

Capecitabine Therapy of Central Nervous System Metastases from Breast Cancer

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Abstract Central nervous system (CNS) metastases from breast cancer carry a poor prognosis. Systemic chemotherapy is often ineffective due to the impermeability of the blood-brain barrier (BBB) and inherent chemoresistance of CNS metastases. There are limited data supporting the use of capecitabine in this setting. Medical records of seven patients with brain metastases from breast cancer who received capecitabine treatment at Memorial Sloan-Kettering Cancer Center from 1994–2006 were reviewed. Treatment outcomes were analyzed retrospectively in those patients. Median time from breast cancer diagnosis to the development of CNS metastasis was 48 (18–165) months. Four patients had brain metastases alone, two patients had both leptomeningeal and brain metastases and one patient had leptomeningeal metastasis alone. Five out of seven patients had failed other treatment modalities before capecitabine. Three patients showed complete response (CR) and three patients had stable disease (SD) after capecitabine. The patient with leptomeningeal disease improved clinically, but refused repeat cerebrospinal fluid (CSF) studies. Median overall and progression-free survival from initiation of capecitabine was 13 and 8 months, respectively, for all patients. Capecitabine may achieve a CR and provide long-term control in patients with both leptomeningeal and parenchymal CNS metastases from breast cancer.

Keywords Breast cancer · Capecitabine · Central nervous system metastases

Introduction

Central nervous system (CNS) metastases in breast cancer patients are generally seen as a late complication of advanced disease. The incidence of CNS metastases have been reported to be as high as 30% in large autopsy series, but symptomatic disease is found in only 10–16% of patients [1, 2].

Treatment of CNS metastases is often difficult and options are frequently limited. Selected patients can be managed with surgical resection or stereotactic radiosurgery (SRS). However, metastases are often multiple and whole brain radiation therapy (WBRT) is required which offers effective but short-term palliation. Additional radiotherapy is not feasible for most patients with recurrent disease due to the risk of neurotoxicity [3].

Chemotherapy for the treatment of CNS metastases is limited by intrinsic drug resistance of the metastases and by the additional obstacle of the blood-brain barrier (BBB), which precludes the entry of water soluble chemotherapeutic agents into the CNS. In addition, p-glycoprotein is highly expressed by the brain capillary endothelium and actively mediates the efflux of some chemotherapeutic agents such as doxorubicin, cyclophosphamide, 5-fluorouracil (5-FU), paclitaxel, docetaxel, and vinorelbine [4, 5]. However, the BBB is at least partially disrupted at the site of a metastasis and the responses to a variety of chemotherapies which are hydrophilic have been described [5]. These results suggest that chemotherapy may have a role as salvage therapy in patients with recurrent disease.

Despite the limited penetration of 5-FU into the CNS, responses to capecitabine, an oral analog of 5-FU, have been reported [6–14]. We describe seven patients with CNS metastases from breast cancer treated with capecitabine chemotherapy.

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Materials and methods

We retrospectively reviewed the data of seven women who were treated at Memorial Sloan-Kettering Cancer Center from 1994 to 2006. All patients had a confirmed histologic diagnosis of breast cancer by excisional biopsy or surgery of their primary lesion. Brain or leptomeningeal metastases were documented on gadolinium-enhanced magnetic resonance imaging (MRI) or by lumbar puncture (LP). Patients received capecitabine 1,000 mg/m² twice daily for 14 days. Treatment cycles were repeated every 21 days. Radiographic responses were assessed with gadolinium MRI according to World Health Organization (WHO) criteria. This study was approved by our Institutional Review Board.

Results

Median age was 38 years (range 34–54). Six patients underwent surgery for localized breast cancer and one patient had metastatic disease at initial diagnosis. Infiltrative ductal carcinoma was the primary pathology in five patients, and two patients had mixed lobular and infiltrative ductal carcinoma. Estrogen receptor (ER) and progesterone receptor (PgR) were both negative in only one patient. Her-2 was assessed by immunohistology and was 3+ in three patients, 2+ in two, negative in one and unknown in another. Prior therapy included cyclophosphamide, methotrexate and 5-fluorouracil (CMF) (40%), both anthracycline and CMF (20%), and anthracycline-based chemotherapy (40%) as adjuvant treatment. Only one patient was treated with neoadjuvant anthracycline-based chemotherapy due to locally advanced disease. Radiation therapy was delivered to all patients, including the two who underwent lumpectomy for early stage disease. After adjuvant radiation therapy, patients whose tumor expressed ER and/or PgR

were placed on Tamoxifen. Before the diagnosis of CNS metastasis, six patients had one or more extracranial organ metastasis; only one patient developed CNS involvement as the first site of metastasis. Median time to CNS metastasis development was 48 (18–165) months after diagnosis of breast cancer. Brain metastases alone were present in four patients, two patients had both brain and leptomeningeal metastases and one patient had leptomeningeal metastasis only at initiation of capecitabine (Table 1).

Capecitabine was given to treat recurrent CNS metastases in five patients who had prior radiotherapy and chemotherapy, and was the initial CNS regimen in two other patients. Three patients achieved a CR (Fig. 1) and three patients had SD following treatment. One patient improved clinically with capecitabine, but refused repeat LP for response assessment. Two CR patients were re-treated with capecitabine for subsequent recurrence of their CNS metastases; one achieved a partial response (PR) lasting five months and the other had a SD for 11 months. Capecitabine was well tolerated in the majority of patients with only two requiring a dose reduction for hand and foot syndrome (Table 2).

Two patients continued to receive trastuzumab throughout their chemotherapy regimens. One of those patients also received letrozole along with trastuzumab and one patient was on goserelin during her entire treatment without interruption. For all seven patients, median overall and progression-free survival from capecitabine chemotherapy was 13 months and eight months, respectively. Three patients expired during follow up due to their progressive systemic and CNS disease.

Discussion

The efficacy of capecitabine in brain metastases from breast cancer has been reported in isolated patients [6–13]

Fig. 1 Axial T1-weighted MRI images after gadolinium. (A) Enhanced dorsal pontine lesion before capecitabine. (B) Complete resolution of enhancing metastasis after seven cycles of capecitabine

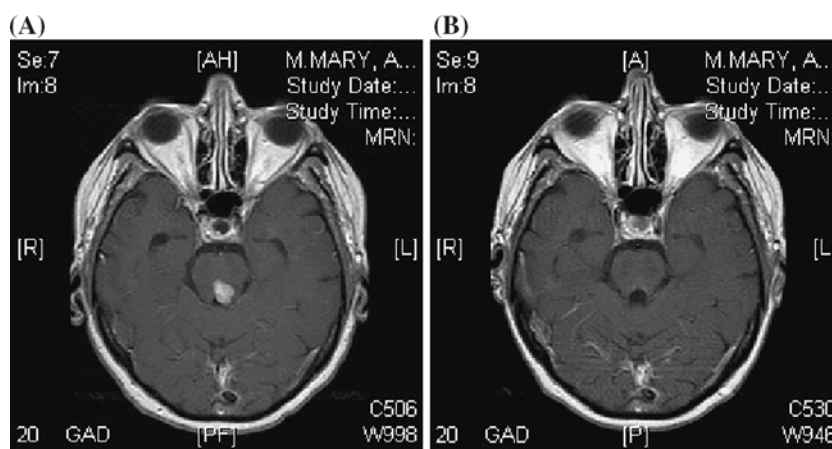


Table 1 Characteristics of breast cancer patients with central nervous system metastases

Patient number	Age	Breast cancer history			Adjuvant CT/RT/HT	Sites of metastasis before CNS	TTP	Location
		Stage	Histology	ER/PgR/Her-2				
1	38	IV	IDC	+/-/3+	None	Lung, liver	35	Brain
2	47	I	IDC	-/-/3+	CMF/RT/None	Local, liver	76	Brain
3	35	IIA	IDC	+/+2+	CMF/RT/Tam	Liver, bone, lung, supraclavicular LAP	72	Brain
4	34	IIIB	IDC	NA	Neoadjuvant AC+T/RT/Tam then letrozole and goserelin	None	18	Brain and leptomeningeal disease
5	54	IIIA	L&IDC	+/+2+	AC+T/RT/Tam	Lung and bone	48	Brain and leptomeningeal disease
6	46	IIIA	L&IDC	+/+/-	A+CMF/RT/Tam	Lung and bone	165	Leptomeningeal disease (Positive cytology only)
7	34	IIIA	DCIS with multifocal IDC	+/+3+	AC+T/RT/Tam	Liver	41	Brain

L: Lobular, IDC: Infiltrative ductal carcinoma, DCIS: Ductal carcinoma in situ, CT: Chemotherapy, RT: Radiation therapy, HT: Hormonal therapy, TTP: Time from the initial diagnosis to CNS progression in months, CMF: Cyclophosphamide, methotrexate, fluorouracil, AC: Doxorubicin, cyclophosphamide, T: Paclitaxel, Tam: Tamoxifen, LAP: Lymphadenopathy, ER: Estrogen receptor, PgR: Progesterone receptor, NA: Not applicable, CNS: Central nervous system

(Table 3); however, the larger phase II and III studies of capecitabine in metastatic breast cancer excluded patients with brain metastases. There is a single phase I study that combined temozolomide and capecitabine in breast cancer patients with metastases to the brain. In this study, Rivera et al. [14] suggested that this combination was active and well-tolerated and may provide an alternative to WBRT for patients with multiple brain metastases. However, the single agent activity of the two individual drugs, temozolomide and capecitabine, against CNS metastases from breast cancer is not known.

Our study combined with other reports in the literature suggests that capecitabine may have an effect as a single agent. Giglio et al. [9] and Tham et al. [12] reported that capecitabine in this patient population demonstrated clear radiographic response and survival ranging between nine months and 3.7 years. Among our patients, more than one-half had a radiographic or clinical response and the longest survival was 44 months. Furthermore, capecitabine may retain efficacy at subsequent recurrence of CNS metastases. Reintroduction of capecitabine to patients who had a prior response achieved a second remission in two of our patients. In the literature, one patient had a favorable response while a second failed to respond after reintroduction of capecitabine [9, 12].

One limitation of our series and others in the literature is the concomitant administration of other anti-cancer drugs.

Two of our patients received trastuzumab during all their chemotherapy regimens including the capecitabine. It is difficult to assess whether continuing trastuzumab had any effect on CNS response in those patients; however, there are a number of reports in the literature suggesting that patients on trastuzumab may be at increased risk for the development of CNS metastases and it seems unlikely that trastuzumab improved CNS control in our patients. Church et al. [13] reported a patient in whom sequential addition of systemic chemotherapy, including capecitabine to continued trastuzumab, resulted in multiple tumor responses.

Current understanding of the pharmacokinetics of capecitabine and its metabolites in brain tumor tissue and CSF are limited. Penetration of this drug through the human BBB may occur via the human concentrative nucleoside transporter (hCNT). Thus far, two isoforms of hCNT have been identified at the cDNA level. hCNT1 is involved in transportation of pyrimidine nucleosides, whereas hCNT2 is a purine preferring transporter. hCNT1 is present in the rat BBB, but it has not been studied in human brain tissue. The metabolite of capecitabine, 5-deoxy-5-fluorouridine (5-DFUR), but not capecitabine itself or 5-FU, is an hCNT1 substrate. This transporter is responsible for the penetration of capecitabine through the BBB and confers its sensitivity to the drug [15]. In addition, the neurotoxicity of high dose 5-FU and capecitabine (reported as 0.1–0.5% in the package insert) is also indirect

Table 2 Capecitabine treatment

Patient number	Total daily dose	Best CNS response	Regimens used for CNS (in order)	TTP	OS	Comments
1	3,500 mg	CR	Capecitabine SRS Gemcitabine and trastuzumab	8	27	Goserelin was used through out all treatments
2	3,500 mg ^a	CR	WBRT Temozolomide Thalidomide SRS Capecitabine Capecitabine Capecitabine and docetaxel Gemcitabine	1 st 14 2 nd 11 3 rd 5	44	SD after 2 nd capecitabine PD after 3 rd capecitabine Trastuzumab was used through out all treatments
3	3,500 mg	SD	SRS WBRT Capecitabine Vinorelbine Gemcitabine	7	13	
4	3,000 mg	SD	WBRT Capecitabine IT MTX	15	18	
5	3,000 mg	SD	IT MTX WBRT SRS Capecitabine	12	12	
6	3,500 mg	NA	Capecitabine	6	6	Clinically symptoms resolved
7	3,500 mg ^a	CR	WBRT Temozolomide Partial BRT Craniotomy High dose MTX and gemcitabine Capecitabine Capecitabine	1 st 5 2 nd 5	12	PR after 2 nd capecitabine Letrozole and trastuzumab were used through out all treatments

IT: Intrathecal, WBRT: Whole brain radiation therapy, BRT: Brain radiation therapy, MTX: Methotrexate, SRS: Stereotactic radiosurgery, CR: Complete response, SD: Stable disease, PR: Partial response, CNS: Central nervous system, TTP: Time to progression in months, from capecitabine, OS: Overall survival in months, from capecitabine, NA: Not assessed

^a Dose reduction

evidence that drug can penetrate the BBB in humans to a limited degree [16].

It is also possible that capecitabine transfer is enhanced if the BBB has been damaged secondary to WBRT. However, in our study, capecitabine resulted in a radiographic CR in one patient with brain metastasis and clinical improvement in another patient with leptomeningeal disease both of whom were radiotherapy naive. Rogers et al. [7] and Fabi et al. [11] have also demonstrated tumor regressions in

brain and leptomeningeal metastases with capecitabine prior to WBRT.

In conclusion, this study demonstrates that both leptomeningeal and parenchymal disease from breast cancer can be successfully treated and controlled over a long period of time with systemic capecitabine therapy. In contrast to other treatment modalities, such as WBRT and intrathecal methotrexate, capecitabine is well tolerated and has no associated neurologic toxicity. Capecitabine may be an

Table 3 Case reports of capecitabine in breast cancer patients with central nervous system metastases

Age	ER/PgR/ Her-2	TTP	Location	Total daily dose and schedule of capecitabine	Best radiologic CNS response to capecitabine	Reference
54	-/-+	17	Brain and leptomeningeal disease	2,400 mg/day 3 weeks on and 1 week off and WBRT	CR	6
42	+NR/NR	132	Leptomeningeal disease	3,000 mg/day 2 weeks on and 1 week off	PR	7
41	-/-NR	168	Brain and leptomeningeal disease	3,000 mg/day 2 weeks on and 1 week off	PR	8
38	-/-NR	23	Leptomeningeal disease	2,500 mg/m ² /day 2 weeks on and 1 week off	1st attempt CR 2nd attempt PD	9
53	+/+/-	42	Brain	2,000 mg/m ² /day 2 weeks on and 1 week off	CR	10
37	-/-+	36	Brain	2,000 mg/m ² /day 2 weeks on and 1 week off	PR	11
51	-/-/-	30	Brain and leptomeningeal disease	1,000 mg/m ² /day during WBRT then 2,500 mg/m ² /day 2 weeks on and 1 week off	1st attempt and 2nd attempt CR	12
40	+NR/+	76	Brain	2,500 mg/m ² /day 2 weeks on and 1 week off	PR	13

ER: Estrogen receptor, PgR: Progesterone receptor, NR: Not reported, TTP: Time from the initial diagnosis to CNS progression in months, CNS: Central nervous system, CR: Complete response, PR: Partial response, PD: Progressive disease, WBRT: Whole brain radiation therapy

appropriate treatment alternative for patients with CNS metastases, particularly at time of tumor recurrence.

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