients with HER2+ MBC are more likely to develop CNS metastases than those with HER2-negative MBC; estimates range from 21–48%.[4,5]
- Predictors of development and incidence of CNS metastases in patients with HER2+ MBC are, however, not well defined.
- Trastuzumab, a humanized, monoclonal antibody directed against the extracellular domain of HER2, has demonstrated clinical activity in advanced HER2+ breast cancer.[6,9] After the introduction of trastuzumab in the late 1990's, clinicians observed an apparent increase in the incidence of CNS metastases in women with HER2+ MBC. This increase is likely multifactorial, and may include both inherent biological factors associated with the aggressive nature of HER2+ breast cancer, and improvements in overall survival (OS) associated with trastuzumab-based therapy. Predictors of development and incidence of CNS metastases in patients with HER2+ MBC, however, are not well defined.
- registHER a large multicenter prospective observational study of 1023 patients, has the largest study population of patients with newly diagnosed HER2+ MBC. This study, which offers a unique opportunity to study the natural history of HER2+ MBC, also allows characterization of HER2+ breast cancer that has metastasized to the CNS.

OBJECTIVES

- To assess the incidence and predictors of CNS metastases and to observe outcomes among patients with HER2+ MBC enrolled in the registHER study.

METHODS

Study Design

- registHER is a United States-based cohort study of male and female patients with newly diagnosed (within 6 months) HER2+ MBC, treated in community and academic settings.
- Treatments for MBC are administered according to standard of care by the treating physician; prior or planned treatment with trastuzumab was not required for enrollment.
- Patient data (including demographics, tumor characteristics, sites of first metastases and subsequent progression, systemic treatment received and response to treatment) were collected at enrollment and updated every 3 months thereafter. Tumor progression was assessed by physicians using standard practice.
- registHER patients with identified CNS metastases were studied in this analysis; CNS metastases were defined as either leptomeningeal metastases (LM) or metastases to the brain parenchyma.
- Additional data on whether CNS metastases were diagnosed due to symptoms or via routine screening, the presence or absence or LM (investigator determined), and primary treatment of the CNS metastases was requested.

Statistical Methods

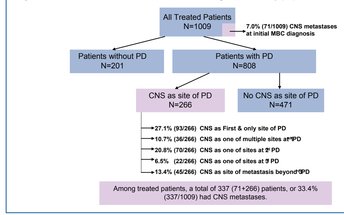
- Analyses incorporate all follow-up data on registHER patients as of January 2, 2008.
- Time-to-CNS metastases was defined as the time from the date of first metastases (either loco-regional or distant) to the date of diagnosis of CNS metastases.
- OS after CNS metastases was defined as the time from diagnosis of first CNS metastases to the date of death from any cause, or last follow-up.
- OS was defined as the time between a patient's initial metastatic diagnosis and death from any cause or last follow-up.
- Median, ranges and 25th and 75th percentiles are reported for time-to-event data. Time-to-CNS metastases and survival after CNS metastases were estimated by the Kaplan–Meier product limit method.
- Patients were classified as receiving trastuzumab if they received ≥21 cumulative days of trastuzumab at any time following their first CNS event. Patients were classified as not receiving trastuzumab if they had no trastuzumab exposure following their first CNS event. Five patients were not included in either group because their time on trastuzumab following CNS metastasis was <21 days.
- To compare the survival of two treatment groups, the Cox proportional hazards model was used to adjust for relevant baseline covariates including: age, ECOG status, chemotherapy use after first CNS progression, radiation treatment, and surgery. These variables were considered significant predictors of treatment group assignment or prognostic for survival.

RESULTS

Patients and Incidence of CNS metastases

- From December 2003 to February 2006 1023 patients were enrolled at 240 sites in the United States. Median follow-up time from metastatic diagnosis was 25 months.
- Of 1023 patients, 1009 (98.6%) patients were diagnosed with and treated for MBC and were therefore eligible for inclusion in this analysis (Figure 1).
- Of patients with MBC, 33% (337/1009) developed CNS metastases—7% (71/1009) had clinically apparent CNS metastases at the time of their initial MBC diagnosis and 26% (266/1009) developed CNS metastases as a later site of disease progression (Figure 1).

Figure 1. Incidence of CNS metastases in the registHER study population



- Additional data specific to diagnosis and initial treatment was requested on patients with identified CNS metastases and was collected on 270/337 patients.
- For the 266 patients with CNS metastases on whom additional CNS-specific data was collected, 8.6% were described as having LM, with or without parenchymal disease (Table 2a).
- Development of neurologic symptoms led to diagnosis of CNS metastases in 74% of these patients (197/270) (Table 1).
- Just over 2% (23/1009) of patients were described as having LM, with or without parenchymal disease (Table 1).

Table 1. Diagnosis of CNS metastases

	No. of Patients	%
Neurologic symptoms present		
Yes*	197	74.3*
Missing	72	
Leptomeningeal involvement		
No	243	91.0*
Yes	23	9.2*
Missing	70	

*Of the 337 patients with CNS metastases, data was available for 270 patients.

Baseline characteristics

- Patients with CNS metastases were younger, more likely to be hormone receptor (HR)-negative and had a higher disease burden than patients without CNS metastases (Table 2).

Table 2. Demographic and baseline characteristics by presence of CNS metastases

	Any CNS Metastases (n=337)		No CNS Metastases (n=672)	
	No. of Patients	%	No. of Patients	%
Age (yr)				
<50	145	43	249	37.1
50–64	136	40.4	267	39.7
65+	56	16.6	156	23.2
Hormone receptor status[‡]				
Positive	144	42.7	394	58.6
Negative	176	52.2	257	38.2
Unknown	17	5.0	21	3.1
Number of metastatic sites				
1	125	37.1	339	50.4
2+	212	62.9	333	50.0
ECOG				
1	135	40.1	321	47.8
2+	24	7.1	37	5.5
Unknown/missing	178	52.8	314	46.7
Prior therapy (Stage I–III only)[†]				
Trastuzumab-based without hormones	20	8.0	25	5.2
Trastuzumab-based with hormones	2	0.8	8	1.7
Hormones only	15	6.0	43	8.9
Hormones and chemotherapy	51	20.4	114	23.7
Chemotherapy only	115	46.0	207	43.0
Other therapy	0	0.0	2	0.4
No prior therapy	47	18.8	81	16.8

CNS=central nervous system.
* Two patients in the no CNS group received hormones with other therapy.

Initial treatment after CNS Metastasis

- Initial CNS-directed treatment included whole brain irradiation (75.9%; 205/270), stereotactic irradiation (13%; 35/270), surgical resection of the brain lesion(s) (7.8%; 21/270), and/or systemic therapy (17.8%, 48/270) (Table 3).

Table 3. Initial local treatment administered for CNS metastases

	No. of Patients	%
Treatment for CNS metastases		
Whole brain radiotherapy	205	75.9*
Stereotactic radiotherapy	35	13.0*
Surgical resection	21	7.8*
Systemic therapy	48	17.8*
Missing**	67	

*Of the 337 patients with CNS metastases, data was available for 270 patients.
**Multiple responses can be given for these categories

Time to CNS progression

- For patients without clinically apparent CNS disease initially, who developed CNS metastases during treatment for MBC (n = 266), the median time to first CNS event was 12.8 months (range 0.8–40.9 months) (Figure 2).
- Among the subset of patients who had CNS metastases as their first and only site of progression after MBC diagnosis, median time to first CNS event was 9.6 months (range 0.8– 35.4 months).
- Within the population of patients with diagnosis of CNS metastasis after MBC diagnosis, 31.2% (83/266) were receiving their first line of therapy for MBC at the time of detection of CNS metastasis; 34.6% (92/266) were receiving second-line therapy; and 34.2% (91/266) were in later lines of therapy (Figure 3).
- Of patients with a CNS event after metastatic diagnosis), 95% (252/266) had received ≥21 days of trastuzumab prior to development of CNS metastases.

Figure 2. Incidence of CNS metastases in HER2+ MBC patients with time (n=266).

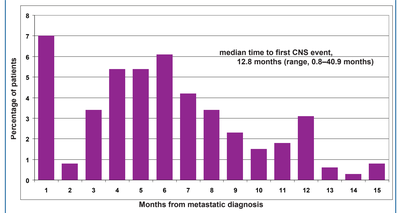
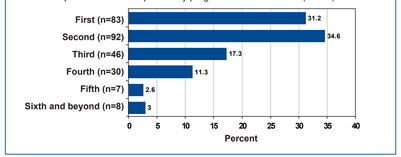


Figure 3. Line of treatment at first CNS progression. Line of treatment defined as the treatments patients received up until any progressive disease event (n=266).



Trastuzumab after CNS metastases

- Of the patients diagnosed with CNS metastases, 61% (206/337) received ≥21 days of trastuzumab after their CNS diagnosis, whereas 37% (126/337) did not.
- Of the 266 patients who were not initially diagnosed with CNS metastases, 64% (169/266) received ≥21 days of trastuzumab, whereas 34% (92/266) did not receive drug.
- Approximately 2% of patients (5/266) received <21 days of trastuzumab; their data were excluded from subsequent analyses.

Survival following MBC diagnosis

- Among the 337 patients with CNS metastases, 212 deaths were reported and the median OS from the date of initial MBC diagnosis was 24.6 months (range, 1.2–51.0 months; data not shown).
- For the 66.6% of patients (672/1009) who did not have CNS metastases, 227 deaths were reported and the median survival from MBC diagnosis was 44.6 months (range, 0.5–126.3 months; data not shown).

Survival following CNS metastases

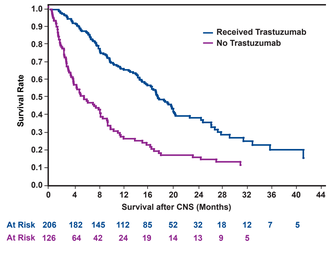
- Median survival after the diagnosis of CNS metastases for the entire cohort (n=337) was 13.5 months (Table 3).
  - For patients presenting with CNS metastases at time of initial MBC diagnosis (n=71), median survival after CNS diagnosis was 23.2 months (Table 3).
  - For patients diagnosed with CNS metastases as a site of later progression (n=266); median survival was 9.6 months post-CNS diagnosis (Table 3).
  - For patients with reported LM disease (n=23), median survival from time of CNS diagnosis was 5.8 months (range 0.8–48.4 months) (data not shown).
- For the 206/337 (61%) patients who received trastuzumab for ≥21 days following diagnosis of CNS disease, median survival was 17.5 months, whereas for the 126 (37.4%) patients who did not receive trastuzumab following CNS metastases, median survival was 5.5 months (Table 3 and see Figure 4).
- After adjusting for additional clinical and tumor characteristics, patients who received trastuzumab following CNS diagnosis had a decreased hazard of death (HR=0.49) compared with those who were not treated with trastuzumab after CNS metastases diagnosis (Table 3).
- A sensitivity analysis was performed that removed the 13 patients who had <21 days of survival post CNS and the 35 patients who had no treatment after their first CNS met. After removing these 48 (38%) patients, the reduction in risk of death beyond CNS progression remained similar (adjusted HR=0.51; 95% CI: 0.366, 0.71) for patients receiving trastuzumab following CNS progression.
- Other factors most strongly associated with improved survival were treatment with chemotherapy and surgery after CNS diagnosis (Table 3).
- After adjusting for additional clinical and tumor characteristics, patients who received trastuzumab following CNS diagnosis had a decreased hazard of death (HR=0.49) compared with those who were not treated with trastuzumab after CNS metastases diagnosis (Table 3).

Table 4: Survival following CNS metastases

	No. Deaths (%)	Median OS; [months (range)]
All patients with CNS metastases (n=337)*	212 (62.9)	13.5 (0–48.5)
Patients with CNS metastases at MBC diagnosis (n=71)	44 (62)	23.2 (1.2–48.4)
Patients who developed CNS metastases after MBC diagnosis (n=266)	168 (63.2)	9.6 (0–48.5)
Treatment pattern for all patients following first CNS metastases[†]		
Received trastuzumab for ≥21 days at any time following first CNS event (n=206)[‡]	117 (56.8)	17.5 (1.2–48.5)
Did not receive trastuzumab after first CNS event (n=126)	94 (74.6)	5.5 (0–42.5)
Trastuzumab received after CNS event		**Hazard Ratio (95% CI)**
Unadjusted HR		0.41 (0.31, 0.54)
Adjusted HR (adjusted for age, ECOG, chemotherapy after CNS, radiation therapy, surgery)		0.49 (0.36, 0.66)
Univariate analysis of post-CNS survival (n=337)		**Hazard Ratio (95% CI)**
Radiation treatment[§]		0.89 (0.67 to 1.19)
Chemotherapy after CNS metastases[§]		0.54 (0.41 to 0.71)
Surgery[§]		0.49 (0.25 to 0.96)
Age (continuous in years)		1.02 (1.01 to 1.03)
Number of metastatic sites (1 vs. 2+)		0.94 (0.71 to 1.24)
Stage I-III, MBC ≤12 mo after initial dx vs Stage IV		1.72 (1.11 to 2.67)
Stage I-III, MBC >12 mo after initial dx vs. Stage IV		0.98 (0.71 to 1.35)
ECOG PS		
≥2 vs 0 or 1		1.72 (1.03 to 2.87)
Unknown or missing vs 0 or 1		0.98 (0.74 to 1.30)

* Includes all patients who had CNS metastatic diagnosis.
† Includes patients whose first CNS event occurred after their initial metastatic diagnosis.
‡ May be slightly overestimated due to amount of censoring in patients near the median.
§ Comparison of treatment relative to no treatment.

Figure 4. Unadjusted survival after CNS metastases for patients who had received ≥21 days of trastuzumab (blue) or no trastuzumab after diagnosis of CNS metastases (purple).



CONCLUSIONS

- As systemic therapy of HER2-positive MBC improves, CNS involvement is becoming more clinically evident.
- Approximately one third of registHER patients had CNS metastases—7.0% had CNS metastases at MBC diagnosis and 26.3% of patients aquired them as a later site of progression.
- CNS metastases occur relatively early in the course of disease, at a median time of approximately one year after metastatic diagnosis.
- In 74% of patients, the development of neurologic symptoms led to diagnosis of CNS metastases.
- Of HER2-positive MBC patients with CNS involvement queried, 8.6% were reported to have LM involvement.
- Median survival after diagnosis of CNS metastases was 13.5 months.
- Use of trastuzumab following development of CNS metastases was associated with longer survival.
- Surgery and treatment with chemotherapy after diagnosis of CNS metastases is also associated with longer survival.
- This large study population allows a unique opportunity to study the natural history of HER2-positive MBC in patients who develop CNS disease.

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