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Clinical Profile and Outcome of Patients With Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer With Brain Metastases: Real-World Experience

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abstract

PURPOSE There are sparse data in patients with human epidermal growth factor receptor 2 (HER2)–positive breast cancer with brain metastases from real-world settings, especially where access to newer targeted therapies is limited.

METHODS This was a single institution, retrospective cohort study of patients with HER2-positive breast cancer diagnosed between January 2013 and December 2017 to have brain metastases and treated with any HER2-targeted therapy. The main objectives were to estimate progression-free survival (PFS) and overall survival (OS) from the time of brain metastases.

RESULTS A total of 102 patients with a median age of 52 (interquartile range, 45-57) years were included, of whom 63 (61.8%) had received one line and 14 (13.7%) had received two lines of HER2-targeted therapies before brain metastasis, 98 (96.1%) were symptomatic at presentation, 22 (25.3%) had solitary brain lesion, 22 (25.3%) had 2-5 lesions, and 43 (49.4%) had ≥ 5 lesions. Local treatment included surgical resection in nine (8.9%) and radiotherapy in all (100%) patients. The first HER2-targeted therapy after brain metastasis was lapatinib in 71 (68.6%), trastuzumab in 19 (18.6%), lapatinib and trastuzumab in three (2.9%), trastuzumab emtansine in four (3.9%), and intrathecal trastuzumab in five (4.9%) patients. At a median follow-up of 13.9 months, the median PFS and OS were 8 (95% CI, 6.2 to 9.8) months and 14 (95% CI, 10.8 to 17.2) months, respectively, with a 2-year OS of 25% (95% CI, 16.7 to 34.4). The median PFS in patients who received lapatinib-capecitabine regimen (n = 62) was 9.0 (95% CI, 7.3 to 10.7) months.

CONCLUSION There was a substantial clinical benefit of local and systemic therapy in patients with brain metastases and HER2-positive disease in a real-world setting with limited access to newer HER2-targeted drugs.

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INTRODUCTION

The development of brain metastasis is one of the most devastating consequences of breast cancer. Approximately 50% of patients with human epidermal growth factor receptor 2 (HER2)–positive metastatic breast cancer eventually develop brain metastases.[1] The higher incidence of brain metastases in this subtype is attributed to an inherent tropism of HER2-positive cancer cells for the central nervous system and improved survival of patients because of various HER2-directed therapies. The HER2 tyrosine kinase inhibitors (lapatinib, neratinib, and tucatinib) can cross the blood-brain barrier (BBB) more efficiently compared with antibody-based anti-HER2 agents and antibody-drug conjugates. Therefore, prior use of the type of anti-HER2 therapies can influence the incidence of brain metastasis.[2]

The initial treatment of brain metastasis typically includes local therapy such as surgical resection, stereotactic radiosurgery (SRS), with or without whole-brain radiation therapy (WBRT), or whole-brain radiotherapy.[3] The majority of these patients develop intracranial progression within 6-12 months of local therapy. Current guidelines recommend that patients with stable systemic disease at the time of brain-only progression should continue the same systemic therapy until further progression. There is limited evidence to guide further treatment in patients who develop progressive brain metastasis despite local therapy. Moreover, patients with brain metastasis have often been excluded from most trials evaluating HER2-targeted therapies, thus making treatment decisions in such patients more challenging.

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

What is the outcome of patients with human epidermal growth factor receptor 2 (HER2)–positive breast cancer with brain metastasis treated with HER2-targeted therapy in a real-world setting with limited access to newer targeted therapies?

Knowledge Generated

In this single-institution retrospective cohort study, 102 HER2-positive patients with brain metastasis achieved a median progression-free survival of 8 months and a median overall survival of 14 months, when treated with multimodality treatment including radiotherapy, trastuzumab and/or lapatinib, and chemotherapy. The difference between progression-free survival and overall survival suggests that further treatment after progression is worthwhile in many patients. Our results also suggest that combining radiotherapy with concurrent lapatinib is feasible, can improve outcomes and deserves to be evaluated further, and intrathecal trastuzumab is a promising treatment in patients with leptomeningeal involvement.

Relevance

There is substantial clinical benefit of multimodality treatment in patients with HER2-positive breast cancer and brain metastases in real-world settings.

Emerging data suggest that local treatment, along with targeted therapies, can improve outcomes in patients with brain metastasis. There is a paucity of data on the outcome of HER2-positive patients with brain metastasis, especially from developing countries with limited access to newer HER2-targeted drugs, which is important to establish a baseline for future analyses. We undertook this retrospective analysis to evaluate the treatment pattern and outcome of patients with HER2-positive breast cancer with brain metastasis in a real-world clinical setting in a tertiary cancer center in India.

METHODS

Study Design

This study is a retrospective analysis of a single-center database conducted after obtaining approval from the Institutional Ethics Committee. Patient consent was waived by the Ethics Committee.

Patient Identification

The study population comprises patients with HER2-positive breast cancer diagnosed with brain metastasis between January 2013 and December 2017. HER2-positive status was defined as either HER2 immunohistochemistry 3+ staining or amplification by HER2 fluorescence in situ hybridization. Brain metastases were diagnosed by computed tomography and/or magnetic resonance imaging in patients with neurological signs and/or symptoms. Patients with leptomeningeal carcinomatosis, defined as cerebrospinal fluid cytology positive for malignant cells and/or relevant imaging findings, were also included.

Procedures

Patients' records, including electronic medical records, were used to extract data according to a predefined case record form. Extracted data included demographic information, clinical examination findings including neurological examination, Eastern Cooperative Oncology Group performance status, stage at initial diagnosis, tumor characteristics including estrogen and progesterone receptor status, HER2 receptor status, treatment details in (neo)adjuvant setting, site of first metastasis, sites of distant metastasis, treatment received before developing brain metastasis, local therapy (surgery, radiotherapy, or SRS) for brain metastasis, systemic therapies received after developing brain metastasis, radiological reports, disease status at various time points after developing brain metastasis, toxicities due to local therapies and/or systemic therapies, and death.

Treatment of Brain Metastasis

Patients with brain metastasis were treated on the basis of the number, size, and site of parenchymal lesions with at least one of the following treatment modalities: surgical resection, followed by postoperative RT (focal or WBRT), WBRT, or single-dose radiosurgery (SRS). Surgical resection was considered for single large lesions with midline shift or significant edema with none or stable extracranial disease and estimated life expectancy of more than or equal to 6 months. Focal RT was considered for lesions up to 3 cm. If the above criteria were not fulfilled, patients were treated with WBRT after surgical resection. Systemic therapies included lapatinib either alone or with capecitabine, trastuzumab, or trastuzumab emtansine. Patients with the leptomeningeal disease were treated with intrathecal trastuzumab along with systemic HER2-targeted therapies.

Study Definitions and Statistical Analyses

The study end points were progression-free survival (PFS) and overall survival (OS) after the development of brain metastasis. PFS was defined as the time interval between the date of diagnosis of brain metastasis and the date of first documented clinical and/or radiological disease progression

or death due to any cause, whichever was earlier. OS was defined as the time interval between date of diagnosis of brain metastasis and death due to any cause. Time to brain metastasis was defined as the time interval between initial diagnosis of breast cancer and development of brain metastasis. Patients who did not experience the events for PFS and OS on the data cutoff date on February 28, 2019, were censored.

Patient characteristics were summarized using descriptive statistics. Survival outcomes (PFS and OS) were estimated by the Kaplan-Meier method. Median times were estimated with their 95% CI. SPSS software version 22.0 was used for statistical analyses (SPSS Inc, Chicago, IL). The study is registered with Clinical Trials Registry—India (CTRI) identifier: 2017/12/016439.

RESULTS

Patient Characteristics

A total of 102 patients with a median age of 52 (interquartile range [IQR], 47-57) years were included in the study. Table 1 describes the baseline characteristics of patients at first diagnosis of breast cancer and at the time of brain metastasis. An overwhelming majority (n = 98, 96.1%) of patients had neurological symptoms at the time of diagnosis of brain metastasis, 43 (42.1%) patients had more than five brain lesions, and five (5%) patients had leptomeningeal disease.

Prior Treatment

Thirty-two (31.6%) patients had received prior HER2-targeted therapy (trastuzumab) in the (neo)adjuvant setting. In terms of HER2-targeted therapy in the metastatic setting before diagnosis of brain metastases, 20 (19.6%) patients had not received any HER2-targeted therapy, 63 (61.8%) patients had received one line, 14 (13.7%) patients had received two lines, and five (4.9%) patients had received three lines of HER2-targeted therapy. In terms of chemotherapy in the metastatic setting before diagnosis of brain metastases, 2 (2%) patients had received none, 31 (30.4%) patients had received one line, 42 (41.2%) patients had received two lines, and 27 (26.4%) patients had received three lines of chemotherapy. Two (2%) patients with de novo brain metastatic disease were treatment naive (chemotherapy and HER2-targeted therapy) at the time of diagnosis of brain metastasis.

Brain metastasis developed during adjuvant therapy or within 6 months of completion of adjuvant therapy in 18 (17.6%) patients.

Time to Brain Metastasis

The median time from initial diagnosis of breast cancer to brain metastasis was 19 (IQR, 13-39) months in all patients, 19 (IQR, 13-40) months in patients with any prior HER2-targeted therapy either in (neo)adjuvant or metastatic settings (n = 82), and 18 (IQR, 13-35) months in patients without any prior HER2-targeted therapy (n = 20). Brain was the first site of metastasis in 24 (23.5%) patients, of whom 16 had received prior adjuvant trastuzumab and eight had not received it.

Treatment of Brain Metastasis

In terms of local therapy for brain metastasis, one (1%) patient received none, 87 (85.3%) patients received WBRT alone, three (2.9%) patients received SRS alone, five (2.9%) received WBRT and SRS, one (1%) patient underwent surgery alone, and seven (6.9%) patients underwent surgical resection, followed by postoperative radiation therapy.

At the time of diagnosis of brain metastases, 43 (42.2%) patients had documented disease progression in at least one site other than brain. All patients (n = 102) received some systemic therapy after completion of local therapy for brain metastases. Sequential radiation therapy and systemic therapy was the most common treatment pattern. Systemic HER2-targeted therapy was either added or changed in 91 (89.2%) patients after the diagnosis of brain metastases while prior HER2-targeted therapy was continued in six (5.8%) patients, for a total of 97 (95%) patients who received systemic HER2-targeted therapy immediately after the diagnosis of brain metastasis. The remaining five (4.9%) patients received HER2-targeted therapy in subsequent lines of treatment, after further disease progression. The first-line HER2-targeted therapies in these 97 patients included lapatinib (71 [69.6%] patients) either alone or in combination with capecitabine, trastuzumab (19 [18.6%] patients), trastuzumab-emtansine (4 [3.9%] patients), and lapatinib with trastuzumab combination (3 [2.9%] patients). A total of five (4.9%) patients in this cohort received intrathecal trastuzumab for leptomeningeal disease (Table 2).

Subsequent Treatment after the First Progression in Brain Metastasis

The subsequent treatments in patients who progressed on capecitabine and lapatinib combination (n = 58) were trastuzumab in 12 (20.7%), trastuzumab emtansine in eight (13.8%), a continuation of lapatinib with change in chemotherapy in seven (12.1%), chemotherapy alone in five (8.6%), and only supportive care in 26 (44.8%) patients. Thirteen (12.7%) patients received radiation to the brain (either focal radiotherapy or whole-brain radiotherapy) at the time of progressive disease in the brain.

Survival

At a median follow-up of 13.5 (range, 1-55) months, there were 91 PFS events and 80 deaths on the data cutoff date. The median PFS after brain metastasis was 8.0 (95% CI, 6.2 to 9.8) months, and the median OS was 14.0 (95% CI, 10.8 to 17.2) months, with a 2-year OS of 25% (95% CI, 16.7 to 34.4; Fig 1). The median PFS in patients treated with capecitabine and lapatinib combination was 9.0 (95% CI, 7.3 to 10.7) months (Fig 2), and in those treated with trastuzumab (with or without chemotherapy) it was 7.0 (95% CI, 2.7 to 11.3) months. The median PFS of patients who underwent surgery was 22.0 (95% CI, 0.0

TABLE 1. Baseline Characteristics

Characteristic	Overall Cohort (N = 102)	Patients Treated With Lapatinib and Capecitabine (n = 62)
Median age, years (range)	52 (29-70)	52 (33-67)
Comorbidities, No. (%)		
Diabetes	13 (12.7)	6 (9.7)
Hypertension	15 (14.7)	10 (16.1)
Cardiac illness	2 (2)	2 (3.2)
Grade of tumor, No. (%)		
II	7 (6.9)	3 (4.8)
III	78 (76.4)	48 (77.4)
Unknown	17 (16.7)	11 (17.7)
ER and/or PR positive	40 (39.2)	19 (30.6)
Stage at initial presentation, No. (%)		
Localized	68 (66.7)	40 (64.5)
Metastatic	34 (33.3)	22 (35.5)
Prior (neo)adjuvant HER2-directed therapy received, No. (%)	40 (39.2)	23 (37.1)
Previous HER2-directed therapy in metastatic setting, No. (%)		
None	20 (19.6)	8 (12.9)
1 line	63 (61.8)	47 (75.8)
≥2 lines	19 (18.6)	7 (11.3)
Type of HER2-directed therapy in metastatic setting, No. (%)		
Trastuzumab	82 (80.4)	48 (77.4)
Lapatinib	9 (8.8)	1(1.6)
Pertuzumab	2 (2)	2 (3.2)
TDM1	1(1)	—
Neurologic symptoms, No. (%)		
Present	98 (96.1)	60 (96.8)
Absent	4 (3.9)	2 (3.2)
No. of brain metastasis, No. (%)		
1	22 (21.6)	12 (19.3)
2-5	22 (21.6)	12 (19.3)
> 5	43 (42.1)	29 (46.8)
Missing information	15 (14.7)	09 (14.5)
Metastatic sites, No. (%)		
Liver	43 (42.1)	27 (43.5)
Lung	48 (47.0)	30 (48.4)
Bones	53 (52.0)	33 (53.2)
Lymph nodes	40 (39.2)	26 (41.9)
Brain alone	24 (23.5)	12 (19.3)

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor; TDM1, trastuzumab emtansine.

to 54.1) months, and the median OS was 25.0 (95% CI, 22.1 to 27.9) months. The median PFS of patients with leptomeningeal disease was 8.0 (95% CI, 1.6 to 14.4) months, and the median OS was 19.0 (95% CI, 8.3 to 29.7) months.

Brain-Only Metastasis

The brain was the only site of metastasis in 24 (23.5%) patients, of whom 6 (25%) could undergo surgery. These patients achieved a median PFS of 10 (95% CI, 5.2 to 14.8) months and OS of 21.0 (95% CI, 18.1 to 23.9) months.

TABLE 2. Treatment Received After Developing Brain Metastasis

Treatment	Overall Cohort (N = 102)	Treated With Capecitabine and Lapatinib (n = 62)
Local therapy		
Surgical resection	9 (8.8)	5 (8.1)
SRS	4 (4)	2 (3.2)
WBRT	93 (91.2)	58 (93.5)
SRS plus WBRT	4 (4)	2 (3.2)
Targeted therapy		
Yes	97 (95)	62 (100)
No	5 (5)	—
Type of anti-HER2 therapies (in first line)		
Lapatinib	71 (69.6)	62 (100)
Trastuzumab	19 (18.6)	—
Lapatinib plus trastuzumab	3 (2.9)	—
TDM1	4 (3.9)	—
Type of anti-HER2 therapies (in second line)		
Lapatinib	15 (14.7)	7 (11.3)
Trastuzumab	15 (14.7)	11 (17.7)
Lapatinib plus trastuzumab	4 (3.9)	1 (1.6)
TDM1	12 (11.8)	8 (12.9)
Chemotherapy received		
Anthracycline	2 (2)	—
Taxanes	7 (6.9)	—
Capecitabine	69 (67.6)	62 (100)
None	17 (16.7)	—
No of lines of systemic therapies received (targeted and/or chemotherapy)		
One line	102 (100)	62 (100)
Two lines	52 (51.0)	32 (51.6)
Three lines	17 (16.7)	11 (17.7)

Abbreviations: HER2, human epidermal growth factor receptor 2; SRS, stereotactic radiosurgery; TDM1, trastuzumab emtansine; WBRT, whole-brain radiation therapy.

DISCUSSION

There has been an improvement in the outcomes of patients with HER2-positive metastatic breast cancer because of newer HER2-targeted agents, but the presence of brain metastases continues to be associated with poor prognosis. Our analysis of the real-world outcome in these patients suggests a substantial clinical benefit of multimodality treatment in some of them, with a 2-year OS of 25%. Notably, almost 15% of patients could receive three or more lines of HER2-targeted therapy after developing brain metastasis.

The majority of patients (80%) in our cohort had received at least one line of HER2-targeted therapy in a metastatic setting before the development of brain metastasis which suggests good compliance to standard practice guidelines. Our analysis showed that patients who received prior HER2-targeted therapy (predominantly trastuzumab) before diagnosis of brain metastases had a similar time to development of brain metastasis compared with those who did not receive any prior HER2-targeted therapy (19 months *v* 18 months). Some previous studies have suggested a longer time to development of brain metastases in patients with prior use of HER2-targeted therapy.[4] It is likely that this result is because of the heterogeneous timing of prior HER2-targeted therapy, ([neo]adjuvant, metastatic, or both), and the small numbers of patients (n = 20) who did not receive any prior HER2-targeted therapy, leading to an imprecise estimate. The lower use of HER2-targeted therapy in our population is due to high cost of drugs and lack of reimbursement facilities for all patients. Most (96.1%) of our patients had symptomatic brain metastasis because routine screening for brain metastasis was not done in the absence of clinical signs and symptoms of central nervous system involvement.[5-7]

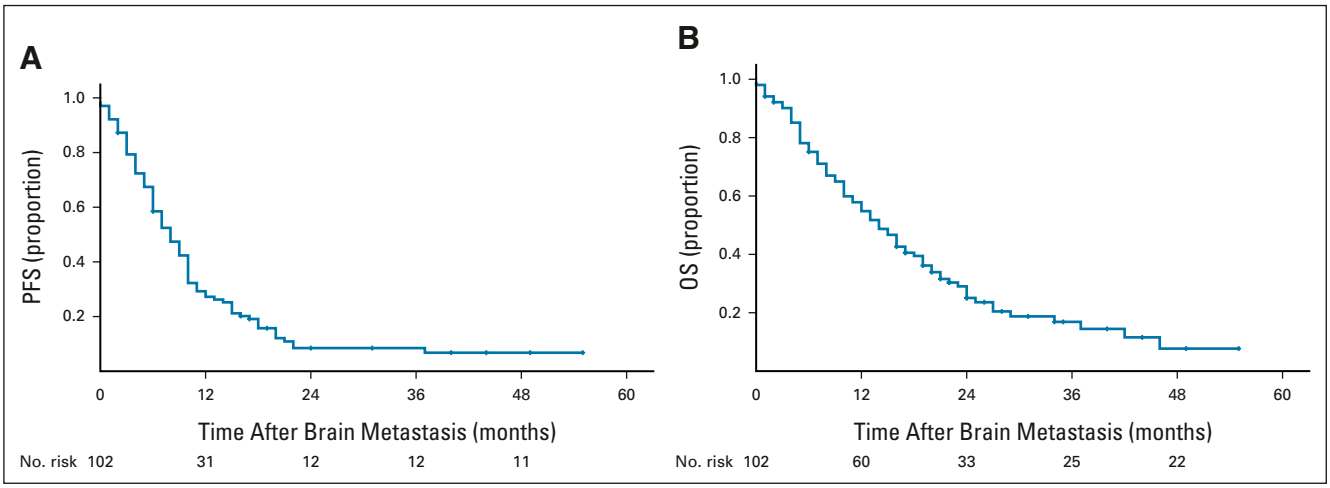

FIG 1. (A) PFS and (B) OS in study population. OS, overall survival; PFS, progression-free survival.

Most patients in our cohort received local therapy (WBRT or SRS or surgery or a combination thereof) as part of their treatment plan for brain metastasis, in compliance with standard guidelines. After development of brain metastasis, most of our patients (69.6%) received lapatinib-based therapy as the initial line of systemic therapy because of perceived higher penetration of BBB by lapatinib.[8-12] The majority of patients (77.4%) treated with lapatinib had previously received trastuzumab, and lapatinib was used in combination with capecitabine in 80% of those who received this drug.

The median PFS in patients who received lapatinib and capecitabine after local therapy was 9 months, which is higher than the previously published median PFS of 3.7-5.6 months.[9,12-16] The improved PFS in our cohort could be due to early initiation of systemic therapy within 1 week of completion of radiation therapy, and in some patients, lapatinib given concurrently with radiation therapy. There is preclinical evidence of synergism between lapatinib and radiotherapy, likely mediated by radiation-induced DNA damage and modulation of molecular pathways such as angiogenesis, cell cycle regulation, cell survival signaling, and cancer-host immune interaction.[17] Radiation-induced hypoxia is one of the most potent stimuli for the induction of VEGF via the phosphatidylinositol 3-kinase/Akt (protein kinase B) signal transduction pathway or the mitogen-activated protein kinase pathway. Lapatinib binds reversibly to the cytoplasmic domains of both epidermal growth factor receptor and HER2, which then blocks the activating signaling cascades in the mitogen-activated protein kinase and phosphatidylinositol 3-kinase pathways, leading to increased apoptosis.[18-24] The combination of lapatinib and radiotherapy administered concurrently has been evaluated in phase I studies and phase II RTOG 1119 study.[25,26] A promising result was seen in a small cohort of 40 patients, where patients who received SRS with lapatinib had better PFS compared with those who did not receive lapatinib.[27]

Trastuzumab has poor ability to cross BBB before the development of brain metastasis but attains a higher CSF concentration after the disruption of BBB either due to brain

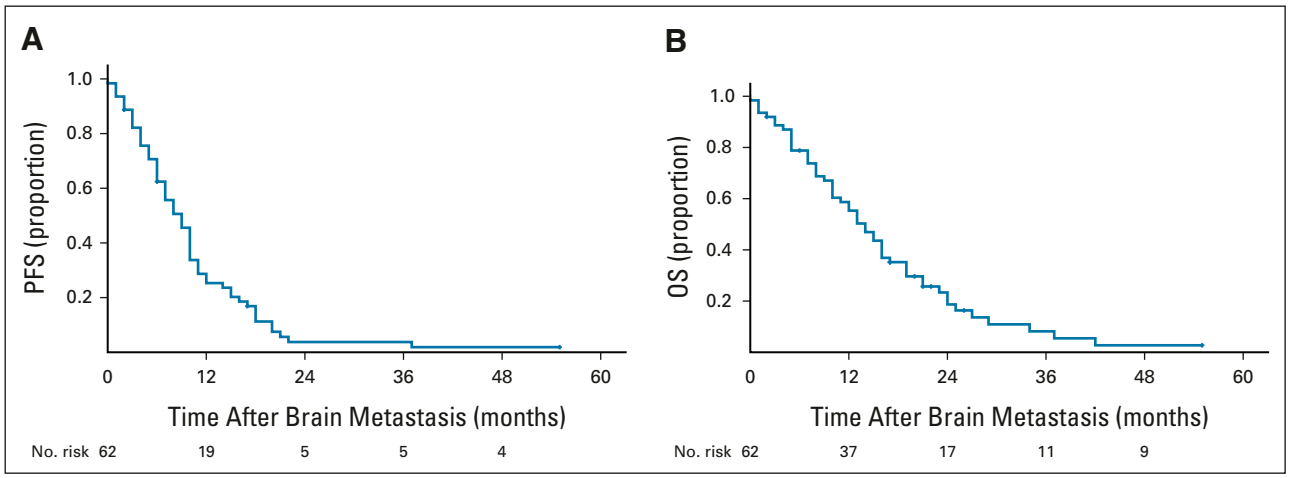

FIG 2. (A) PFS and (B) OS in patients receiving lapatinib and capecitabine after brain metastasis. OS, overall survival; PFS, progression-free survival.

metastasis itself or localized intervention.[28] In our study, 19 patients were given trastuzumab-based therapy after local therapy and achieved a PFS of 7 months and OS of 20 months, consistent with published literature.[29,30] Four of our patients received T-DM1 as first-line therapy after brain metastasis, on the basis of retrospective analysis of phase III EMILIA study. However, no patient showed symptoms of brain edema as reported in retrospective studies.[31,32] The highest PFS (22 months) was seen in a subgroup of patients who underwent surgery or SRS, followed by systemic therapy. Our results suggest that patients with HER2-positive tumors with brain metastasis have a better prognosis compared with other subtypes of breast cancer, and a more aggressive combined modality treatment approach could be considered. An interesting finding in our analysis is the considerable difference between median PFS (8 months) and OS (14 months), which suggests that continued treatment after first or subsequent progression could be therapeutically beneficial in patients with HER2-positive tumors and brain metastases.

The outcome of patients with leptomeningeal disease is dismal. Five of our patients with leptomeningeal involvement were treated with intrathecal trastuzumab and systemic HER2-targeted therapy with a median PFS of 8 months, which suggests that intrathecal trastuzumab is efficacious in this subgroup. However, because of the small number of patients, it is difficult to draw any definite conclusion.[33]

Although the median OS in our patients (14 months) is higher than historical controls without HER2-targeted therapy, and in line with other studies using HER2-targeted therapy, it is significantly shorter than recently reported survival in patients with brain metastasis with the use of newer HER2-targeted therapies.[34-38] This difference could be due to the heavily pretreated patient population in our cohort (60% patients received one line and 20% received two or more lines of HER2-targeted therapies before the diagnosis of brain metastasis), higher disease burden (50% patients had $>$ 5 lesions), and surgical resection in only a minority of patients (8.8%) compared with 28%-40% in other studies. It is also likely that the use of newer HER2-targeted therapies results in better outcomes compared with lapatinib and trastuzumab.

Our study also indirectly suggests the effect of availability of lower-cost biosimilar or generic versions of drugs on access. While only 32 patients (31.6%) of our cohort had received prior adjuvant HER2-targeted therapy, all managed to receive HER2-targeted therapy after the development of brain metastases. Biosimilars of trastuzumab and generic versions of lapatinib were progressively introduced in India by various pharmaceutical companies from 2015 onward, which led to lower prices of these drugs. Some patients who could not afford the innovator brand of trastuzumab in the adjuvant setting (the only version available then) could afford the biosimilar/generic versions of the drugs when they developed metastatic disease after a few years.

Our study has several strengths. There is a high precision in estimates of PFS (92 events in 102 patients) and OS (80 deaths in 102 patients) because a large proportion of patients have experienced events at the time of analysis. The results will likely inform patient management in many parts of the world where access to expensive HER2-targeted therapies is limited. Our study has some limitations, including its retrospective nature, inclusion of only those patients who received HER2-targeted therapy, and less precise ascertainment of response as part of routine clinical practice. Specifically, an analysis of the cohort of contemporaneous patients who did not receive any HER2-targeted therapy would have allowed some estimate of the benefit of these treatments in this patient population. We have not evaluated prognostic factors in our cohort because of the heterogeneous characteristics of included patients. The sample size is small, and the patient characteristics (number and kinds of prior therapies) and treatments for brain metastatic disease (both local and systemic) are heterogeneous. Thus, the results of the prognostic factor (univariable and multivariable) analyses may not be accurate, given the number of covariates that need to be controlled and limited power. Finally, quality of life or the effect of treatment on neurocognitive function was not assessed in our patient population. It is likely that future studies in patients with HER2-positive disease and central nervous system metastases will be prospective, and such patients will be systematically included in clinical trials, as was done in the HER2CLIMB trial, which has led to significant improvement in outcomes.[39,40]

In conclusion, there is good clinical efficacy of combined modality treatment, comprising radiotherapy, chemotherapy, and lapatinib or trastuzumab, in patients with breast cancer with brain metastases who have HER2-positive tumors. There may be clinical benefit by continuing treatment beyond the first disease progression in such patients. Intrathecal trastuzumab is a promising treatment in patients with leptomeningeal involvement.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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