Original Research

Pyrotinib combining with radiotherapy on breast cancer with brain metastasis

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Impact statement

Prognosis of HER2-positive BCBM is improved though the treatment of active BM remains super difficult in clinic. In current investigations, 29 patients who had active BM in HER2-positive BC were enrolled. The PFS, OS, CBR, and so forth were analyzed among patients undergoing WBRT. We discovered that WBRT combined with pyrotinib is safe and effective for the treatments of active BM in HER2-positive BC. WBRT combined with sequence pyrotinib + capecitabine is more effective and less toxic than concurrent treatment. The combination mode of radiotherapy and targeted therapy are independent risk factors for active BM prognosis.

Abstract

With the extensive application of anti-human epidermal growth factor receptor-2 (HER2) targeted therapy, the prognosis of HER2-positive breast cancer brain metastasis (BCBM) has been improved greatly. Due to the lack of prospective randomized controlled studies; however, the treatment of active brain metastasis (BM) remains a difficulty in clinic. Based upon the retrospective studies, an effective approach of radiotherapy combined with pyrotinib in HER2-positive BCBM treatment was investigated in present research. In all, 29 patients who had active BM in HER2-positive breast cancer (BC) and underwent whole-brain radiotherapy (WBRT) combined with pyrotinib from January 2019 to May 2021 were enrolled. The progression-free survival (PFS), overall survival (OS), clinical benefit rate (CBR), objective response rate (ORR), and drug-related adverse events (AEs) were analyzed among patients undergoing WBRT combined with concurrent or sequence pyrotinib + capecitabine. After the systematic treatments using WBRT combined with pyrotinib + capecitabine, the mPFS and mOS of BM patients were 6.5 months and 15.5 months, respectively. PFS (7.2 *vs* 6.2 months, $p = 0.038$) and OS (19.0 *vs* 14.0 months, $p = 0.014$) were longer after sequence treatments than those after concurrent treatment. The central nervous system (CNS) ORR of sequence treatment was superior to that of concurrent treatment (80.4% *vs* 58.6%, $p < 0.05$). Vomiting (17.2%) and diarrhea (10.3%) were the most common adverse reactions ⩾ grade 3. WBRT combined with pyrotinib is safe and effective for the treatments of active BM in HER2-positive BC. WBRT combined with sequence pyrotinib + capecitabine is more effective and less toxic than concurrent treatment. Therefore, sequence treatment is potentially a preferred regimen for patients with active BM in HER2-positive BC. The size and number of BM lesions, presence or absence of hepatic metastasis, and combination mode of radiotherapy and targeted therapy are independent risk factors for active BM prognosis.

Keywords: Breast cancer, pyrotinib, trastuzumab, human epidermal growth factor receptor-2 (HER2), whole-brain radiotherapy (WBRT), brain metastasis

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Introduction

Recently, breast cancer (BC) patients have had a gradually extended survival period with the improvement in diagnosis/treatment technology and the evolution of drugs, but the incidence rate of brain metastasis (BM) has also risen steadily.[1,2] Following lung cancer, BC has become one of the malignancies that most prone to BM.[3] BM will ultimately occur in 30% of BC according to statistics, up to 50% of which is in human epidermal growth factor receptor-2 (HER2)-positive BC.[4] In addition, central nervous system (CNS) progression causes nearly half of deaths in patients with HER2-positive advanced BC.[5] Therefore, the treatment of HER2-positive BC remains a great challenge in clinics, which is a research hotspot and interesting field.[6]

No standard therapeutic regimen has been determined for BCBM, and local (surgery, whole-brain, and/or stereotactic radiotherapy) and systemic therapies are currently adopted.[7–9] Characterized by a small molecular weight, strong ability to penetrate through the blood-brain barrier (BBB) and definite anti-intracerebral tumor activity, tyrosine kinase inhibitors (TKIs) have been favored highly in the

systematic BM treatments.[10,11] As shown in the LANDSCAPE study,[12] the response rate of lapatinib combined with capecitabine is 66% in the BM treatments, and the median time to progression (TTP) is 5.5 months. In contrast, NALA study[13] proved that after treatment with neratinib + capecitabine, the progression-free survival (PFS) is superior, and the BM incidence rate becomes significantly lower (22% *vs* 29.2%, hazard ratio [HR] = 0.6, 95% confidence interval [CI] = 0.6~1.01). In the HER2CLIMB study,[14] the PFS and overall survival (OS) of BM patients are prolonged to be 9.9 months and 18.1 months, respectively, by tucatinib combination therapies. Moreover, pyrotinib is a new type of TKI independently developed by China, which has exhibited good efficacy on BM. According to the PHENIX study,[15] pyrotinib combined with capecitabine improves greatly the PFS of BM patients comparing with capecitabine alone (6.9 months vs 4.2 months, $p = 0.011$). As the first study to achieve significant efficacy for treating active brain metastases, PEMEATE data showcased that pyrotinib achieved 74.6% objective response rate (ORR) with 11.3 month mPFS.[16] In a retrospective study, the median PFS (mPFS) of BM patients in the pyrotinib group is better than that in the lapatinib group (6.5 months *vs* 3.5 months; $p < 0.05$).[17]

The intracranial disease control rate of TKIs is seemingly higher than that of traditional anti-HER2 monoclonal antibodies, but the timing and mode of radiotherapy for BM has been in dispute.[18] Little data can be found on anti-HER2 targeted therapy combined with radiotherapy (whole-brain radiotherapy (WBRT), stereotactic body radiotherapy (SBRT) or stereotactic radiosurgery (SRS)) for BM, and there are especially rare reports on active BM. To understand the efficacy and safety of pyrotinib combined with radiotherapy in the active BM treatments, and to explore the optimal therapeutic strategy for patients, we conducted for the first time a case-control study on pyrotinib combined with WBRT for active BM treatments in HER2-positive BC.

Materials and methods

Study population and data collection

In this multi-center retrospective case-control study that conducted in the Affiliated Tumor Hospital of Xinjiang Medical University, Affiliated Chinese Medicine Hospital of Xinjiang Medical University, Bazhou People's Hospital, Hami Cancer Hospital, Yili Friendship Hospital and People's Hospital of Aksu, 29 patients who had active BM in HER2-positive BC from January 1, 2019 to May 31, 2021 were enrolled. In all, 15 cases underwent WBRT combined with concurrent pyrotinib + capecitabine, while 14 cases underwent WBRT combined with sequence pyrotinib + capecitabine. The follow-ups ended on March 31, 2022. Ethics committee in The 3rd Affiliated Teaching Hospital of XinJiang Medical University (Affiliated Tumor Hospital) approved this study (approval no. (2018)

Inclusion criteria. (1) Patients pathologically diagnosed with HER2-positive BC and measurable CNS metastasis (one or more brain parenchymal lesions with the longest diameter ⩾ 10 mm), and without any CNS treatments (WBRT, SRS, surgery, systemic or combination therapy); (2) those with an Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) score ⩽ 2; (3) those with an expected survival period ⩾ 3 months; and (4) those with normal heart, lung, liver, and kidney functions and normal blood routine before treatments, and no contraindication to treatment.

Exclusion criteria. (1) Pregnant or lactating women, (2) patients who used to undergo pyrotinib treatment, (3) those who previously underwent CNS treatments (WBRT, SRS, surgery, systemic or combination therapy), or (4) those with loss of treatment information or receiving < 2 cycles of pyrotinib treatment.

Treatment and dose adjustment

All patients underwent the pyrotinib + capecitabine systemic therapy for 21 d as one period. The initial dose and the dose for local treatment such as radiotherapy (Table 1) were selected by physicians based on previous clinical test results, general health status and patients' preferences, which were recorded in the electronic medical records. Written informed consents were obtained from all patients.

Assessment criteria

The primary endpoints were PFS and OS defined as the duration from the start of pyrotinib administration to the progression of disease confirmed by computed tomography/magnetic resonance imaging (CT/MRI) scan or to the death from any cause or the last follow-up, respectively. The secondary endpoints included ORR, clinical benefit rate (CBR) and safety. ORR refers to the proportion of complete response (CR) and partial response (PR) cases, i.e. ORR = CR + PR. CBR refers to the proportions of CR, PR and stable disease (SD) cases, i.e. CBR = CR + PR + SD. The severity of adverse reactions (grade 0-4) was determined in accordance with the National Cancer Institute-Common Terminology Criteria for Adverse Events version 4.0 (NCI-CTC v4.0).

Statistical methods

In accordance with NCCN and CSCO diagnosis and BC treatment guidelines, the combination of targeted and mono-chemotherapy is generally adopted in the second- and later-line systemic treatment of HER2-positive advanced BC, and capecitabine is the preferred chemotherapy drug. However, there is no standard for local treatment of BM yet, and WBRT, SRS or surgery as well as simple systemic treatment rather than the combination with local treatment can be selected. According to NCCN guidelines, WBRT is the first choice for local treatment of patients with active BM, and the standard dose is D = 30 Gy/10 f.[19] Due to the limitation of hospital equipment and technical conditions, SRS is not carried out in most regions. In current study, based upon the patients' willingness for treatment and compliance, 29 patients that enrolled underwent WBRT combined with concurrent pyrotinib + capecitabine ($n = 15$, 51.7%) and WBRT combined with sequence pyrotinib + capecitabine ($n = 14$, 48.2%). Categorical variables were compared between the two groups by Pearson's χ^2 test or Fisher's

Table 1. Patient characteristics at presentation with active brain metastasis.

Characteristics	WBRT concurrent pyrotinib ($n=15$)	WBRT sequence pyrotinib ($n=14$)
Age, median (range, year)	57 (36–66)	55 (40–67)
HR status		
HR negative	8 (53%)	6 (43%)
HR positive	7 (47%)	8 (57%)
ECOG performance status		
0	3 (20%)	5 (36%)
1	9 (60%)	6 (43%)
2	3 (20%)	3 (21%)
Metastatic sites		
Brain	15 (100%)	14 (100%)
Lymph nodes	12 (80%)	8 (57%)
Lung	10 (67%)	6 (43%)
Hepatic	10 (67%)	7 (50%)
Bone	8 (53%)	9 (64%)
Pleura	2 (13%)	0
Local recurrence	1 (7%)	2 (14%)
No. of brain metastatic		
⩽3	7 (47%)	7 (50%)
>3	8 (53%)	7 (50%)
Size of brain metastatic		
⩽2 cm	9 (60%)	10 (71%)
>2 cm	6 (40%)	4 (29%)
PriorHER2-targeted therapy		
Trastuzumab	13 (87%)	14 (100%)
Lapatinib	4 (27%)	3 (21%)
T-DM1	0	1 (7%)
Pertuzumab	5 (33%)	4 (29%)

WBRT: whole-brain radiotherapy; ECOG: Eastern Cooperative Oncology Group; HR: hormone receptor; T-DM1: trastuzumab emtansine.

exact test. Abnormally distributed continuous variables were compared by nonparametric Mann–Whitney U test, and Kaplan-Meier estimates of OS were compared using log-rank test. The median survival time and 95% CI were estimated. The regulatory effect of covariates on OS was assessed through univariate and multivariate Cox proportional hazards models. SPSS was employed for statistical analysis. The clinical characteristics of patients were subjected to descriptive statistics. $p<0.05$ was considered as statistically significant. Survival analysis and visualization were performed by R (version 4.0.4; https://www.r-project.org/).

Results

Baseline characteristics

WBRT combined with concurrent or sequence pyrotinib + capecitabine was conducted on 29 patients with active (symptomatic) BM that enrolled from January 1, 2019 to May 31, 2021, and the patients' baseline data are shown in Table 1. The median age was 55 (36–67) years old, and 15 cases (51.7%) were positive for hormone receptor. BM complicated with metastasis at other sites was found in 27 cases (93.1%), and 19 cases (65.5%) had ⩾3 metastatic sites. In terms of anti-HER2 targeted therapy, 27 patients (93.1%) were treated with trastuzumab, 7 patients (24.1%) were treated with lapatinib, and 9 patients (31.1%) were treated with pertuzumab, 1 (3.4%) of whom received T-DM1 treatment. In all, 15 patients (51.7%) underwent WBRT combined with concurrent pyrotinib + capecitabine, while 14 patients (48.2%) received WBRT combined with sequence pyrotinib + capecitabine.

Treatment management

The dosage of WBRT was D = 30 Gy/10 f for all patients in accordance with the NCCN guidelines. In the systemic therapy, 21 cases (72.4%) underwent the pyrotinib treatment with a standard dose of 400 mg/d initially, and the dose was reduced in 8 cases (27.6%). The dose was reduced in 15 cases throughout the treatment, especially in concurrent treatment group, where the dose was reduced to 240 mg in more than 50% cases ($n=8$) and to 160 mg in 1 case. In sequence treatment group, 57.1% cases ($n=8$) received the maximum tolerated dose, and the dose was basically 320 mg even if reduced (Figure 1).

Outcomes

Characteristics. The median follow-up period was 16.5 months, and 29 (100%) and 24 (82.8%) cases reached PFS and OS, respectively. The overall mPFS was 6.5 (5.975–7.025) months (Figure 2A), and the overall median OS (mOS) was 15.5 (13.503–17.497) months (Figure 2B).

Differences in survival outcomes between the two groups. In current study, 29 patients with active (symptomatic) BM underwent WBRT combined with concurrent pyrotinib + capecitabine ($n=15$, 51.7%, concurrent treatment group) and WBRT combined with sequence pyrotinib + capecitabine ($n=14$, 48.2%, sequence treatment group). The PFS and OS were compared between sequence treatment group and concurrent treatment group. It was found by log-rank test that PFS (7.2 *vs* 6.2 months, $p=0.038$) and OS (19.0 *vs* 14.0 months, $p=0.014$) had statistically significant differences between the two groups (Figure 3A). The treatment of active BM, WBRT combined with sequence pyrotinib + capecitabine is superior to concurrent treatment in PFS and OS.

Differences in survival outcomes among patients with different stratification factors. Hepatic metastasis occurred in 17 cases (56.8%), while the remaining 12 cases (43.2%) had no hepatic metastasis, and Kaplan-Meier test indicated a significant difference regarding OS between the two groups (14.5 *vs* 19.0 months, $p=0.005$), telling us that the prognosis of patients with hepatic metastasis is significantly worse than that of patients without hepatic metastasis. In addition, patients with ⩽3 BM lesions had longer OS than those with more than >3 BM lesions (19.0 *vs* 13.5 months, $p=0.001$). The OS had no statistically significant difference between patients with the longest BM lesion diameter ⩽2 cm and those with the longest BM lesion diameter >2 cm (19.0 *vs* 13.5 months, $p=0.095$) (Figure 3).

Cox regression analysis of influencing factors for patient OS. The association between clinicopathological characteristics and OS of BM patients was explored by Kaplan-Meier and univariate Cox regression analysis. The data revealed that

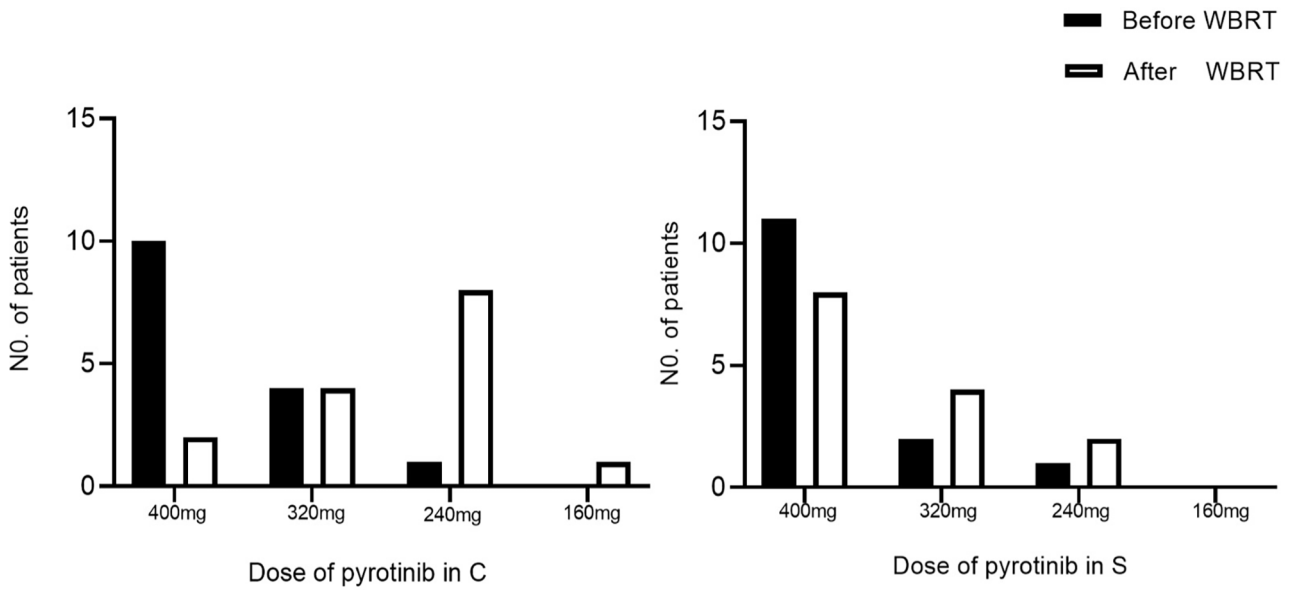

Figure 1. Dosages of systemic therapy before and after radiotherapy between two groups.

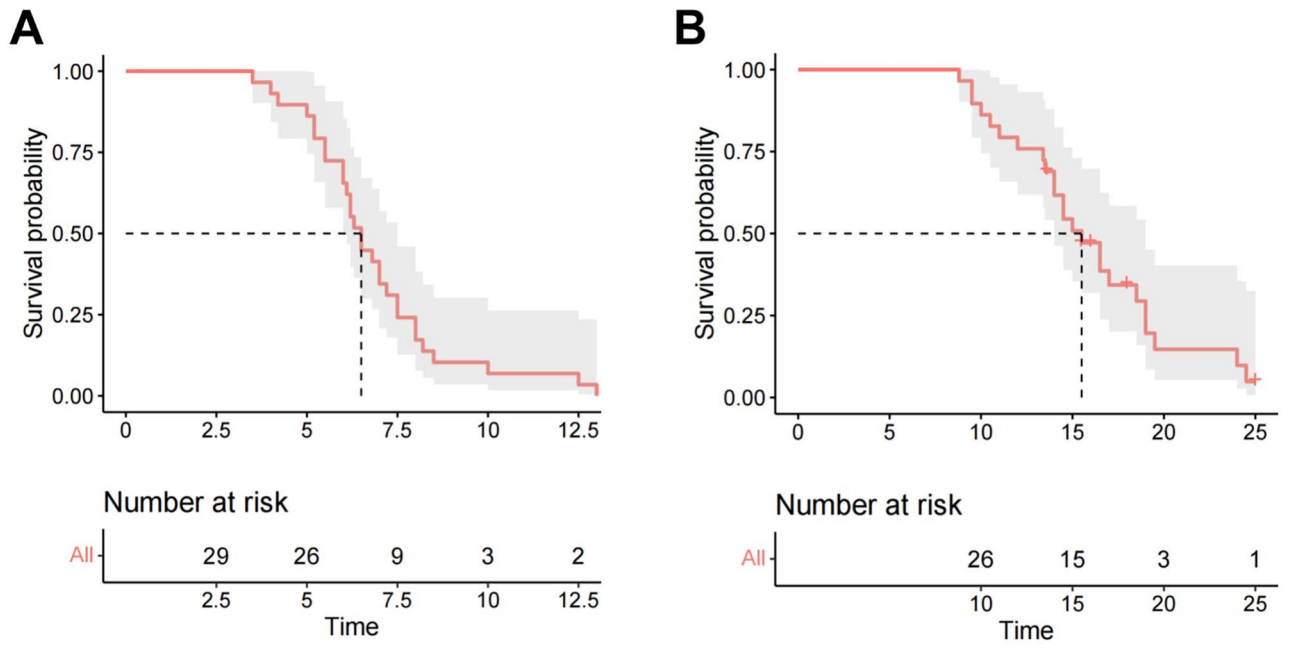

Figure 2. Progression-free survival and overall survival in patients with active BM at baseline. (A) Progression-free survival of all patients. (B) Overall survival of all patients.

only the size and number of BM lesions, presence or absence of hepatic metastasis and treatment mode were possible predictive indexes for the OS of active BM patients. After clinicopathological indexes were incorporated into multivariate Cox analysis, we found that the BM lesion size and number, presence or absence of hepatic metastasis and treatment mode were independent prognostic factors regarding the OS of active BM patients (Figure 4).

Totally, there were 109 measurable BM lesions among the 29 patients, and the administration data were summarized. We discovered that overall ORR of intracranial lesions was 69.7%. As for different therapeutic regimens, the intracranial ORR of WBRT combined with concurrent pyrotinib + capecitabine was 58.6%, while intracranial ORR of WBRT combined with sequence pyrotinib + capecitabine was 80.4%. The results of Pearson's χ^2 test showcased that there was a statistically significant difference regarding the ORR of intracranial lesions between two groups ($p = 0.014$) (Table 2; Figure 5).

Toxic and side effects

All patients' adverse events (AEs) with all grades were recorded. Diarrhea, nausea and vomiting were the most

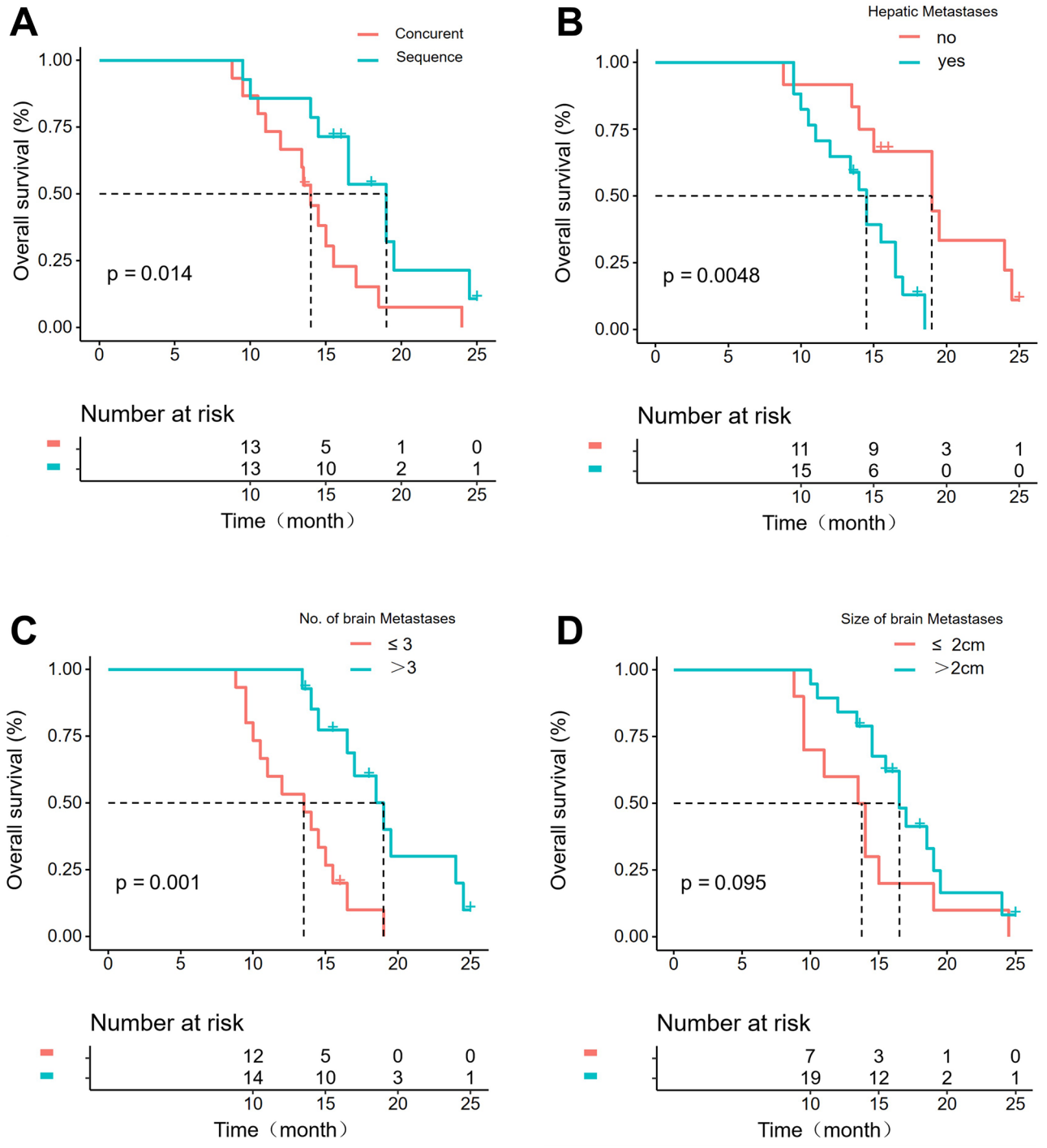

Figure 3. Survival curve in patients with BM at baseline. (A) Overall survival curves of patients with active BM (WBRT Concurrent Pyrotinib group and WBRT Sequence Pyrotinib). (B) Overall survival curves of patients with active BM (with and without hepatic metastases). (C) Overall survival curves of patients with active BM (number of brain metastasis: ⩽3 and >3). (D) Overall survival curves of patients with active BM (Size of brain metastasis: ⩽2 cm and >2 cm).

common AEs. Diarrhea occurred in 20 cases (68.9%), including 3 cases (10.3%) ⩾ grade 3. Nausea and vomiting occurred in 24 cases (82.7%), including 5 cases (17.2%) ⩾ grade 3. AEs ⩾ grade 3 also included 3 cases of neutropenia (10.3%), 2 cases of leukopenia (6.9%), 2 cases of hand-foot syndrome (6.9%), 2 cases of fatigue (6.9%), and 1 case for each of thrombocytopenia, anemia, neurotoxicity and weight loss (1.6%) (Table 3).

There were 14 cases (93.3%) of nausea and vomiting in concurrent treatment group, including 4 cases (26.7%) with diarrhea ⩾ grade 3. There were 10 cases (71.4%) of nausea and vomiting in sequence treatment group, including 1 case (7.1%) of diarrhea ⩾ grade 3. According to the Fisher's exact probability test, the incidence rate of nausea and vomiting was different between the two groups, *i.e.* it was higher in concurrent treatment group ($p < 0.001$).

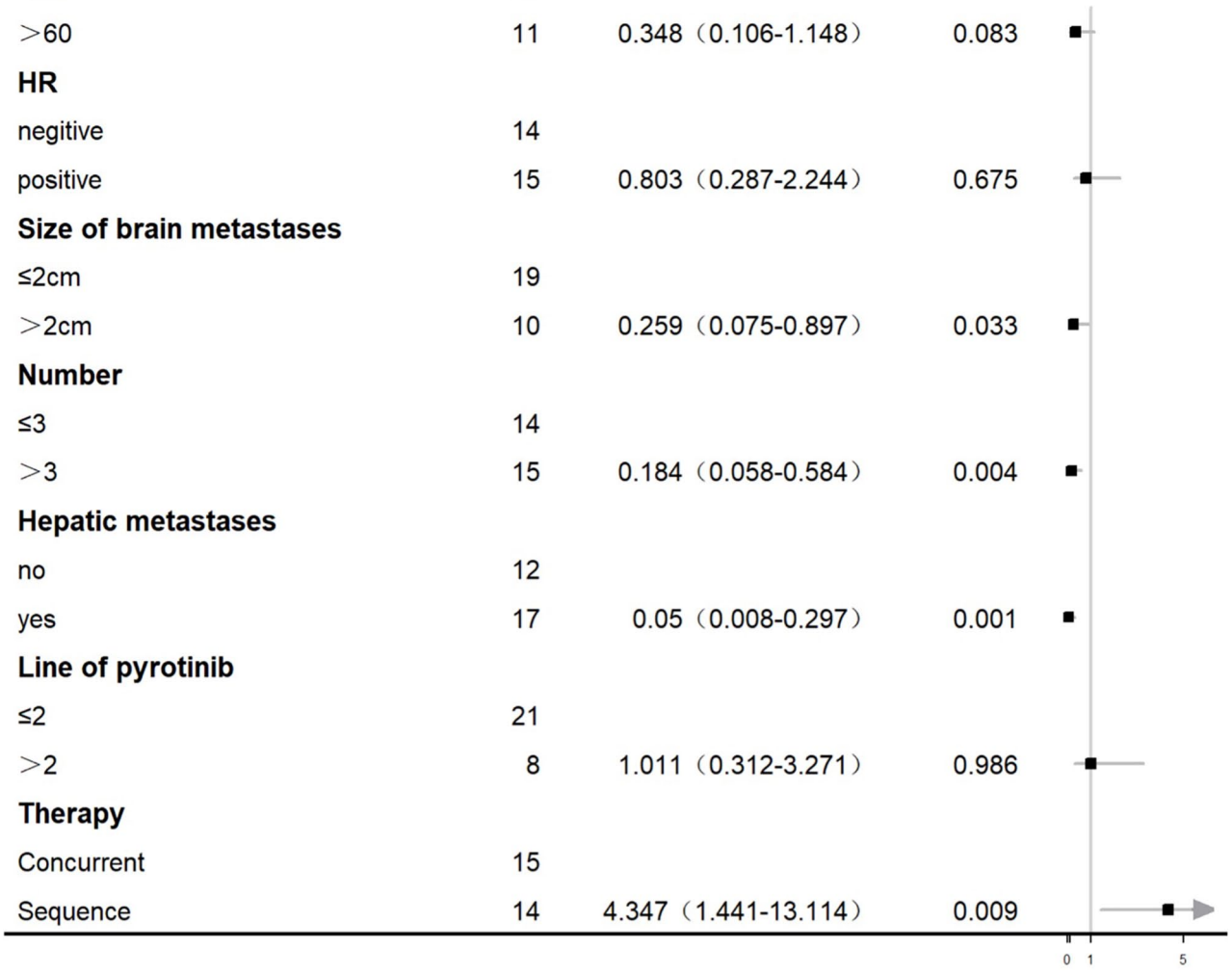

Figure 4. Multivariate Cox regression forest map.

Table 2. Individual lesion objective response rates.

Characteristic	All lesions	WBRT concurrent pyrotinib	WBRT sequence pyrotinib
Number of lesions	109	58	51
Objective response	76 (69.7%)	34 (58.6%)	41 (80.4%)
Complete response	29 (26.6%)	12 (20.7%)	17 (33.3)
Partial response	47 (43.1%)	22 (37.9%)	24 (47.1%)
Stable disease	26 (23.9%)	18 (31.1%)	7 (13.7%)
Progressive disease	7 (6.4%)	6 (10.3%)	3 (5.9%)

WBRT: whole-brain radiotherapy.

Discussion

BM is one main reason of mortality for HER2-positive advanced BC patients, and local treatment combined with anti-HER2 systemic treatment is recommended for it though the optimal combination and mode remain inconclusive.[20] The optimal management of BM is still a clinical problem that urgently to be solved.[21] Despite a hot research topic, there are few prospective studies specifically assessing the active BM treatments. Majority BM patients, especially active (symptomatic) BM, are excluded from clinical trials.[22] The number of clinical trials on BCBM is less than 1% of that on BC, and the results related to primary endpoints were published in only 22% of these trials. No positive results were obtained in most of the trials, so there are surprisingly few trials that published.[23] Multiple factors lead to small number of trials on BCBM. For example, BM is associated with a poor prognosis, so the enrollment of BCBM patients is limited to avoid influencing the outcomes of trials. In addition, the BBB is a great challenge since it cannot be effectively penetrated by most treatment drugs.[24] Although data upon T-DXd for BM have been recently published, an mPFS of 15.0 m in the DESTINY-Breast03 study Cortés *et al.*[25] and an optimal overall intracranial response rate of 73.3% in Tuxedo-1 study Bartsch *et al.*[26] for active BM were satisfied. However, the

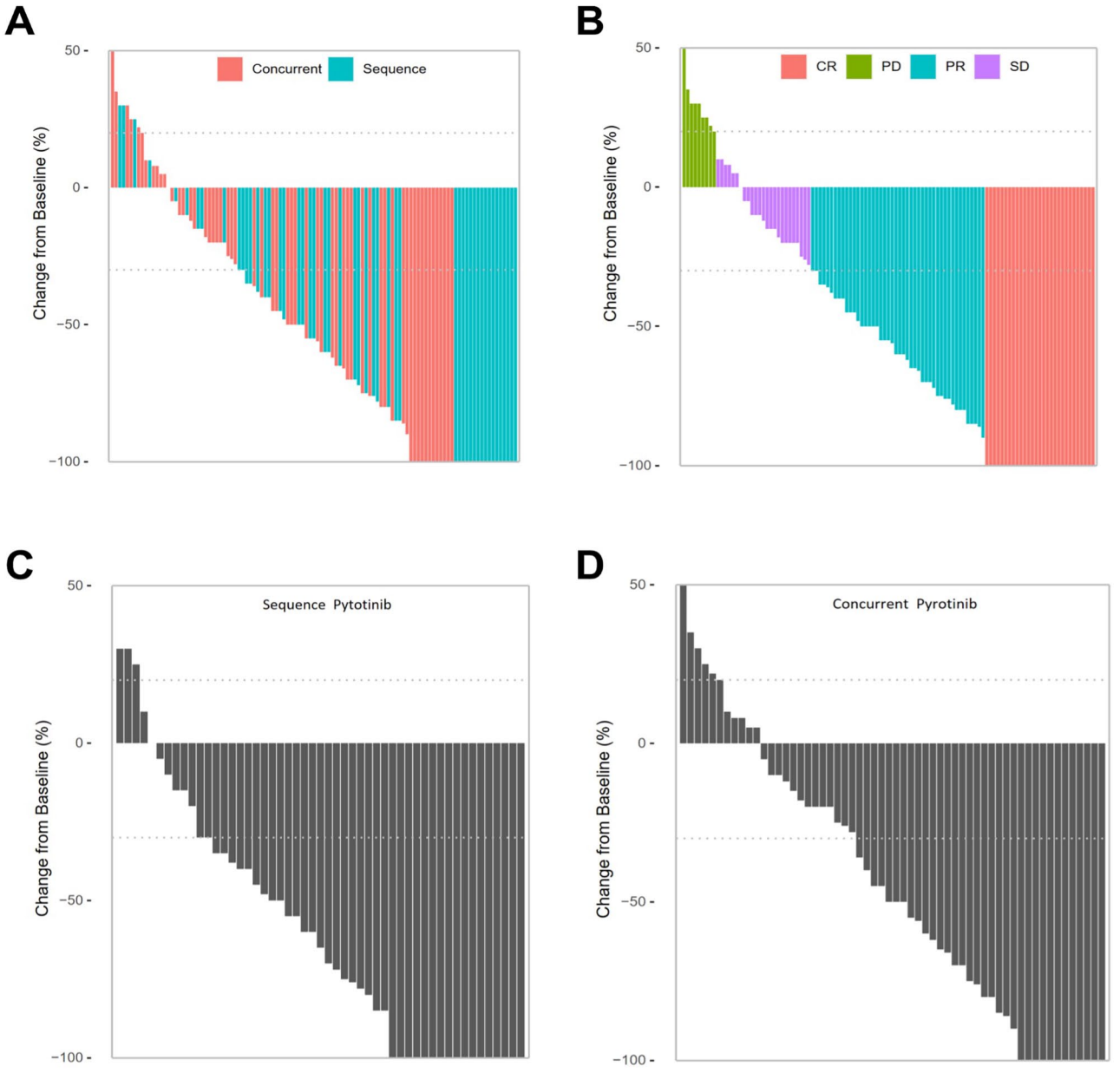

Figure 5. Waterfall plots depicting best objective response among the 109 treated lesions. (A) Best objective response stratified by therapy (red = concurrent pyrotinib, blue = sequence pyrotinib). (B) Best objective response stratified by overall response after full radiographic follow-up (red = complete response, blue = partial response, purple = stable disease, green = progressive disease). (C) Best objective response among 109 lesions treated with WBRT + sequence pyrotinib. (D) Best objective response among 109 lesions treated with WBRT + concurrent pyrotinib.

high cost and lack of listing in China mainland have made it out of reach for majority of patients.

TKIs characterized by a small molecular weight and easy penetration through the BBB have displayed good prospects in BM treatments.[16,27] However, patients with active BM have been enrolled so far only in HER2CLIMB, which is a large-scale randomized controlled trial. Trastuzumab and capecitabine combined with tucatinib improved the response rate of intracranial lesions (from 20.0% to 47.3%), CNS PFS (from 4.1 months to 9.5 months; $p < 0.001$), and OS (from 11.6 months to 20.7 months; $p = 0.004$) of 174 patients with active BM.[28] The clinical activity of pyrotinib for active BM treatments has also been verified by the single arm PERMEATE study.[29] In new brain metastases, ORR of pyrotinib was 74.6%, and mPFS was 11.3 months. This provides strong basis for further study of pyrotinib regarding BM treatment. Unfortunately, the effect and timing of radiotherapy (WBRT) combined with TKIs in active BM treatment were not involved in above studies.

There are no standard treatment approaches for BCBM. From previous studies regarding small molecule combined with radiotherapy for active brain metastasis treatments, TKI combined with radiotherapy could improve the treatment efficacy. While it was not clear whether there is a difference between the synchronous and the sequence. In this paper, the first case-control study on WBRT combined with pyrotinib in the treatment of active BM in HER2-positive BC was conducted. In this paper, the first case-control study on WBRT combined with pyrotinib in the treatment of active

Table 3. Adverse events in the modified intention-to-treat population.

Adverse event	Concurrent pyrotinib ($n=15$)		Sequence pyrotinib ($n=14$)	
	Any grade	Grade ⩾ 3	Any grade	Grade ⩾ 3
Diarrhea	10	1	10	2
Neutropenia	7	2	6	1
Hand-foot syndrome	4	1	5	1
Leukopenia	4	1	5	0
Anemia	5	1	4	0
Thrombocytopenia	4	0	4	0
Nausea and vomiting	14	4	10	1
Fatigue	5	1	4	1
ALT/AST increased	3	0	4	0
Rash	1	0	2	0
Neurotoxicity	4	0	3	0
Weight loss	8	1	6	0
Hypertension	2	0	1	0
Dyspnea	2	0	0	0
Gait disturbance	1	0	0	0
Memory impairment	2	0	2	0
Dizziness	3	1	2	0

ALT: alanine aminotransferase; AST: aspartate aminotransferase.

BM in HER2-positive BC was conducted. In regard to the selection of pyrotinib synchronous or sequence WBRT regimens, patient's willingness to the treatment and the cooperation should be taken into considerations. The overall ORR of intracranial lesions was 69.7% among the 29 patients with active BM (totally 109 measurable BM lesions), which was lower than that in Cohort A of PERMEATE study (74.6%). As for different therapeutic regimens, the intracranial ORR of WBRT combined with concurrent pyrotinib + capecitabine was 58.6%, while that of WBRT combined with sequence pyrotinib + capecitabine was 80.4%. The results derived from Pearson's χ^2 test showcased that there was a statistically significant difference between the two groups ($p=0.014$). It indicated that the combination of pyrotinib and WBRT affects the objective response rate of patient intracranial lesions, and sequence WBRT is superior to concurrent pyrotinib therapy.

In terms of long-term efficacy, PFS (6.2 *vs* 7.2 months, $p=0.038$) and OS (14.0 *versus* 19.0 months, $p=0.014$) had statistically significant differences between concurrent treatment group and sequence treatment group, indicating that WBRT combined with sequence pyrotinib + capecitabine has better efficacy on active BM than WBRT combined with concurrent pyrotinib + capecitabine. The possible reasons are as follows: (a) significant side effects such as nausea, vomiting and diarrhea are caused by pyrotinib + capecitabine, and cranial radiotherapy also leads to nausea and vomiting as reported. Such side effects were worsened by concurrent treatment, so that the dose of pyrotinib was reduced in most patients in concurrent treatment group. Specifically, its dose was reduced to 240 mg in more than 50% cases ($n=8$), but only in 7.1% cases ($n=1$) in sequence treatment group. According to the phase I clinical study of pyrotinib, the overall response rate (87.5%) is higher and the mPFS (59.4 weeks) is longer in 400 mg group compared with other low-dose groups.[30] (b) It is reported that the BBB is more open to BM lesions at 2–4 weeks after cranial radiotherapy, and this is exactly the best opportunity for systemic therapy.[31] In sequence treatment group, the full-dose systemic therapy began in such an "optimal time window," ensuring the efficacy. (c) The use of steroid hormones was enhanced in concurrent treatment group due to more significant nausea, vomiting and headache. As a result, the activity of drugs metabolized by the CYP3A4 pathway is inevitably affected.[32] The metabolism of pyrotinib *in vivo* is primarily catalyzed by CYP3A4,[33] so the drug concentration in patients without receiving the full-dose systemic therapy was further reduced in concurrent treatment group, thus affecting the efficacy. The above results have evidence from other tumors: Patients with BM in epidermal growth factor receptor (EGFR-mutant) nonsmall-cell lung cancer (NSCLC) have the longest OS after EGFR-TKI sequence therapy following radiotherapy.[34] Mastorakos *et al.*[35] proved that the targeted therapy started 1 week after radiotherapy has the optimal efficacy on BM in malignant melanoma. Certainly, we noticed that in present study, even in the sequence treatment group, the PFS was lower than that in the PERMEATE study A cohort (7.2 Vs. 11.3 months). However, it should be noted that there was no control group in the PERMEATE study. And the study included more patients with no or unmeasurable peripheral lesions (54.2%), that is, more patients with pure brain metastases or only peripheral bone metastases were included. Our study accounted for only 13.8% of the population. Therefore, we believe that this study proposes a combination therapy for patients with HER2-positive active BM. While since the sample size was too small, specific effects and underlying mechanisms of different combinations of pyrotinib and WBRT demanded furthermore studies.

In this study, the prognosis of active BM was explored through multivariate Cox regression analysis incorporating all clinicopathological indexes of patients. The results illustrated that the size and number of BM lesions were OS-related factors in BM, which was consistent with the report in Hackshaw *et al.*[36] Moreover, presence or absence of hepatic metastasis and combination mode of radiotherapy and targeted therapy were revealed to be independent risk factors for BM prognosis.

Being consistent with the results from previous clinical trials,[15,16] diarrhea and vomiting were the most common grade 3~4 adverse reactions in present study. What is noteworthy is that there were more severe gastrointestinal reactions in concurrent treatment group than sequence treatment group. Specifically, there were 14 cases (93.3%) of nausea and vomiting in concurrent treatment group, including 4 cases (26.7%) of diarrhea ⩾ grade 3. There were 10 cases (71.4%) of nausea and vomiting in sequence treatment group, including 1 case (7.1%) of diarrhea ⩾ grade 3. According to Fisher's exact probability test, the incidence rate of nausea and vomiting had a statistically significant difference between the two groups ($p<0.001$). As mentioned above, the patients in concurrent treatment group had poor tolerance, the dose of pyrotinib was reduced to 240 mg in most patients, and steroid hormones were used significantly more in concurrent treatment group. Although all AEs were effectively controlled by treatment, the safety and efficacy of drugs are directly affected by the changes in plasma concentration or metabolic behaviors due to symptomatic drug interactions.[37] In present

study, more severe gastrointestinal reactions were avoided, and the full-dose systemic therapy was realized by WBRT combined with sequence pyrotinib + capecitabine thereby guaranteeing the efficacy. The AEs associated with radiotherapy-induced cognitive impairment in current study were all graded 1–2 and there were no differences between the two groups. The possible reason was that patients that enrolled were relatively young, with only 5 (17.2%) elderly patients being more than 60 years old. With the developments of new anti-HER2 targeted therapies such like antibody-drug conjugates and small molecule TKIs, new treatment options are offered for BM patients. The method and timing of radiotherapy intervention has become controversial. On one hand, combined radiotherapy might exacerbate the toxic and side effects such as cognitive impairments. On the other hand, we would like to improve the efficacy of BM treatment as much as possible. Studies have demonstrated that small molecule TKIs have synergistic effects with radiotherapy,[38] which are good radiosensitizers.[39] In the real-world treatment paradigm, majority of BM patients are treated by WBRT.[40] We need to conduct more research to target treatment according to different patient subgroups. Current study provides an indispensable reference with respect to optimal strategies for applicable BM management.

This study had some limits. First, as a retrospective study rather than a prospective study, current study had selection and information biases.[41] Second, the sample size was moderate, so the findings remain to be verified by large-sample clinical studies. Third, pertuzumab and T-DM1 were less used by patients enrolled due to cost or accessibility.

Despite all the deficiencies, this is the first study regarding radiotherapy combined with pyrotinib in the active BM treatments, which was a tough issue in clinics. The outputs provide important references for future studies on radiotherapy combined with other TKIs or targeted therapy in the BCBM treatment.

Conclusions

The treatment of BM is to avoid or delay the progression of neurological disorders, prolong the survival period as far as possible, and keep the patients' quality of life.[42] In present study, both short-term efficacy (ORR) and long-term efficacy (FPS and OS) of WBRT + sequence pyrotinib were superior to those of WBRT + concurrent pyrotinib. After the sequence treatment, the survival time of patients is extended and the toxic reactions are reduced, so the patients are more likely to have a higher quality of life. The size and number of BM lesions, presence or absence of hepatic metastasis, and combination mode of radiotherapy and targeted therapy are independent risk factors for the active BM prognosis. While more studies are needed to better explore the risk factors and prognosis-improving therapeutic methods for BM.

AUTHORS' CONTRIBUTIONS

All authors participated in the design, interpretation of the studies and analysis of the data and review of the manuscript; X.P.M., Y.L., Z.H.Z., L.L., and B.Z. conducted the experiments, C.Y.G. supplied critical reagents, X.P.M., Y.L., Z.H.Z., L.L., C.Y.G., D.L., B.Y.L., and B.Z. wrote the manuscript.

DECLARATION OF CONFLICTING INTERESTS

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