ORIGINAL RESEARCH

Efficacy and Safety of Radiotherapy Combined with Pyrotinib in the Treatment of HER2-Positive Breast Cancer with Brain Metastases

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Purpose: To explore the efficacy and safety of pyrotinib combined with different radiotherapy modes in human epidermal growth factor receptor 2 (HER2)-positive breast cancer (BC) patients with brain metastasis (BM).

Patients and Methods: This study is a retrospective analysis of patients diagnosed with BM who underwent treatment with pyrotinib between November 2018 and April 2023. A total of 66 patients were administered radiotherapy in conjunction with pyrotinib (Group A), while 26 patients received pyrotinib as a standalone treatment (Group B). Within Group A, 18 patients underwent conventional fractionated radiotherapy (2Gy/F), while 48 patients received hyperfractionated radiotherapy (HFRT) (≥3Gy/F). The primary endpoints were intracranial progression-free survival (IC-PFS) and overall survival (OS). The secondary endpoints were objective response rate (ORR) and clinical benefit rate (CBR).

Results: The ORR of Group A was 54.5% (36/66), while the ORR of Group B was 34.6% (9/26) (P= 0.047). The CBR of Group A was 89.4% (59/66) and that of Group B was 69.2% (18/26) (P= 0.041). The IC-PFS between Group A and Group B were 12 months and 8 months, respectively (P< 0.001), and the OS were 20 months and 16 months, respectively (P= 0.065). In Group A, the IC-PFS and OS between the conventional fractionation radiotherapy group and the HFRT group were 10 months and 12 months, respectively (P= 0.001) and 16 months and 24 months, respectively (P< 0.001). No serious adverse reactions were observed in Group A and Group B.

Conclusion: For HER2-positive BC patients with BM, it is recommended to adopt the treatment mode of HFRT combined with pyrotinib, which can improve the local control and survival of patients.

Keywords: breast cancer, human epidermal growth factor receptor type 2, brain metastasis, pyrotinib, radiation therapy, hyperfractionated radiotherapy

Introduction

Breast cancer (BC) has become one of the most common malignant tumors in global and is the major cause of cancer-related death in women.[1] As a highly heterogeneous disease, BC has different prognoses with different molecular typing. Human epidermal growth factor receptor 2 (HER2)-positive BC accounts for 15%–20% of all BC, HER2-positive BC progresses faster, is prone to relapse and metastasis, and has shorter patient survival and poorer prognosis.[2,3] According to the latest data, the incidence of brain metastasis (BM) in BC is second only to non-small cell lung cancer, accounting for 10%–16% of primary tumors.[4,5] HER2 overexpression, hormone receptor negativity and multiple regional lymph node metastases are risk factors for BM, among which HER2 overexpression is the main risk factor. BM seriously affects the survival quality of patients and is one of the main causes of death in advanced BC patients. Studies have confirmed that 20% of BC patients die from BM.[6–8] Along with improvement of technology, the survival time of BC patients is

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gradually prolonged, but the incidence of BM also steadily increasing,[9,10] and poor treatment of BM is becoming the main reason of death in these patients.[11,12]

Brain radiotherapy is the most common and effective treatment for BM,[13] and radiation therapy is usually used for unresectable BM, which includes whole-brain radiotherapy (WBRT), stereotactic radiotherapy (SRS) and hyperfractio-nated radiotherapy (HFRT).[14] SRS such as gamma knife and X-knife, can be used for those with fewer metastases, while WBRT is preferred for patients with multiple BM.[15] WBRT can cause a certain degree of cognitive adverse effects, including somnolence, fatigue, memory and learning disabilities, which reduces the quality of life of the patients.[16] The results of SRS are not always satisfactory, especially in larger diameter BM. On the one hand, a single high-dose radiotherapy may increase the risk of acute and late central nervous system toxicities. On the other hand, there are limitations of tolerated doses in peripheral critical organs.[17] HFRT is a viable alternative to SRS and is increasingly becoming the treatment of choice for BM, which can not only provide high-dose radiation therapy to obtain good local intracranial control, but also minimize the occurrence of toxic side effects of the central nervous system.[18]

Systemic therapy has the advantage of controlling both intracranial and extracranial metastatic lesions as opposed to local therapy, and HER2-targeted therapy has been shown to be effective in patients with HER2-positive BM. Currently, available HER2-targeted drugs can be categorized into small-molecule tyrosine kinase inhibitors (TKIs), monoclonal antibodies, and antibody-drug conjugates (ADCs). The efficacy of monoclonal antibodies (such as trastuzumab and pertuzumab) on BM is not ideal.[19] The blood–brain barrier (BBB) provides considerable resistance to chemotherapeutic agents.[20] Compared with monoclonal antibodies and ADCs, TKIs are more advantageous in penetrating the BBB, and TKIs have shown good efficacy in HER2-positive BC, especially in BCBM.[21–24]

To date, four epidermal growth factor receptor (EGFR)-TKIs have been approved (namely lapatinib, pyrotinib, neratinib and tucatinib), all of which have shown promising efficacy in the treatment of patients with BM.[25] Pyrotinib, a small-molecule TKIs independently developed in China, is an irreversible and potent TKIs against HER1, HER2 and HER4. In patients with HER2-positive metastatic BC previously treated with trastuzumab, paclitaxel, and/or anthracy-clines, pyrotinib plus capecitabine increased mPFS by 5.7 months compared with lapatinib in combination with capecitabine (12.5 months vs 6.8 months, P < 0.001), according to the PHOEBE study.[26] PERMEATE, a single-arm, prospective, Phase II study showed that patients with BM that progressed after radiotherapy received pyrotinib combined with capecitabine, and the intracranial ORR was 42.1% and PFS was 5.6 months, while the intracranial ORR was 74.6% and PFS was 11.3 months in patients with BM that did not receive radiotherapy.[27] Pyrotinib has been proven to be an effective and safe drug for tumor treatment, disease control, and controllable adverse reactions.[28] Pyrotinib may offer physicians a new treatment option for patients with HER2-positive advanced BC especially those with BM. With the development of small molecule targeted agents, improvements in intracranial control may outweigh local treatments alone, including WBRT, SRS and surgery. Recently published data suggest that the addition of most types of targeted therapies is safe and does not increase radiotherapy toxicity.[29–31]

All of the above studies have shown the role of drugs and radiotherapy in HER2-positive BCBM, however, there are few data on the combination of radiotherapy and pyrotinib in the treatment of HER2-positive BCBM in the real world, and no study has shown which radiotherapy fractionation mode can achieve the best efficacy. The aim of this paper is to investigate the efficacy and safety of radiotherapy combined with pyrotinib and different modes of radiotherapy fractionation in patients with HER2-positive BCBM, in order to determine the best treatment mode for these patients.

Materials and Methods
Inclusion Criteria
1. Invasive BC with pathologically confirmed HER2-positive expression, defined as HER2 +++ on immunohistochemical staining and/or positive by fluorescence in situ hybridization; 2. BM confirmed by MRI or enhanced CT (patients with contraindications to MRI, at least one or more lesions and brain metastases ≥1cm); 3. Age ≥18 years and ≤80 years, female; 4. Estimated survival of not less than 2 months; 5. ECOG score 0–2; 6. Normal major organ function and no contraindication to treatment.

Exclusion Criteria

1. Patients with BM or other causes of cerebral hemorrhage confirmed by CT or MRI; 2. Patients with multiple factors affecting oral administration and absorption of drugs; 3. Patients with serious concomitant diseases; 4. Women who are pregnant or breastfeeding; 5. Uncompleted radiotherapy and lost to follow-up.

Clinical Data

We collected data of 92 patients with HER2-positive BCBM who were diagnosed with BCBM in the Department of Oncology of the First Affiliated Hospital of Bengbu Medical College from November 2018 to April 2023 and were treated with brain radiotherapy combined with pyrotinib or pyrotinib alone. Of these patients, 66 received radiotherapy combined with pyrotinib (group A) and 26 received pyrotinib alone (group B). In group A, 18 patients received conventional fractionated radiotherapy (2Gy/F, 36–60Gy/18-30F), and 48 patients received HFRT (≥3Gy/F, 30–60Gy/5-18F). The position of patients for radiotherapy was supine and fixed with thermoplastic cephaloplast. The radiotherapy equipment was 6MV-X-ray medical linear accelerator, and the planning system was Pinnacle system. Using CT simulation positioning machine or MRI positioning, and then target area outlining, GTV is defined as the imaging visible brain metastatic lesions, excluding the surrounding oedema area, the PTV for GTV three-dimensional outward 3mm generation and based on the anatomical barriers to modify the use of dose-volume histograms (DVH) to assess the target volume of the conformity, homogeneity, the amount of critical organs and critical organ volume. Each time the patient was positioned, it was ensured that the patient's positional fixation was consistent with that of the simulated positioning, and the error was within the permissible range, and the radiotherapy was performed under the guidance of cone-beam CT images. All patients received 1 cycle of pyrotinib in combination with capecitabine over 21 days, with the initial dose and local treatment (dose and mode of radiotherapy) selected by the physician based on the results of previous clinical trials and the patient's condition, and recorded in the electronic medical record.

Assessment of Baseline Clinical Characteristics

Patient information such as age, hormone receptor type, TNM stage, metastases at diagnosis, ECOG score, extracranial metastases, number of brain metastases, size of brain metastases, prior HER2-targeted therapy, and radiotherapy were collected from the electronic medical record system.

HER2 overexpression was defined as a HER2 3+ or positive FISH gene test. Estrogen receptor (ER) and progesterone receptor (PR) status were measured by IHC. A positive IHC result was defined as ER/PR ≥1%. Hormone receptor (HR) positive was defined as ER/PR positive, and HR negative was defined as ER and PR negative.

Assessment of Efficacy

Baseline examination of all measurable lesions was performed before treatment, and routine imaging examination and measurement were performed. According to RECIST v1.1, complete remission (CR) was defined as the disappearance of all target lesions, partial remission (PR) was defined as a ≥30% reduction in the total length diameter of baseline lesions, disease progression (PD) was defined as an increase in the total length diameter of baseline lesions by >20%, a minimum absolute increase of 5 mm, or the appearance of new lesions, and stable disease (SD) was defined as a reduction in the total length diameter of baseline lesions but not reaching PR or an increase but not reaching PD, objective remission rate (ORR) was defined as CR+PR, and clinical benefit rate (CBR) was defined as CR+PR+SD ≥6 months. Overall survival (OS) was defined as the time from initiation of pyrotinib to death. Intracranial progression-free survival (IC-PFS) was defined as the time from the initiation of pyrotinib to the first appearance of PD in an intracranial lesion. Adverse reactions were assessed according to CTCAE 5.0.

Follow Up

As of July 2023, there were 66 patients in group A, 54 patients achieved IC-PFS and 45 patients died of PD or other causes. There were 26 patients in group B, 25 patients achieved IC-PFS and 15 patients died of PD or other causes.

Statistical Analysis

Count data were expressed as cases (%), and comparisons between groups were made using the χ^2 test or Fisher's exact probability method, and survival analyses and confidence intervals were estimated using the Kaplan–Meier method. The moderating effect of covariates on OS was assessed by univariate and multivariate Cox proportional risk models. SPSS 27.0 was used to complete all statistical tests with a significance level of 0.05 for two-sided tests.

Results

Baseline Characteristics

Ninety-two patients with HER2-positive BM treated with pyrotinib-based therapy from November 2018 to April 2023 were included in this research. The baseline data of the patients are shown in Table 1, including 66 patients in the radiotherapy combined with pyrotinib group (group A) and 26 patients in the pyrotinib group (group B), which accounted for 71.7% and 28.3% of the overall proportion, respectively. The median age of the patients was 52 (27–79) years, 38 (41.3%) patients were hormone receptor positive, 64 (70%) patients with liver, bone or lung metastases, 7 (7.6%) patients had metastases in all three sites, 73 (79.3%) patients with ECOG scores of 0–1, and 19 (20.7%) patients with scores of 2. In terms of anti-HER2 treatment, 59 (64.1%) patients had received trastuzumab and 18 (19.6%) patients received trastuzumab combined with pertuzumab. We also divided the patients in group A into the conventional segmentation group (2Gy/F) and the HFRT group (≥3Gy/F) according to the different modes of radiotherapy segmentation. The data of the patients in the two groups are shown in Table 2.

Table 1 Patient Characteristics at Presentation

Characteristics		Radiotherapy +Pyrotinib (n=66)	Pyrotinib (n=26)	P
Age (year)	≤52	34 (51.5%)	15 (57.7%)	0.593
	>52	32 (48.5%)	11 (42.3%)	
HR status	HR negative	37 (56.1%)	17 (65.4%)	0.413
	HR positive	29 (43.9%)	9 (34.6%)	
T stage	T1	17 (25.8%)	3 (11.5%)	0.377
	T2	23 (34.8%)	12 (46.2%)	
	T3	22 (33.3%)	9 (34.6%)	
	T4	4 (6.1%)	2 (7.7%)	
N stage	N0	4 (6.1%)	1 (3.8%)	0.166
	N1	21 (31.8%)	4 (15.4%)	
	N2	17 (25.8%)	9 (34.6%)	
	N3	24 (36.4%)	12 (46.2%)	
ECOG	0	19 (28.8%)	6 (23.1%)	0.321
	1	36 (54.5%)	12 (46.2%)	
	2	11 (16.7%)	8 (30.8%)	
Metastatic sites	Lung	20 (30.3%)	11 (42.3%)	0.273
	Bone	30 (45.5%)	9 (34.6%)	0.343
	Hepatic	18 (27.3%)	9 (34.6%)	0.486
No. of brain metastatic	≤3	33 (50%)	11 (42.3%)	0.506
	>3	33 (50%)	15 (57.7%)	
Size of brain metastatic	≤2cm	24 (36.4%)	15 (57.7%)	0.062
	>2cm	42 (63.6%)	11 (42.3%)	
PriorHER2-targeted therapy	Trastuzumab	43 (65.2%)	16 (61.5%)	0.867
	Trastuzumab +Pertuzumab	12 (18.2%)	6 (23.1%)	
	Others	11 (16.6%)	4 (15.4%)	

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HR, Hormone-receptor.

Table 2 Clinical Data of Group A Patients

Characteristics		Conventional Segmentation (n=18)	HFRT (n=48)	P
Age (year)	≤52	8 (44.4%)	26 (54.2%)	0.482
	>52	10 (55.6%)	22 (45.8%)	
HR status	HR negative	9 (50.0%)	28 (58.3%)	0.544
	HR positive	9 (50.0%)	20 (41.7%)	
T stage	T1	3 (16.7%)	14 (29.2%)	0.040
	T2	3 (16.7%)	20 (41.7%)	
	T3	10 (55.6%)	12 (25.0%)	
	T4	2 (11.1%)	2 (4.2%)	
N stage	N0	1 (5.6%)	3 (6.3%)	0.553
	N1	5 (27.8%)	16 (33.3%)	
	N2	3(16.7%)	14 (29.2%)	
	N3	9 (50.0%)	15 (31.3%)	
ECOG	0	5 (27.8%)	14 (29.2%)	0.755
	1	9 (50.0%)	27 (56.3%)	
	2	4 (22.2%)	7 (14.6%)	
Metastatic sites	Lung	6 (33.3%)	14 (29.2%)	0.743
	Bone	10 (55.6%)	20 (41.7%)	0.313
	Hepatic	8 (44.4%)	10 (20.8%)	0.069
No. of brain metastatic	≤3	4 (22.2%)	30 (62.5%)	0.004
	>3	14 (77.8%)	18 (37.5%)	
Size of brain metastatic	≤2cm	7 (38.9%)	17 (35.4%)	0.794
	>2cm	11 (61.1%)	31 (64.6%)	
PriorHER2-targeted therapy	Trastuzumab	9 (50.0%)	34 (70.8%)	0.015
	Trastuzumab +Pertuzumab	2 (11.1%)	10 (20.8%)	
	Others	7 (38.9%)	4 (8.3%)	

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HR, Hormone-receptor.

Characteristics

With a median follow-up of 25 months, IC-PFS and OS were achieved in 79 (85.9%) and 60 (65.2%) patients. The overall IC-PFS was 11 months (9.993–12.007) (see Figure 1a), and the overall OS was 20 months (18.417–21.583) (see Figure 1b).

Differences in Survival Outcomes Between the A Group and B Group

Comparing IC-PFS and OS between group A and group B, The Log rank test showed that there was a statistically significant difference in IC-PFS (12 months vs 8 months, $P < 0.001$) (see Figure 1c) and OS (20 months vs 16 months, $P = 0.065$) (see Figure 1d) between the two groups. For HER2-positive BC patients with BM, the efficacy of radiotherapy combined with pyrotinib was better than that of pyrotinib alone in terms of IC-PFS and OS. The ORR of patients in group A was 54.5% (36/66), 7 patients reached CR and 29 patients reached PR. The ORR of patients in group B was 34.6% (9/26), no patient reached CR and 9 patients reached PR. The intracranial response rate in group A was higher than that in group B and was statistically significant ($P = 0.047$). The CBR of patients in group A was 89.4% (59/66), 27 patients reached SD, of which 23 patients had SD duration ≥6 months. The CBR of patients in group B was 69.2% (18/26), 14 patients reached SD, of which 9 patients had SD duration ≥6 months. The CBR of group A was higher than that of group B, and it was statistically significant ($P = 0.041$). More detailed information can be found in Table 3.

Differences in Survival Outcomes Between Conventional Fractionated Radiotherapy Group and HFRT Group

We also divided the patients in group A into the conventional segmentation group (2Gy/F) and the HFRT group (≥3Gy/F) according to the different modes of radiotherapy segmentation. A statistically significant difference was found between the two
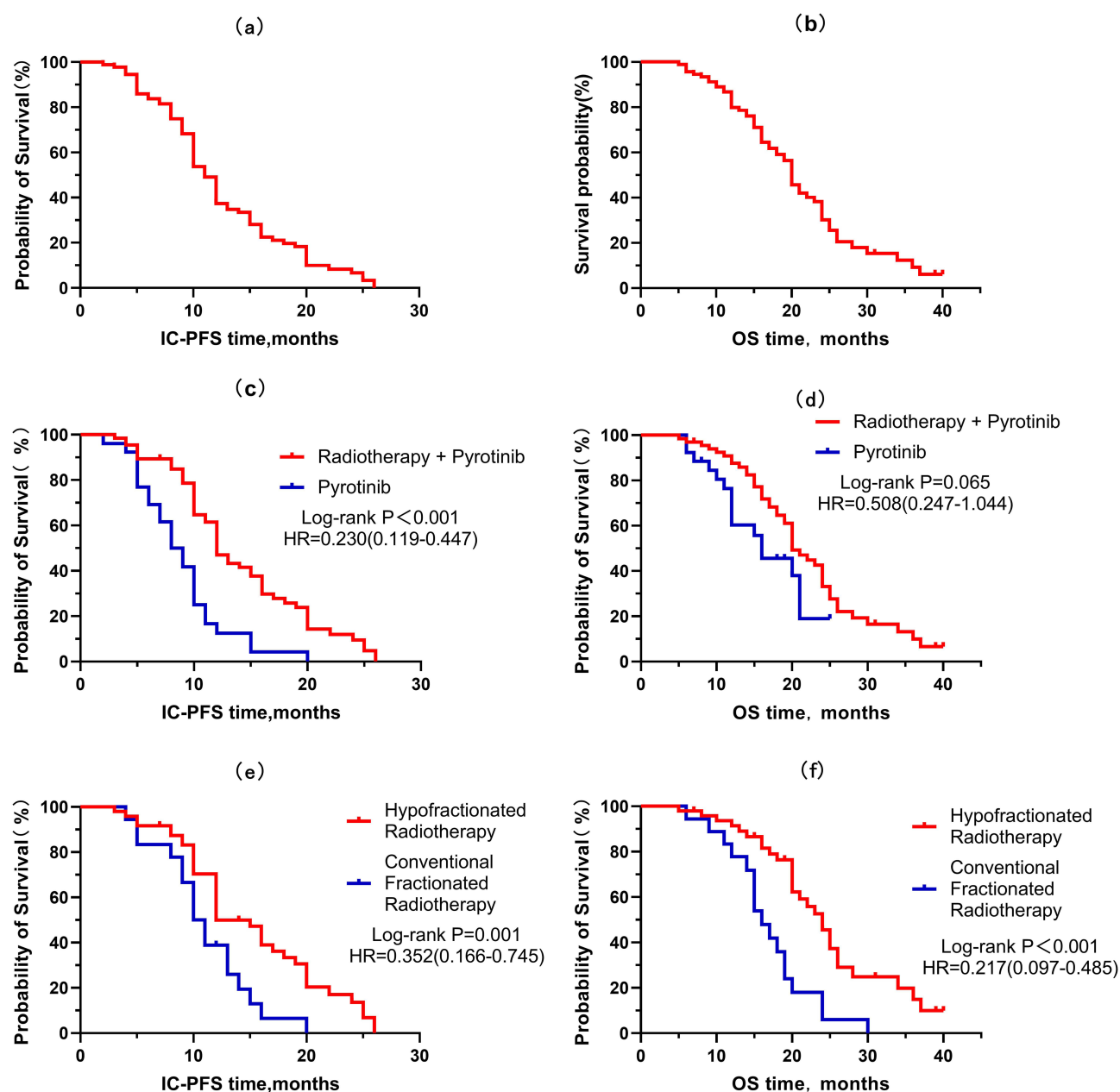
Figure 1 (**a**) IC-PFS of all patients; (**b**) OS of all patients; (**c**) IC-PFS curves of patients (Radiotherapy with Pyrotinib group and Pyrotinib group); (**d**) OS curves of patients (Radiotherapy with Pyrotinib group and Pyrotinib group); (**e**) IC-PFS curves of patients (Conventional Fractionated Radiotherapy group with Hypofractionated Radiotherapy group); (**f**) OS curves of patients (Conventional Fractionated Radiotherapy group with Hypofractionated Radiotherapy group).

groups by the Log rank test in terms of IC-PFS (10 months vs 12 months, P = 0.001) (see Figure 1e), and the difference in OS (16 months vs 24 months, P < 0.001) (see Figure 1f). The results showed that the patients with HFRT could get better local control and long-term prognosis compared with the patients with normal segmentation, the difference was statistically significant (P < 0.001). The results indicated that patients treated with HFRT could have better local control and long-term prognosis compared with normal segmentation.

Differences in Survival Outcomes Among Patients with Different Stratification Factors

Lung metastases occurred in 31 (33.7%) patients and 61 (66.3%) patients had no lung metastases, the Kaplan–Meier test showed a significant difference in OS between the two groups (19 months vs 21 months, P = 0.006) (see Figure 2a). Bone metastases occurred in 39 (42.4%) patients and 53 (57.6%) patients had no bone metastases, and the Kaplan–Meier test showed a significant

Table 3 Comparison of the Efficacy for the 2 Groups

Intracranial Outcome	Pyrotinib +Radiotherapy (n=66)	Pyrotinib (n=26)	P
CR	7 (10.6%)	0	
PR	29 (43.9%)	9 (34.6%)	
SD	27 (40.9%)	14 (53.8%)	
SD≥6 months	23 (34.9%)	9 (34.6%)	
PD	3 (4.5%)	3 (11.5%)	
ORR	54.5% (36/66)	34.6% (9/26)	0.047
CBR	89.4% (59/66)	69.2% (18/26)	0.041

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; CBR, clinical benefit rate.

difference in OS between the two groups (17 months vs 21 months, $P= 0.036$) (see Figure 2b). It suggested that the prognosis of patients with lung and bone metastases was significantly worse than that of patients without lung and bone metastases. In addition, the OS of patients with ≤3 BM was longer than that of patients with >3 BM (24 months vs 15 months, $P < 0.001$) (see
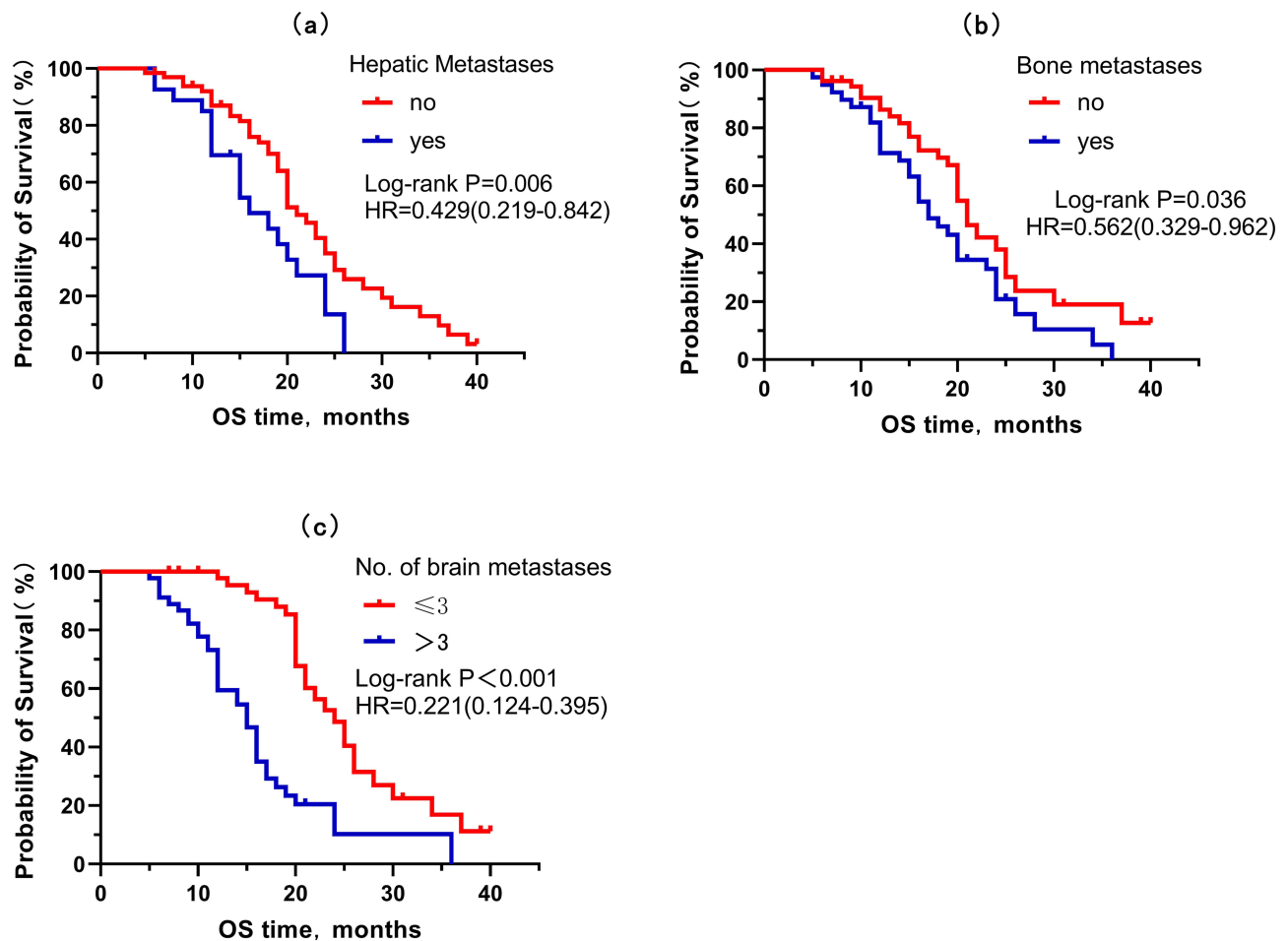

Figure 2 (**a**) Overall survival curves of patients (with and without hepatic metastases); (**b**) Overall survival curves of patients (with and without bone metastases); (**c**) Overall survival curves of patients (number of brain metastasis: ≤ 3 and>3).

). There was no statistically significant difference in the OS of patients with BM ≤2cm and >2cm in maximum diameter (20 months vs 20 months, P = 0.955).

Cox Regression Analysis of Influencing Factors for Patient OS

Univariate Cox regression analysis was used to study the correlation between clinical characteristics and OS in patients with BM from HER2-positive BC. Only T stage, ECOG score, lung, liver, bone metastases, number of BM and radiotherapy mode were found to be possible predictors of OS in patients. After incorporating multifactorial Cox regression analysis, we found that ECOG score, number of BM, and radiotherapy mode were independent prognostic factors for patients' OS (Table 4).

Toxic and Side Effects

No critical untoward reactions, for example, cognitive dysfunction, were observed in patients in both groups. The most usual untoward reaction was diarrhea in both groups A and B (87.9% vs 76.9%). Grade 3 or higher adverse reactions were observed in 39.4% of patients in group A (26/66) and 34.6% of patients in group B (9/26). There were no treatment-related deaths in either group A or group B. Specific safety data are shown in Table 5.

Table 4 Analysis of the Correlation Between Clinical Factors and Overall Survival

Characteristics		Univariate Analysis		Multivariate Analysis	
		HR (95% CI)	P	HR (95% CI)	P
Age (year)	≤52	1	0.750		
	>52	0.919 (0.549–1.541)			
HR status	HR negative	1	0.525		
	HR positive	1.179 (0.709–1.961)			
T stage	T1	1	<0.001	1	0.247
	T2	0.915 (0.463–1.806)		0.580 (0.274–1.229)	
	T3	3.724 (1.767–7.848)		1.348 (0.520–3.494)	
	T4	2.637 (0.926–7.513)		1.018 (0.327–3.171)	
N stage	N0	1	0.278		
	N1	1.788 (0.523–6.113)			
	N2	1.977 (0.561–6.962)			
	N3	2.766 (0.819–9.345)			
ECOG	0	1	<0.001	1	<0.001
	1	3.123 (1.526–6.390)		2.115 (0.935–4.782)	
	2	26.967 (10.353–70.244)		12.127 (3.939–37.334)	
Metastatic sites	Lung	2.085 (1.204–3.612)	0.009	1.782 (0.981–3.236)	0.058
	Bone	1.696 (1.014–2.836)	0.044	1.519 (0.827–2.788)	0.178
	Hepatic	1.863 (1.061–3.272)	0.03	1.260 (0.673–2.357)	0.470
No. of brain metastatic	≤3	1	<0.001	1	0.025
	>3	3.803 (2.203–6.565)		2.355 (1.115–4.971)	
Size of brain metastatic	≤2cm	1	0.957		
	>2cm	1.014 (0.607–1.696)			
PriorHER2-targeted therapy	Trastuzumab	1	0.425		
	Trastuzumab+Pertuzumab	0.679 (0.366–1.258)			
	Others	0.617 (0.234–1.629)			
Radiotherapy mode	No	1	0.001	1	0.024
	Conventional segmentation	1.181 (0.585–2.385)		0.677 (0.311–1.475)	
	HFRT	0.406 (0.208–0.794)		0.347 (0.159–0.760)	

Abbreviations: HR, hazard ratio; CI, confidence interval; HR, Hormone-receptor; ECOG, Eastern Cooperative Oncology Group; No, No radiation therapy.

Table 5 Treatment-Related Adverse Reactions in the 2 Groups

Adverse Reactions	Pyrotinib+Radiotherapy, n (%)		Pyrotinib, n (%)	
	All Grades	≥3	All Grades	≥3
Cognitive dysfunction	0	0	0	0
Diarrhea	58 (87.9)	16 (24.2)	20 (76.9)	5 (19.2)
Nausea	30 (45.5)	5 (7.6)	12 (46.2)	1 (3.8)
Anemia and Vomiting	26 (39.4)	0	11 (42.3)	0
Hand-foot syndrome	16 (24.2)	2 (3.0)	6 (23.1)	1 (3.8)
Fatigue	13 (19.7)	0	4 (15.4)	0
Dizziness	10 (15.2)	0	4 (15.4)	0
Rash	5 (7.6)	0	1 (3.8)	0
ALT/AST increased	19 (28.8)	0	9 (34.6)	0
Neutrophils decreased	15 (22.7)	3 (4.5)	10 (38.5)	2 (7.7)
Platelet decreased	9 (13.7)	0	5 (19.2)	0

Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase.

Discussion

BCBM seriously threatens the life of BC patients. In recent years, the diagnosis and treatment of BC patients have made great progress, but the prognosis of patients with BM is still poor, these patients lack active and effective treatment.[32] Relatively little research has been done on the treatment of BCBM, and most patients with BCBM have been excluded from clinical trials of new drugs.[5] Local therapy combined with anti-HER2 systemic therapy is currently recommended for these patients, but the optimal modality remains unclear.[33] Therefore, more studies are needed to explore how to improve the survival of these patients. This study included 92 patients with HER2-positive BCBM and aimed to determine the best treatment for this group of patients and prolong the survival of patients with HER2-positive BCBM.

The BBB prevents chemotherapeutic drugs and targeted drugs, for instance, trastuzumab and pertuzumab from entering the central nervous system (CNS), so these drugs have limited effect on BM,[34] Compared to monoclonal antibodies, the physical properties of small-molecule TKIs allow them to cross the BBB, thereby increasing the concentration of the drug in CNS, suggesting that TKIs may be a reasonable therapeutic route for the treatment of CNS metastases.[35] In the PHENIX trial, capecitabine combined with pyrotinib increased mPFS by 7.0 months (11.1 months vs 4.1 months, $P < 0.001$) and ORR (68.6% vs 16.0%, $P < 0.001$) compared with capecitabine alone in patients with HER2-positive metastatic BC, as well as longer PFS in patients with BM (6.9 months vs 4.2 months, $P = 0.011$), suggesting that patients with BM could benefit from pyrotinib treatment.[36] In another retrospective study, patients in the pyrotinib group had better mPFS than those in the lapatinib group (6.5 months vs 3.5 months, $P < 0.05$).[37] The remission rate of brain symptoms with pyrotinib treatment is as high as 100%, which significantly improves the quality of life of patients.[38] Therefore, any drug for BM must have the permeability of BBB. Recently, a new scheme for the treatment of BCBM is to use a nano-sized drug delivery system, which brings a new treatment scheme for such patients.[39]

Radiotherapy is a routine option for local control of BM. Earlier studies have indicated that radiotherapy can improve the permeability of BBB and improve the efficacy of drugs,[40] Concurrent pyrotinib treatment enhances radiotherapy sensitivity.[41] Local control rates for BM treated with pyrotinib and radiotherapy were higher than those for BM not treated with radiotherapy, and remission of cranial symptoms treated with considering the patient's willingness for treatment, patients were selected for treatment with pyrotinib or radiotherapy combined with pyrotinib regimen. In this study, intracranial ORR in group B was 34.6%, which was lower than cohort A (74.6%) of the PERMEATE study, which may be due to the fact that most of the patients enrolled in this study had metastases from multiple sites. For the different treatment regimens, the intracranial ORR in cohort A was 54.5%, whereas the intracranial ORR in cohort B was 34.6%, which was significantly different between the two groups ($P = 0.047$), and the CBR in cohort A (89.4%) was significantly higher than that in cohort B (69.2%), which was statistically significant ($P = 0.041$). The study demonstrated that radiotherapy in combination with pyrotinib could affect the patients' intracranial ORR and was significantly superior to that of pyrotinib alone. In addition, there are some preclinical molecular targets that can improve the efficacy of

radiotherapy and the treatment of BCBM, novel pathways under investigation include targeting long non-coding RNAs or transcription factors that may drive BC metastasis to the brain and reduce treatment efficacy.[42] Through the study of these new pathways and transfer factors, therapeutic effects can be better improved in the future.

In the PERMEATE trial, the median IC-PFS of patients with BM treated with pyrotinib combined with capecitabine was 5.6 to 11.3 months.[27] In this study, the median IC-PFS of patients in group B was 8 months, which was basically consistent with the results of previous studies, and patients in group A received radiotherapy combined with pyrotinib, and their median IC-PFS was 12 months, which was higher than that of earlier studies,[43] IC-PFS was statistically different between the two groups (P < 0.001). Research by Chen et al[30] 79 patients with BM from HER2-positive BC were included, 35 patients in group A received pyrotinib in combination with radiotherapy, and 44 patients in group B were treated with pyrotinib or at an interval of greater than 3 months from radiotherapy to the brain, and the results of the study showed that IC-PFS was better in group A than in group B (15.0 months vs 6.0 months, P = 0.056). Consistent with the results of this research, the addition of radiotherapy prolonged IC-PFS in patients, and radiotherapy combined with pyrotinib treatment had better local efficacy than pyrotinib alone, but this was a retrospective study, and future large-sample prospective randomised controlled trials are needed to better understand the efficacy of radiotherapy combined with pyrotinib.

Similar to previous studies,[30] compared with pyrotinib alone, radiotherapy combined with pyrotinib did not significantly improve the OS of the patients, in this study the median OS of group A and B was (20 months vs 16 months, P = 0.065). The OS of group A was better than that of group B, but not statistically significant, which may be due to the small sample size in this study.

Previous studies have shown that single SRS is not always feasible, especially in BM of larger diameters and/or located in the vicinity of critical structures, and that single high-dose radiotherapy is not only limited by the maximum tolerated dose to the surrounding organs at risk (such as brain stem or optic nerve, etc.), but also increases the risk of acute and late CNS side effects.[17] HFRT is mostly used in this situation to maintain a high rate of intracranial control while reducing radiation-induced CNS toxicity. A study by Fokas et al showed that[44] HFRT can be used for BM with large diameters and/or in the vicinity of key structures, and there is no significant difference between HFRT and SRS in terms of median survival and local progression-free survival. HFRT has low central nervous system toxicity and is an effective and safe treatment. In the study of patients with BM from lung cancer, the large split-mode radiotherapy has a short duration, saves medical resources and does not increase the incidence of adverse effects and has a high safety profile.[45] In this study, we divided group A into conventional segmentation group (2Gy/F) and hypofractionated radiotherapy group (≥3Gy/F) according to different radiotherapy segmentation modes, and the IC-PFS (10 months vs 12 months, P = 0.001) and OS (16 months vs 24 months, P < 0.001) between the two groups, and the results showed that patients treated with hypofractionated radiotherapy had a better local control rate and long-term prognosis.

In this research, we investigated the prognosis of patients with HER2-positive BCBM by Cox regression analysis. The results showed that T stage, ECOG score, lung, liver, bone metastases, number of BM, and radiotherapy mode were possible predictors of OS in patients. This is in agreement with Hackshaw[46] Ma et al.[31] After multifactorial Cox regression analysis, we found that ECOG score, number of BM, and radiotherapy mode were independent prognostic factors for OS in patients. In a study from the SEER database (n = 206913), the incidence of BM was higher in patients with multiple extracranial metastases (bone, liver, and lung) than in patients with bone metastases alone (28.0% vs 8.6%), suggesting that visceral metastases are a risk factor for BM.[47] Some studies have identified several potential biomarkers associated with BCBM, and their quantitative analysis may be a reliable indicator for evaluating the rationality of MRI imaging in BC patients with asymptomatic BM.[48] Brain MRI screening is only recommended when a patient has symptoms of suspected intracranial metastases, and the chances of early treatment of BM will be greater if closer brain monitoring can be performed when the patient has high-risk factors like visceral metastases.[27]

Showing no difference with earlier issued data,[31,36] The security analysis of this research showed that the most usual untoward reaction was diarrhea. No critical untoward reaction was observed in either group, suggesting that the overall safety tolerability of pyrotinib for BM was acceptable, the safety of radiotherapy combined with pyrotinib was manageable, and the addition of radiotherapy did not significantly increase side effects in patients.

The major strengths of this research are that it is the first to investigate the prognostic impact of different radiotherapy segmentation modalities in patients with HER2-positive BCBM, and it further explores the availability and security of radiotherapy combined with pyrotinib versus pyrotinib therapy alone in a realistic study. However, this was a retrospective study with a small sample size, and there were some biases and confounders in the results (eg, the study did not control for the modality of radiotherapy, such as HFRT, HFRT+WBRT, WBRT), and these confounders may have impacted patient survival. In the next, larger randomised controlled trials are needed for determining the optimal treatment modality for BCBM.

Conclusion

Based on these results, the treatment modality of HFRT combined with pyrotinib is recommended for patients with HER2-positive BCBM, which can improve the local control and survival of patients.

Data Sharing Statement

The data supporting the results in the manuscript can be obtained from the corresponding author based on reasonable request.

Ethics Approval and Consent to Participate

This retrospective study approved by the Institutional Review Board of The First Affiliated Hospital of Bengbu Medical College (approval number: 2023YJS152). Given that this study was conducted relying on retrospective data collected as part of routine clinical practice, ethical committee waived the consent, and individual informed consent was not obtained. In this retrospective study, no patient identifiers were used and data were anonymized. This study followed the Declaration of Helsinki (2013 revision)

Disclosure

The authors report no conflicts of interest in this work.

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