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Original Article

Whole-brain radiotherapy and chemotherapy in the treatment of patients with breast cancer and brain metastases

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Abstract: Objective: This paper aims to explore the effects of whole-brain radiotherapy (WBRT) and chemotherapy on patients with breast cancer and brain metastases (BCBM) and on their quality of life (QOL). Methods: Fifty-eight patients with BCBM were recruited as the study cohort and randomly divided into a control group and a study group. The patients in the control group underwent WBRT. Their radiotherapy scheme was as follows: the fractionation was 2.0 Gy/time, and the total dosage was 60 Gy, 5 times/week for 6 weeks. The patients in the study group underwent WBRT plus chemotherapy. Their radiotherapy scheme was the same as the control group's. Their chemotherapy scheme was as follows: carboplatin (0.3 g/m^2) was intravenously injected every day, and the injection was repeated once four weeks later. After the treatment, the patients' adverse reactions were compared between the two groups. Their Karnofsky Performance Status (KPS) scores were also compared to analyze the effects of WBRT plus chemotherapy and radiotherapy alone on the patients' survival statuses. Results: After the treatment, the adverse reactions were not significantly different in the two groups (P>0.05). The objective remission rate in the study group was 79.31%, which was higher than the 34.48% rate in the control group (P=0.001). According to the KPS scores, the QOL of the patients in the study group was significantly improved after the treatment, and the difference was statistically significant compared with the QOL in the control group (P<0.001). The overall survival and the progression-free survival in the study group were longer than they were in the control group (both P<0.01). Conclusion: Compared with WBRT alone, WBRT plus chemotherapy is safe and markedly effective in treating patients with BCBM, and it can improve their QOL and prolong their survival times. Therefore, this combined treatment is worthy of clinical application and further research.

Keywords: Breast cancer and brain metastases, whole-brain radiotherapy, chemotherapy, prognosis, quality of life

Introduction

Among women, breast cancer is the most common malignant tumor prone to brain metastasis. The incidence of breast cancer and brain metastases (BCBM) is 10-16%, and its short survival time and poor prognoses are considered a significant characteristic of the disease [1, 2]. When brain metastases are found, most patients with breast cancer have also developed metastases of the lymph nodes, bones, liver, and lungs. Clinical data indicate that 15%-25% of the metastatic brain tumors originate from the breasts [3, 4]. There are many methods for treating patients with BCBM, among which-whole brain radiotherapy (WBRT) is the standard treatment that can significantly improve the patients' quality of life (QOL) and prolong their survival times [5, 6]. Some chemotherapeutic drugs that can cross the blood-brain barrier (BBB) have been widely used in the treatment of BCBM [7]. The biggest advantage of WBRT is that it can significantly improve the functions of the central nervous system and prolong patients' survival times. This method is considered the standard treatment for brain metastases especially when there are more than three brain metastases, and the median survival time can be prolonged by 4-6 months [8]. WBRT plus chemotherapy maintains the

functions of the nervous system in the patients to the maximum extent and has remarkable short-term efficacy, but its effects on the patients' long-term prognosis have rarely been studied. Therefore, this study is designed to explore the effects of this combination on the clinical efficacy in and the long-term prognosis of patients with BCBM.

Materials and methods

General information

This study was approved by the Hospital Ethics Committee of Jiangsu Provincial Corps Hospital of the Chinese People's Armed Police Forces. From 2008 to 2014, 58 female patients with BCBM in Jiangsu Provincial Corps Hospital of Chinese People's Armed Police Forces were recruited as the study cohort. The patients ranged in age from 35 to 73 years old, and their average age was 48.5 years old. The patients were randomly divided into the control group and the study group (n=29 each). The control group consisted of 7 cases of luminal A breast cancer, 5 cases of luminal B breast cancer, 8 cases of HER2+ breast cancer, and 9 cases of triple negative breast cancer (TNBC). The study group consisted of 8 cases of luminal A breast cancer, 5 cases of luminal B breast cancer, 6 cases of HER2+ breast cancer and 10 cases of TNBC, respectively. All the patients in the study cohort signed the informed consent form.

Inclusion and exclusion criteria

Inclusion criteria: Patients who met the pathological diagnosis of BCBM [9]; patients who ranged in age from 18 to 75; patients whose expected survival times were ≥3 months; patients who were confirmed to have brain metastases for the first time and had ≥3 lesions; patients whose brain lesions could not be treated with surgical resection and stereotactic radiosurgery (SRS) after consultation with surgeons and radiotherapists; patients who had stable lesions and no visceral crises except brain metastases.

Exclusion criteria: Patients who could not tolerate brain radiotherapy due to cardiopulmonary insufficiency; patients who were receiving systemic chemotherapy with other drugs; patients who had previously received other molecular targeted therapies; and patients whose expected survival times were <3 months.

Methods

Classification of breast cancer: Due to its heterogeneity, breast cancer can be divided into luminal A breast cancer (ER+PR+HER2-), luminal B breast cancer (ER+PR+HER2+), HER-2$^+$ breast cancer (ER-PR-HER2+), and TNBC (ER-PR-HER2-) based on its immunohistochemical characteristics [10]. The different subtypes of the disease have different clinical features, metastatic characteristics and prognoses.

WBRT: Control group: WBRT was administered on the patients in the control group, with a linear accelerator used for X-ray therapy. The energy was 6 MV, and the range of the irradiation was the whole brain, and the fractionation was 2.0 Gy/time, with a total dosage of 60 Gy, 5 times/week for 6 weeks.

WBRT plus chemotherapy: Study group: The patients in the study group received the same WBRT as the patients in the control group and synchronously received chemotherapy and subcutaneous injections of GM-CSF (granulocyte-macrophage colony-stimulating factor). The drug for the chemotherapy was carboplatin injected intravenously at 0.3 g/m^2 every day, and the injection was repeated four weeks later. GM-CSF was injected subcutaneously at 150 μg/d for one week.

Outcome measures

Main outcome measures: 1) Short-term efficacy: Efficacy evaluation: The efficacy was evaluated at 12 weeks after the treatment, and divided into complete remission (CR), partial remission (PR), stable disease (SD), and progression of the disease (PD) [11]. CR indicated that all lesions disappeared without new lesions, and that all the tumor markers were lower than their ceiling values, which were maintained for at least 4 weeks. PR indicated that the sum of the maximum diameters of the tumors was reduced by at least 30%, which was maintained for more than 4 weeks. PD indicated that the sum of the maximum diameters of the tumor target lesions increased by at least 20% when compared with the minimum value

during the period of observation, or new lesions were found. SD indicated that the tumor changes were between PR and PD, i.e. the sum of the maximum diameters did not decrease to the standard of PR or increase to the standard of PD. Objective remission rate (ORR) (%) = (CR + PR)/total number of cases. 2) Toxic reactions: According to the National Cancer Institute Common Toxicity Criteria Version 4.0 (NCI-CTC4.0), the toxic and side effects of radiotherapy and chemotherapy were recorded. The effects included hematological toxicity, the toxicity of other systems (such as nausea and vomiting, diarrhea, constipation, abnormal liver function, abnormal renal function, cardiac dysfunction, alopecia), and peripheral nervous system toxicity, which can be divided into grades 0-4 based on their severity [12]. 3) Follow-ups: All the included patients were followed up through outpatient services or call visits once every month. The overall survival (OS) after the radiotherapy and chemotherapy was recorded: the time from the beginning of radiotherapy and chemotherapy to a patient's death or to the end time of observing the patients who were included in this study. Progression-free survival (PFS) was recorded: the time from the patients' random grouping to their tumor progression that was confirmed for the first time.

Secondary outcome measures

Karnofsky Performance Status (KPS): The OS of the patients was assessed by the KPS at 12 weeks after the treatment. Zero points indicated the patients' deaths, 10 points indicated that the patients were critically ill and died soon after, 20 points indicated that they were seriously ill and needed to be hospitalized, 30 points indicated that they were barely able to take care of themselves, 40 points indicated that they were unable to take care of themselves and needed special care, 50 points indicated that they needed care, 60 points indicated that some patients needed assistance and most patients could take care of themselves, 70 points indicated that they could take care of themselves but could not maintain normal life and work, 80 points indicated that they could barely move and suffered from certain symptoms and signs, 90 points indicated that they could carry out normal activities and suffered from mild symptoms, 100 points indicated that they could carry out normal activities and had no symptoms [13].

Statistical methods

The statistical software SPSS 22.0 was used. Continuous variables were expressed as the mean ± standard deviation ($\bar{x}$ ± sd). t tests were used for the data confirming to a normal distribution and homogeneity of variance, and rank sum tests were used for the data that did not conform to a normal distribution or homogeneity of variance. One-way analyses of variance (ANOVA) were used to determine whether there were differences between multiple groups, and the Bonferroni method was used for the post hoc pairwise comparisons between groups if there was a difference. The Kaplan-Meier method was used for the survival analysis, and log-rank tests were used for the univariate analyses of the prognosis. When $P<0.05$, a difference was statistically significant.

Results

Comparison of the general clinical data

Sixty patients were initially included in this study, with 30 in the observation group and 30 in the control group. One case in the control group withdrew from this study because she could not undergo complete WBRT, and one case in the observation group withdrew from this study after being lost to follow-up. Ultimately, 58 cases were included. There were 29 cases each in the observation and control groups, and the general patient data was not significantly different in the two groups ($P>0.05$; **Table 1**).

Comparison of the short-term efficacy

According to the efficacy comparison, the ORR in the observation group was 79.31%, which was higher than the 34.48% in the control group ($P<0.05$; **Table 2**).

Comparison of the adverse reactions

There were no statistically significant differences in the adverse reactions between the two groups ($P>0.05$). The patients could tolerate the above adverse reactions after receiving symptomatic treatment. See **Table 3**.

Table 1. Comparison of the general patient data ($\bar{x}$ ± sd, n)

Items	Control group (n=29)	Study group (n=29)	χ^2/F	P
Age (years)	48.5±1.9	43.8±2.1	0.521	0.536
Pathological type			0.685	0.721
Luminal A	7	8		
Luminal B	5	5		
HER-2$^+$	8	6		
TNBC	9	10		
Tumor size (cm)			0.274	0.874
<2.0	27	28		
2.0-5.0	74	77		
≥5.0	24	21		
Tumor grading			0.003	0.953
I-II	67	68		
III	58	58		
N staging			0.332	0.570
N0-N1	8	10		
N2-N3	21	19		
Location of extracranial metastasis			0.014	1.000
Bone	28	26		
Lung	20	18		
Liver	11	10		
Other parts	17	15		
Menstruation			0.069	0.792
Premenopausal	14	16		
Postmenopausal	15	13		
Operation mode			0.580	0.446
Breast conserving surgery	5	3		
Radical operation	24	26		
Lymphatic vessel infiltration			0.112	0.738
Yes	5	6		
No	24	23		

Note: TNBC: triple negative breast cancer.

Comparison of the KPS scores

After the treatment, the KPS scores in the study group were higher than the KPS scores in the control group (P<0.05; **Table 4**).

Comparison of the OS and PFS

The OS in the study group was 15.97 months (95% CI: 15.84-22.17), which was higher than the 11.31 months in the control group (95% CI: 4.00-18.00) (χ^2=9.283, P=0.002). The PFS in the study group was 10.24 months (95% CI: 4.00-17.99), which was higher than the 6.86 months in the control group (95% CI: 2.84-9.17) (χ^2=8.971, P=0.002). See **Figures 1** and **2**.

Discussion

Breast cancer is prone to metastasis, and the brain is the most common site. Due to the nature of the site, the metastasis usually causes significant symptoms and seriously affects the patients' QOL and survival time [14, 15]. Distant metastasis is a major cause of death in breast cancer patients. The probability of brain metastasis is different in those with different subtypes of breast cancer. Patients with luminal A breast cancer and TNBC are more likely to suffer from brain metastasis, and the patients with metastasis have short survival times and poor prognoses [16]. The prognosis of breast cancer patients varies with different metastatic sites. Generally speaking, the prognosis is the worst in those with brain metastasis, followed by those with hepatic or pulmonary metastasis, and those with bone metastasis [17, 18].

Since brain metastasis is often complicated with other organic metastases or multiple occurrences, WBRT is an effective and commonly used method to treat the disease, and it has a high remission rate. Due to their special biological and pathological characteristics, clear boundaries, redundant circles, and locations in the junction area between the gray and white matter, brain metastases whose edge enhancement is obvious are easily distinguished using CT or MRI scanning. In addition, most brain metastases are small in size, and

Table 2. Comparison of the short-term efficacy (n, %)

Group	CR	PR	SD	PD	ORR (%)
Study group (n=29)	7 (24.14)	16 (55.17)	3 (10.34)	3 (10.34)	23 (79.31)
Control group (n=29)	2 (6.90)	8 (27.59)	12 (14.38)	7 (24.14)	10 (34.48)
χ^2	12.444				11.881
P	0.006				0.001

Notes: CR: complete remission; PR: partial remission; SD: stable disease; PD: progression of disease; ORR: objective remission rate.

Table 3. Comparison of the adverse reactions (n, %)

Adverse reactions	Leukopenia	Hemoglobin reduction	Thrombocytopenia	Nausea and vomiting	Abnormal liver function	Proteinuria	Hemorrhage
Study group (n=29)							
Grade 1-2	4 (13.79)	7 (24.14)	6 (20.69)	10 (34.48)	4 (13.79)	2 (6.90)	4 (13.79)
Grade 3-4	2 (6.90)	2 (6.90)	2 (6.90)	2 (6.90)	1 (3.45)	0 (0.00)	0 (0.00)
Control group (n=29)							
Grade 1-2	5 (17.24)	8 (27.59)	6 (20.69)	13 (44.83)	4 (13.79)	2 (6.90)	1 (3.45)
Grade 3-4	4 (13.79)	2 (6.90)	5 (17.24)	2 (6.90)	4 (13.79)	1 (3.45)	0 (0.00)
t	0.811	0.278	0.657	0.755	0.808	0.063	2.111
P	0.417	0.781	0.511	0.450	0.419	0.802	0.146

Table 4. Comparison of the KPS scores ($\bar{x} \pm sd$)

Group	KPS scores	t	P
Control group (n=29)	57.98±4.85	4.413	<0.001
Study group (n=29)	64.29±5.98		

Note: KPS: Karnofsky Performance Status.

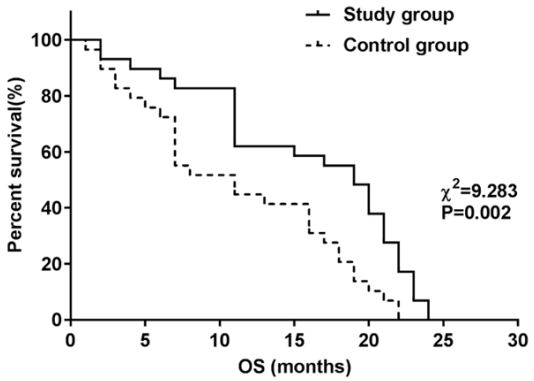

Figure 1. Comparison of the OS. OS: overall survival.

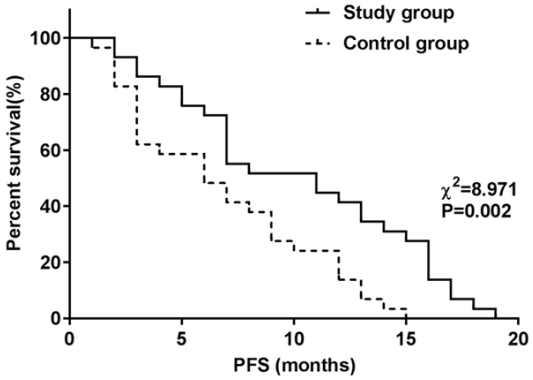

Figure 2. Comparison of the PFS. PFS: progression-free survival.

the diameters of their lesions are generally less than 4 cm. They are space-occupying in most patients who have no normal brain tissue in the tumors, so WBRT is relatively suitable for them [19]. However, the normal brain tissue is limited by the dosage of the radiotherapy, so it is difficult to completely eliminate and kill all the malignant tumors using WBRT. After being subjected to this treatment, more than 30% of patients with BCBM still have local tumors that are difficult to control, so their survival benefits are limited, and their median survival time is only 4-6 months [8]. Therefore, it is essential to strengthen the local control of the tumors using other treatment methods.

In recent years, WBRT plus chemotherapy has been widely recognized as a tumor treatment method [20]. Its local tumor control rate is significantly higher than the local tumor control rate of radiotherapy alone, and the survival time of patients who are subjected to this combined treatment is significantly prolonged [21].

The reasons are as follows: first of all, chemotherapeutic drugs have a better ability to kill systemic tumors. Second, some of the drugs have a certain sensitizing effect on the radiotherapy. Third, this combined treatment can effectively shorten the patients' overall treatment times [22].

As one of the most common, severe illnesses in patients with BCBM and one of the most common toxic and side effects of radiotherapy and chemotherapy, bone marrow depression (BMD) has many notable features such as a significant reduction in leukocytes, hemoglobin, neutrophils, and platelets, and anemia, infections, and bleeding are considered to be the clinical features of patients with the disease [23]. Granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF), thrombopoietin (TPO), and erythropoietin (EPO) are commonly used drugs for clinically treating BMD, and these drugs have a satisfactory short-term efficacy. However, they have no significant effect on increasing the number of erythrocytes or platelets, and they easily lead to side effects (such as the hyperplasia of bone marrow cells) after long-term use [24]. WBRT is the most effective method for treating patients with BCBM. According to previous studies, WBRT plus chemotherapeutic drugs can prolong the survival times of the patients and improve their treatment [25]. Chemotherapy schemes should choose the drugs that can pass through the BBB and that can combine with WBRT to treat the patients; after the combined treatment, the patients' QOL has been improved, so the combination is worthy of clinical application and further research [26]. In an earlier study, the PFS and the OS of patients undergoing WBRT plus chemotherapy and WBRT alone were 10.6 months vs. 7.0 months and 14.9 months vs. 9.0 months, respectively. The incidence of BMD in the combined group did not increase, and the efficacy in this group was better than it was in the radiotherapy alone group [27]. According to another retrospective analysis on 31 patients with HER2+ breast cancer and brain metastases who were treated with trastuzumab (17 cases with 2 mg/kg/week and 14 cases with 6 mg/kg/3 weeks) and concurrent WBRT (26 cases with 30 Gy/10 f), the ORR of the lesions was 74% and the MST was 18 months, without ≥2 grade acute adverse reactions. This suggests that the combined treatment is safe and effective [28]. The results of our study also show that WBRT plus chemotherapy does not increase the incidence of BMD, but it can improve the patients' QOL and prolong their OS and PFS. The findings are consistent with the above research results.

The effects of the combined treatment on BCBM may be related to the following mechanisms: WBRT is a commonly used palliative care method for brain metastases, and it is especially suitable for intracranial tumors, diffuse brain metastases, or multiple potential lesions. Since normal brain tissues receive almost the same dose of irradiation as the tumor tissues, the greatest disadvantage of WBRT is that it has significant side effects and can only be used once in a lifetime, so this method cannot be used a second time even if the tumor recurs in the future [29, 30].

Chemotherapy is another effective method to treat BCBM. First, the drug resistance of cancer cells makes many drugs ineffective. Moreover, due to the particularity of the brain and the existence of the BBB, there are fewer drugs that can pass through the barrier and belong to the class of chemotherapeutic drugs. Second, P-glycoprotein is a protein existing in the brain mainly secreted by the capillary endothelial cells; highly expressed P-glycoprotein can transport the drugs that enter the brain out of it. Therefore, the application and the clinical effects of chemotherapy alone are limited [31, 32]. At present, the drugs that are used to treat breast cancer and that can pass through the BBB include capecitabine, temozolomide, and intra-arterial carboplatin infusion. These drugs have high clinical application values, but the specific mechanisms of their passing through the barrier needs further study [33, 34].

Both WBRT and chemotherapy affect the severe symptoms (such as severe BMD) and survival statuses of patients with BCBM, so relieving the symptoms and improving the survival statuses are the current focus of clinical research. The advantage of WBRT plus chemotherapy is that the BBB can be destroyed after WBRT. It is beneficial for chemotherapeutic drugs to enter brain lesions through the barrier, to inhibit or eliminate the cancer cells in the lesions, and thereby enhance the therapeutic effects on the patients.

The results of this study have shown that WBRT plus chemotherapy is safe and markedly effective in treating patients with BCBM, and it can improve their QOL and prolong their survival times. Therefore, this combined treatment is worthy of clinical application and further research.

Disclosure of conflict of interest

None.

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