

Case Report

Durable remission of brain metastasis of hormone receptor-positive breast cancer with temozolomide and hormone therapy: two case reports and literature review

Kewen He^{1,2}, Zhaoyun Liu^{1,2}, Congxin Wei³, Peiying Zhuo⁴, Zhiyong Yu²

¹School of Medicine and Life Sciences, University of Jinan-Shandong Academy of Medical Science, Jinan 250062, Shandong Province, People's Republic of China; Departments of ²Oncology, ⁴Radiation Oncology, Shandong Academy of Medical Science, Shandong Cancer Hospital Affiliated to Shandong University, Jinan 250117, Shandong Province, People's Republic of China; ³Department of Radiology, Qilu Hospital of Shandong University, Jinan 250012, Shandong Province, People's Republic of China

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Abstract: Brain metastasis is a major cause of morbidity and mortality for women with hormone receptor (HR)-positive breast cancer, yet little is known about the optimal treatment of brain disease in this group of patients. Temozolomide (TMZ) has been shown to improve the survival for patients with glioblastoma. It has been investigated in the treatment of patients with brain metastasis originated from various solid tumors including breast cancer. However, clinical benefit data of TMZ in patients with brain metastasis from breast cancer especially those with HR-positive are still uncertain. The authors describe two patients with brain metastasis from breast cancer who were experienced with TMZ and hormonal therapy, which provided a survival of 17+ and 43+ months. We think that despite the poor prognosis and short survival of patients with brain metastasis, early treatment with TMZ and appropriate hormone therapy may improve the outcome and achieve prolonged palliation in selected HR-positive breast cancer patients with brain metastasis.

Keywords: Breast neoplasms, brain metastasis, chemotherapy, temozolomide, hormone therapy

Introduction

Breast cancer is the second common cause of brain metastasis after lung cancer [1]. It is estimated that 15-25% of patients with brain metastases are due to breast cancer, and about 10-15% of all cases of metastatic breast cancer ultimately develop symptomatic brain metastasis [2]. Brain metastasis is associated with an extremely poor prognosis, which the median overall survival (OS) is 1-2 months without treatment [3]. It has become a major limitation of life expectancy and quality of life in breast cancer patients. In recent years, the incidence of breast cancer brain metastasis has increased due to the improved imaging techniques and systemic treatments of extracranial disease extending patient lifespan. Hormone receptor (HR)-positive breast cancer patients, who comprise the vast majority of patients diagnosed with breast cancer (approximately 70% worldwide) [4], are at lower risk for

brain metastasis compared with those of HER2-positive and triple-negative disease. However, due to the presence of brain metastasis has been an exclusion criterion for nearly all clinical trials on treatment of metastatic breast cancer, no guidelines are directly applicable in the setting of HR-positive disease. So the development of treatment for brain metastasis has become an important clinical challenge [5].

Generally, patients who presented multiple brain metastases would be treated with whole-brain radiotherapy (WBRT) or stereotactic radiosurgery (SRS) which has been recommended as standard of care for this cohort of patients. However, the median OS after brain metastasis for breast cancer remains dismal (median OS 4-6 months) [1, 6], and the patients are often accompanied with neurocognitive impairment and reduced quality of life. Chemotherapy is therapeutically attractive because of its allowance for concurrent treatment of brain

metastasis as well as the systemic tumor. But the poor penetrability of most chemotherapy drugs across the blood-brain barrier (BBB) had limited their efficacy. Temozolomide (TMZ) is an orally administered alkylating agent which crosses the BBB with proven activity in glioblastoma [7-9], as well as used in metastasis tumors from breast cancer [10-15]. As a single-agent, TMZ treatment for brain metastasis achieves objective response rates of 0-4% in breast cancer [10, 12, 13, 16]. Hormone therapy is associated with low toxicity compared with chemotherapy. A large proportion of breast cancer patients retain their sensitivity to hormone therapy even after disease progression on prior endocrine therapy and may respond to another endocrine agent.

Now, we present two HR-positive patients who achieved disappearance of brain metastases and long-term survival of more than 17 months following TMZ and hormonal therapy for brain metastasis from breast cancer. We hope to provide valuable information for future clinical treatment of HR-positive breast cancer patients with brain metastases.

Case report

Patient 1

A 28-year-old premenopausal woman underwent the modified radical mastectomy in June 2004 because of cancer of the right breast; axillary lymph nodes were tumor negative. The primary tumor was ER-positive (60%), PR-positive (60%), HER2-negative, and Ki-67-positive (15%). Postoperatively the right internal mammary lymph nodes were irradiated followed by six cycles of adjuvant chemotherapy (500 mg/m² cyclophosphamide, 40 mg/m² methotrexate, and 500 mg/m² 5-fluorouracil). After that, she was given tamoxifen (20 mg orally per day) for 5 years.

On May 28, 2015, the patient referred to our hospital for multiple pains on the whole body, walking restricted and numbness of nose. MRI showed abnormal intensities in her right occipital lobe and temporal lobe, and multiple hypointensity areas in the whole brain. An endocranium metastasis in the right occipital and temporal lobe was established by MRI (**Figure 1A**). Multiple bone metastases in the spinal column and ribs were revealed by radionuclide bone

scan and CT. A local recurrence was proved by a skin biopsy. The relapsed tumor showed ER-positive (90%), PR-positive (70%), HER2-negative, and Ki-67-positive (10-20%). Zoledronate (4 mg infusion per month) for bone metastases and taxol (175 mg/m² infusion on Day 1) at 14-day intervals were administered. After 6 cycles of taxol, in August 2015, the MRI showed no obvious improvement of brain metastasis. So the patient underwent the bilateral ovariectomy. Then TMZ (150 mg/m² orally on days 1-5 at 28-day intervals) combined with letrozole (2.5 mg orally per day) were started. Five months later, on January 25, 2016, MRI of the brain disclosed disappearance of brain metastasis (**Figure 1B**). A complete response of the brain metastasis was achieved after 5 cycles of TMZ combined with letrozole. Since then, the patient was sustained by letrozole. At last follow-up in December 2016, 17 months after diagnosis of brain metastasis, she is stable (Time-line was shown in [Table S1](#)).

Patient 2

A 44-year-old-woman was diagnosed with the right breast cancer (T2N1M0, IIB) and underwent the right modified radical mastectomy on September 18, 2000. The histopathological examination indicated invasive lobular carcinoma, ER-positive (80%), PR-positive (10%), and HER2-negative, with lymph node metastases (5/11) involved. She received adjuvant chemotherapy of CAF (500 mg/m² cyclophosphamide, 60 mg/m² adriamycin, and 500 mg/m² 5-fluorouracil), followed radiation therapy. After that, tamoxifen (20 mg orally per day) was given for 3 years.

On July 13, 2011, a CT scan indicated multiple metastases of the lung, and then docetaxel (75 mg/m² infusion on Days 1) and cisplatin (25 mg/m² infusion on Days 1-3) at 21-day intervals were administered. No significant improvement of lung metastases was shown by the CT scan after 4 cycles of therapy, so she subsequently changed to navelbine (25 mg/m²) and gemcitabine (1250 mg/m²) infusion for 30 minutes on Days 1 and Days 8 at 21-day intervals. After 2 cycles of therapy, on September 16, 2011, the CT revealed good control of lung metastases but metastasized to her liver. As the patient refused to accept castration, hormone therapy with tamoxifen was administered again.

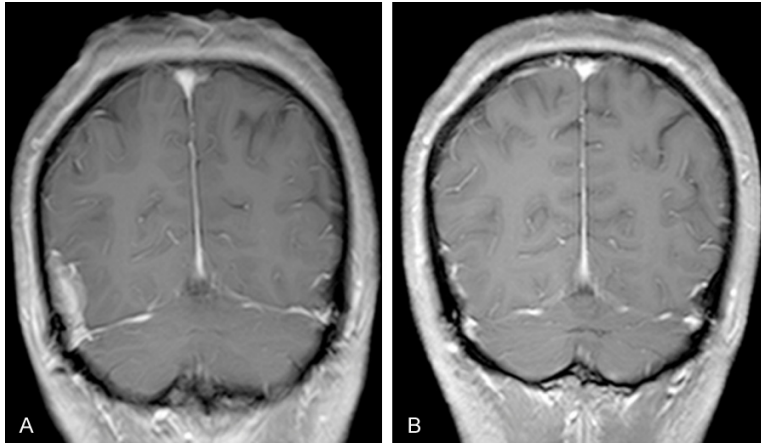


Figure 1. Brain MRI for case 1. A: An endocranium metastasis in the right occipital and temporal lobe (May 28, 2015). B: Nothing abnormal in the brain after treated with five cycles of TMZ and letrozole (January 25, 2016). TMZ = temozolomide.

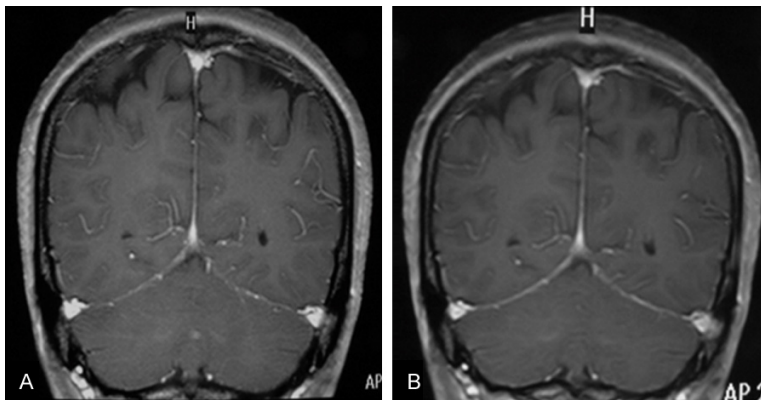


Figure 2. Brain MRI for case 2. A: A 0.4 cm-sized enhanced solitary mass with a surrounding low-intensity area in vermis cerebella (May 20, 2013). B: Nothing abnormal in the brain after therapy with six months of using exemestane and TMZ (January 3, 2014). TMZ = temozolomide.

On May 20, 2013, brain and spine metastases were found on MRI, which detected a 0.4 cm-sized enhanced solitary mass with a surrounding low-intensity area in her vermis cerebella (**Figure 2A**), compression fracture at thoracic-2 (T2), endplate degeneration at lumbar-5 (L5) and sacral-1 (S1). Then the patient was administered chemotherapy with pemetrexed (500 mg/m² infusion on Day 1 at 21-day intervals) and received zoledronate (4 mg infusion per month) for bone metastases. However, after 2 cycles with pemetrexed, the MRI demonstrated a progression of brain metastasis. As the patient was still premenopausal, bilateral ovariectomy was carried out in July 2013. Then exemestane (25 mg orally per day) and TMZ (150 mg/m² orally on Days 1-5 at 28-day intervals)

were started. Six months later, on January 3, 2014, nothing abnormal was detected on the brain MRI (**Figure 2B**). Meanwhile, the CT showed an improvement in lung, liver and bone metastases. Then she was sustained by exemestane. Although the patient has progression of the liver in November 2015, no recurrence of brain metastasis has been noted for more than 35 months since the disappearance of the brain tumor (Timeline was shown in [Table S2](#)).

Discussion

HR-positive breast cancer patients are not only at lower risk for brain metastases relative to those with HER2-positive and triple-negative disease but also associated with better prognoses than other subtypes [17]. A single-institution study that assessed outcomes for 205 breast cancer patients with brain metastases found significant differences in median OS by subtype [18]. Median OS from detection of brain metastases was 3.7 months for triple-negative, 9 months for HER2-positive, and 15 months for HR-positive disease (P =

0.015). In our report, both patients have long-term survival of more than 17 months after treated with TMZ and hormone agents.

Current treatment strategies for patients with HR-positive breast cancer brain metastases are including neurosurgical resection, WBRT/SRS, supportive therapy, and systemic therapy [17, 19]. Although these methods may improve outcomes in breast cancer, the median OS after brain metastasis remains low (median OS 3-9 months [20-22]) as compared with that of other metastases (median OS 22-31.9 months [23, 24]). Factors such as the number of metastatic lesions, the status of systemic metastases, and the availability of systemic therapies are related to treatment options. The NCCN cur-

Table 1. Clinical study of TMZ-based treatments for brain metastases in breast cancer

Regimen	Study	N	Disease control rate ^a (%)	OS (months)	PD (%)
TMZ	Abrey (2001) [12]	10	40	NR	30
	Trudeau (2006) [16]	19	16	NR	79
	Siena (2010) [13]	51	20	NR	80
TMZ + WBRT	Gamboa-Vignolle (2012) [14]	50	66	9.4	8
	Minniti (2014) [15]	28	78.6	8	NR
	Addeo (2012) [27]	36	77	11	23
TMZ + Lapatinib	Azambuja (2013) [28]	15	67	10.9	33
TMZ + Capecitabine	Rivera (2006) [29]	24	62.5	NR	29

N = Number; OS = Overall survival; PD = Progressive disease; TMZ = Temozolomide; NR = Not reported; WBRT = Whole-brain radiotherapy; ^aDisease control rate = Complete response + partial response + stable disease.

rently recommends that patients with 1-3 metastatic brain lesions and limited extracranial disease are treated aggressively with surgery followed by WBRT or, if they have only one brain lesion, with SRS plus WBRT. For patients with more than three metastatic lesions, WBRT or, if with a good performance status and low tumor volume, SRS are the primary treatment [5]. However, the value of WBRT after primary surgery remains controversial due to the potential neurocognitive impairment and reduced quality of life, especially for those with a relatively good prognosis and the potential for prolonged survival [25, 26].

Currently, no systemic therapies are specifically approved for the treatment of breast cancer brain metastasis. The role of cytotoxic therapy for the treatment of brain metastasis in women with HR-positive metastatic breast cancer also remains to be determined. TMZ, an alkylating agent with radiosensitizing properties used in the treatment of glioblastoma, has been evaluated alone and in combination with WBRT or other chemotherapy agents in trials that included breast cancer patients, with mixed results (**Table 1**). Its unique mechanism of action, non-cumulative hematologic toxicity, oral administration and activity in patients with brain tumors provide ample rationale for its application in breast cancer brain metastasis. Several phase II trials suggested a modest activity of single-agent TMZ, with an overall disease control rates of 16-40%, in recurrent or progressive brain metastases from breast cancer [12, 13, 16]. Gamboa and colleagues [14] showed a significantly increased objective response (78.6% vs. 48.1%) and progression-free survival (11.8 vs. 5.6 months) for patients treated with WBRT plus TMZ than those with WBRT

alone. These findings are concordant with the data from Minniti and Addeo [15, 27]. The advantage here is mainly that WBRT disrupts the BBB, thus potentiating a higher penetration of TMZ in the brain. The results of Azambuja et al's trial showed a favorable toxicity profile of TMZ combined with lapatinib, and achieved the disease stabilization in 10/15 assessable HER2-positive patients [28]. Another phase I study which examined the efficacy and safety of TMZ in combination with capecitabine demonstrated a disease control rates of 62.5% [29]. The regimen offers a viable alternative to WBRT in patients who have recurrent disease or refuse WBRT because of the known risks of neurocognitive deficits [29, 30]. However, to the best of our knowledge, treatment of brain metastasis with TMZ and hormone therapy in HR-positive breast cancer patients has not previously been reported. Moreover, TMZ has a major disadvantage of activity against systemic breast cancer, because the majority of patients with central nervous system involvement have the coexisting systemic disease [1].

Hormone therapy plays an important role in the treatment of HR-positive metastatic breast cancer; however, the effects of hormone therapy specifically on brain metastases are unclear. Numbers of case reports demonstrate responses in the brain for tamoxifen-treated women, as well as responses to other hormone therapies, such as letrozole and megestrol acetate [1, 11, 31-35].

In conclusion, we presented two patients with brain metastasis from HR-positive breast cancer who had been successfully treated with TMZ and hormone therapy. Despite the poor prognosis and short survival of patients with

brain metastasis, treatment with TMZ and appropriate hormone therapy may improve the outcome and achieve prolonged palliation in selected HR-positive breast cancer patients with brain metastasis. Further observation of the method with a large sample size would be necessary for the clinical practice to evaluate its therapeutic effects for brain metastasis from HR-positive breast cancer.

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Disclosure of conflict of interest

None.

Ethics statement

All clinical investigations were in accordance with the ethical guidelines of the Declaration of Helsinki. Ethical approval was obtained from the Committee of Ethics in Shandong Cancer Hospital affiliated to Shandong University. A written informed consent was obtained from each subject involved in the study.

Address correspondence to: Dr. Zhiyong Yu, Department of Oncology, Shandong Academy of Medical Sciences, Shandong Cancer Hospital Affiliated to Shandong University, 440 Ji-Yan Road, Jinan 2501-17, Shandong Province, People's Republic of China. Tel: 0086-0531-67626960; E-mail: drzhiyongyu@aliyun.com

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TMZ and hormonotherapy for brain metastasis

Table S1. Timeline of the disease and interventions for case 1

Date	Events	Diagnostic testing	Interventions
2004 June 16	Right breast cancer	Pathological diagnosis: invasive ductal carcinoma without axillary lymph node metastasis (0/18); IHC: ER + >60%, PR + >60%, Ki-67 +15%, Her2 (-)	Modified radical mastectomy; CMF; radiotherapy; tamoxifen
2015 May 28	Bone metastases; brain metastasis	Brain MRI; CT of cervical, chest, abdomen and pelvis; Ultrasound of whole body	Zoledronate; taxol
May 31	Recurrence of the right chest wall	Needle aspiration for chest wall metastasis; IHC: ER (+90%), PR (+70%), Ki-67 (+10-20%), Her2 (-)	
August 25	No obvious improvement of brain metastasis	Brain MRI	
August 27	Bilateral ovary metastases	Pathological diagnosis: poorly differentiated adenocarcinoma	Bilateral ovariectomy; letrozole + TMZ
2016 January 25	Brain CR	Brain MRI	Letrozole

CMF: Cyclophosphamide, methotrexate and 5-fluorouracil; IHC: Immunohistochemical; ER: Estrogen receptor; PR: Progesterone receptor; TMZ: Temozolomide; CR: Complete response.

Table S2. Timeline of the disease and interventions for case 2

Date	Events	Diagnostic Testing	Interventions
2000 September 18	Right breast cancer	Pathological diagnosis: invasive lobular carcinoma, with lymph node metastases (5/11) involved; IHC: ER +80%, PR +10%, Her2 (-)	Modified radical mastectomy; CAF; radiotherapy; tamoxifen
2011 July 13	Lung metastases	Chest CT	TP
September 16	Liver metastases	Chest CT	NG; TAM
2013 May 20	Brain metastasis; bone metastases; liver PD	Brain MRI; CT of cervical, chest, abdomen and pelvis	Pemetrexed; zoledronate
July 19	Brain metastasis PD	Brain MRI	Bilateral ovariectomy; Exemestane; TMZ
2014 January 3	Brain CR; improvement in lung, liver and bone metastases	Brain MRI; chest CT	Exemestane
September 3	Liver SD; bone SD	Brain MRI; chest CT	Exemestane
2015 November 17	Liver PD	Brain MRI; chest CT	Everolimus
2016 December 11	Liver SD	Brain MRI; chest CT	Everolimus

IHC: Immunohistochemical; CAF: Cyclophosphamide, adriamycin and 5-fluorouracil; ER: Estrogen receptor; PR: Progesterone receptor; TP: Docetaxel and cisplatin; NG: Navelbine and gemcitabine; TMZ: Temozolomide; SD: Stable disease; CR: Complete response; PD: Progressive disease.