Phase II Study of Systemic High-dose Methotrexate and Intrathecal Liposomal Cytarabine for Treatment of Leptomeningeal Carcinomatosis From Breast Cancer

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Abstract

Metastatic breast cancer frequently leads to brain metastases and, less commonly, leptomeningeal carcinomatosis (LC). Once cerebrospinal fluid involvement occurs, the prognosis is poor. There are limited treatment options available, but none offer significant survival benefit. Methotrexate, given systemically at high doses (3.5-8 gm/m^2), achieves cytotoxic concentrations in the CSF and has been shown to prolong survival in patients with LC. Intrathecal liposomal cytarabine has been shown to increase time to neurologic progression in patients with breast cancer and LC. The combination of these 2 agents in LC has not been studied extensively. Here, we present the results of the phase II study with this combination showing promising efficacy and very good tolerability.

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Introduction

Metastatic brain tumors are the most common intracranial neoplasms in adults. The incidence rate is estimated to be as high as 10 per 100,000 population, and in the United States alone, over 100,000 patients are expected to develop brain metastases each year.[1-3] Technological progress and development of new imaging techniques (high resolution magnetic resonance imaging [MRI]) allow for earlier detection and frequently better outcomes. At the same time, more effective treatments of the systemic disease prolong survival but permit development of intracranial metastatic disease.

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Brain metastases and leptomeningeal carcinomatosis (LC) lead to significant morbidity and ultimately shorten survival. It is estimated that about 10% of patients with cancer will develop brain metastases during their illness. Brain metastases from breast carcinoma are among the most common primary cancers, surpassed only by lung cancer. Treatment options are limited and survival rates for patients affected with central nervous system (CNS) metastases are short. New approaches to therapy are desperately needed.

Background

Conventional treatment of metastases from solid tumors, including breast cancer, includes surgery (usually for solitary lesions) and radiotherapy. Radiotherapy delivered in the form of either stereotactic radiosurgery or whole brain radiotherapy (WBRT) is widely used. WBRT has been considered the standard of care for intracranial control, but recent studies have suggested that with a limited number of lesions (up to 4), stereotactic radiosurgery may be an efficacious and less toxic alternative.[4]

Responses to radiation therapy can be significant and occur in 40% to 90% of patients. They are frequently associated with clinical improvement, but the effects are not long lasting, on average extending survival by 5 to 7 months.[3] WBRT can be associated with significant neurocognitive side effects and decrease in quality of life,

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including moderate to severe dementia that can occur several months to years after treatment.[5] WBRT may also limit utilization of blood-brain barrier (BBB)-penetrating therapies in the future.

The combination of WBRT with chemotherapy has been studied. Multiple agents, including nitrosoureas, teniposide, and fotemustine, have been utilized, showing encouraging responses but with high toxicity rates and unchanged overall survival (OS).[6] Temozolomide, a lipid soluble alkylating agent that can cross the BBB and has had success in glioma, has been combined with WBRT in phase II trials for breast and other solid cancers and provides a limited benefit when compared to WBRT alone.[7-10]

The role of systemic and local chemotherapy in the treatment of metastatic disease from solid tumors is problematic. Intrinsic drug resistance of the metastases, as well as pharmacologic issues related to the BBB that will not allow water soluble particles to penetrate the CNS, diminishes the efficacy of conventionally used systemic therapies.[11,12] In addition, p-glycoprotein is highly expressed by brain capillary endothelium and actively mediates efflux of some chemotherapeutics.[12,13]

However, the BBB is at least partially disrupted at the site of brain metastasis, and this may allow hydrophilic agents to enter.[13] Responses to chemotherapy using hydrophilic chemotherapeutics have been described. Unfortunately, many patients develop CNS metastases late in the course of their disease when they are frequently not chemotherapy-naive and might be resistant to standard BBB penetrating therapies. Two approaches can be used to bypass the BBB and achieve cytotoxic concentrations within the CNS. Local therapies with intrathecal (IT) administration of the chemotherapeutics into cerebrospinal fluid (CSF) can treat neoplastic meningitis (NM), but are not effective in cases of bulky leptomeningeal disease or parenchymal brain lesions.[14] Systemic therapies with agents penetrating both the CSF compartment and brain parenchyma can offer an attractive alternative.[14]

Chemotherapy alone for treatment of brain metastases has had a very limited role traditionally, although this is changing with the development of novel targeted therapy for some cancers (non−small-cell lung cancer, melanoma). It has usually been reserved for patients who have failed prior therapies or for patients who had "chemosensitive" disease (lymphoma, small-cell lung cancer, breast cancer). In breast cancer, specifically, early trials from the 1980s identified that response rates of the CNS disease are comparable to responses in systemic disease when chemotherapy is given prior to WBRT. Objective response rates of up to 59% were described with regimens containing capecitabine, cyclophosphamide, fluorouracil, prednisone, vincristine, and methotrexate.[15-18]

The combination of cisplatin and etoposide in the upfront setting was studied in 2 phase II studies. Of the 78 patients, 12 achieved complete and 21 partial responses, with median survival ranging from 31 to 58 weeks.[19] Experiences with temozolomide (TMZ), a lipid soluble alkylating agent that is known to cross the BBB, were rather disappointing. Two separate trials failed to show TMZ activity as a single agent in treatment of CNS metastases from breast cancer.[20-22] Combination trials using TMZ with cisplatin or capecitabine has shown modest activity.[10] Capecitabine alone has also been reported to produce responses in both new and recurrent settings, but the number of patients treated has been small.[23] New approaches to treatment of both parenchymal and leptomeningeal metastases are in development and include targeted therapies and immunotherapy.

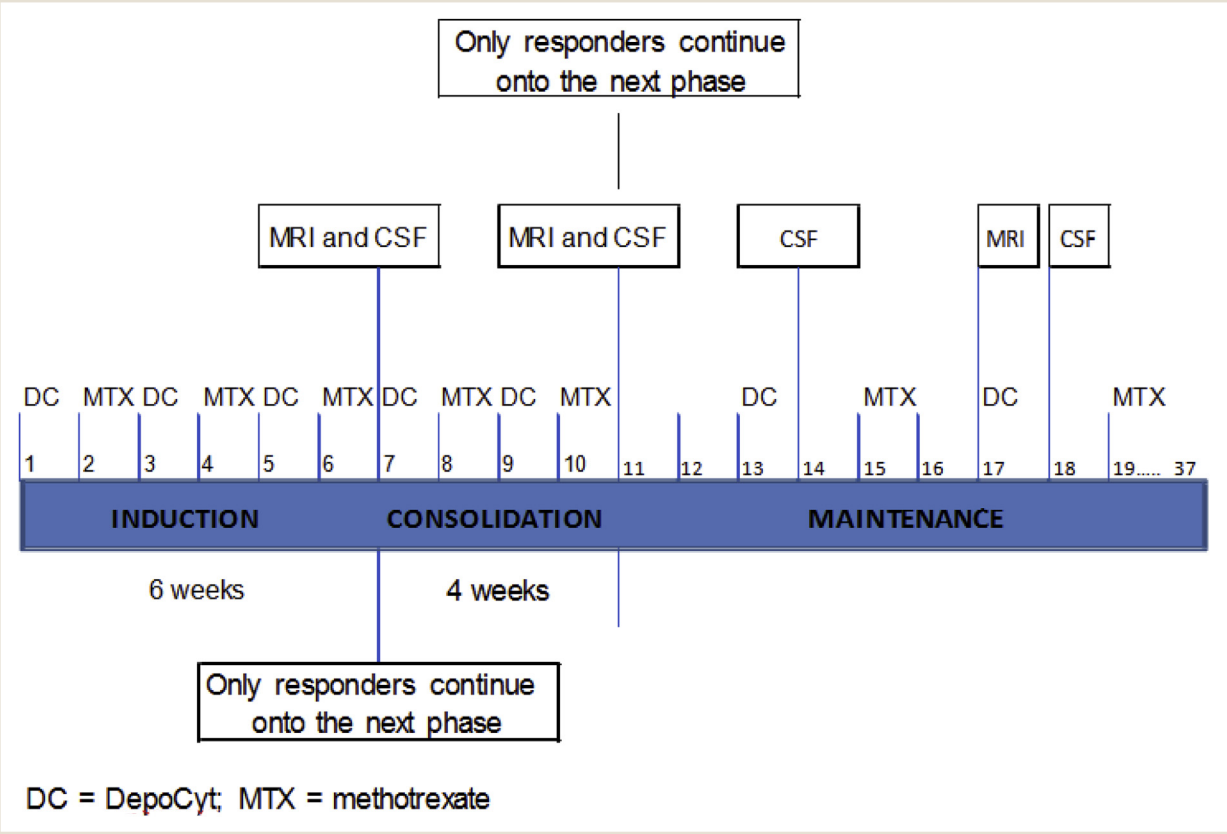
Methotrexate (MTX) is active in breast cancer. It penetrates the BBB when given in high doses (HD-MTX; 3.5 gm/m^2 and above). It has been successfully used as a single agent for therapy of primary CNS lymphoma. Glantz et al and Lassman et al utilized HD-MTX to treat leptomeningeal and parenchymal disease in non-leukemic cancers.[17,24] Lassman et al reported an overall response rate of 28% and median OS of 19.9 weeks, along with a stable disease rate of 35%. However, the therapy was not without side effects, with grade 3 to 4 hematologic toxicity seen in 21% and hepatic toxicity in 9% of patients.[17] Ninety-one percent of patients in this study had metastatic breast cancer, and 14% had isolated leptomeningeal disease.

In a study by Glantz et al, the efficacy of IV systemic HD-MTX (8 mg/m^2) for treatment of LC was compared with that of IT MTX. Only 3 patients with breast cancer were included. Researchers concluded that systemic MTX might be superior to IT MTX for both survival and cytologic clearing of CSF. Toxicity of this approach was also tolerable.[24]

LC often presents with or without parenchymal brain metastases, and can be devastating complication of cancer. The diagnosis is established by identifying cancer cells in the CSF through cytological testing or imaging (MRI). Intra-CSF administration of drugs through regular lumbar punctures or through an intraventricular reservoirs are part of the standard therapy for this condition. When there is bulky disease, focal irradiation may be necessary. From a chemotherapy perspective, the most commonly used drugs in this setting have historically been MTX and cytarabine.[24] Both agents have limitations because they are cell cycle phase-specific, which results in very short half-lives when they are injected into the CSF.[25,26] A non-cell cycle phase-specific agent, triethylenethiophosphoramide (thiotepa) can also be given IT, but it disappears from the CSF within minutes.[27] As a result, exposure of the tumor cells to all 3 agents may be limited and may compromise cytotoxicity. Sustained-release formulations could offer prolonged cytotoxic exposure. One such formulation, sustained-release cytarabine (Depocyt), has been evaluated in phase I, II, and III studies.[28,29] It was demonstrated that cytotoxic CSF concentrations are maintained in both lumbar and ventricular fluid (regardless of the site of drug administration) for $\geq$ 14 days after just one administration. Glantz et al reported that Depocyt produces responses comparable to that of IT MTX and can significantly increase time to neurologic progression in patients with NM from solid tumors.[28] Jaeckle et al reported activity of liposomal cytarabine in NM owing to breast cancer. The median time to neurologic progression in their study was 49 days, and the median survival was 88 days (range, 1-515+).[30] Shapiro et al, in 2006, reported that more patients with NM had clearance of tumor cells from the CSF with liposomal cytarabine than with free cytarabine, with similar drug-related adverse effects.[29]

Combination therapy with systemic and IT approaches has been investigated for treating leptomeningeal metastases from solid tumors. In a study by Bokstein et al, the authors did not find significant differences in response rates, median survival, or proportion of long-term survivors between patients receiving systemic therapy plus radiation to the involved areas with or without IT therapy.[31] Addition of IT treatment to the systemic treatment was, however, associated with increased incidence of both early and late treatment-related complications. The type and schedule of the systemic chemotherapy used in this study varied by patient. Moreover, all

Figure 1 Study Schema



Abbreviations: CR = complete response by radiographic criteria; CSF = cerebrospinal fluid; HD-MTX = high-dose methotrexate; IT = intrathecal; MRI = magnetic resonance imaging; PR = partial response; SD = stable disease.

patients in the IT arm were receiving MTX, potentially contributing to the side effects in patients concomitantly treated with systemic MTX. Given the non-homogeneous patient population in this study (15% lung cancer, 61% breast cancer, and 24% other solid tumors), variations of therapy and lack of information about parenchymal CNS disease and response rate, this approach warrants further investigations in a more uniform population receiving standardized treatment regimen.[31]

Toxicities Associated With IT Chemotherapy

Adverse effects in IT treatment of NM include aseptic or chemical meningitis, which is the most common complication. Infectious meningitis is possible but less likely, though patients with an intraventricular reservoir have a higher risk.[32,33] Leukoencephalopathy has been noted, and the risk is higher in patients who have had radiation prior or concurrently.[34] Myelopathy, seizures, and subdural hygromas in patients who receive therapy via lumbar puncture have been noted.[34] Myelosuppression may be observed in as many as 18% of patients, despite the route of delivery.

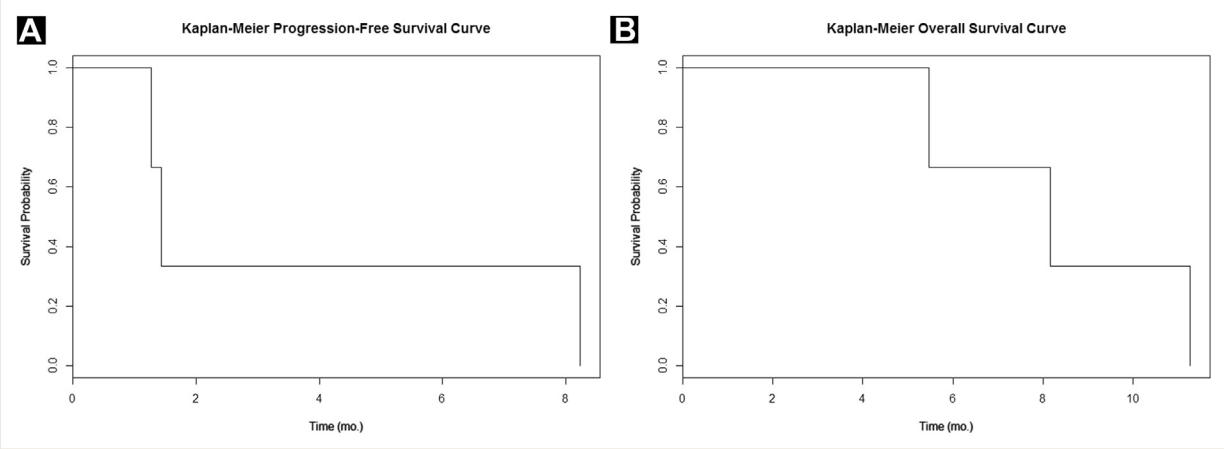
Concerns about safety of the combined systemic and IT therapy, and in particular combination of IT sustained-release cytarabine and systemic HD-MTX were raised by Jabbour et al. Investigators described increased incidence of neurotoxicity in patients with acute lymphocytic leukemia treated with this combination.[35] The

Table 1 Patient Characteristics

Patient	Gender/Age, y	Staging and Histology					Pre-therapy KPS, %
		Tumor Stage	ER	PR	HER2	Parenchymal Involvement	
1	F/50	T3N3M0	+	–	–	–	70
2	F/46	T4cN1M1	+	–	–	+	70
3	F/60	T2N1	+	Unknown	+	+	80

Abbreviations: ER = estrogen receptor; F = female; HER2 = human epidermal growth factor receptor 2; KPS = Karnofsky performance score; PR = progesterone receptor.

Figure 2 Progression-free and Overall Survival in Study Patients



systemic regimen utilized in this study consisted of hyper-CVAD chemotherapy (cyclophosphomide, vincristine, doxorubicin, and dexamethasone) plus HD-MTX and cytarabine. The side effects described included a seizure, pseudotumor cerebri, cauda equine syndrome, and encephalitis. Although it is important to recognize the potential for increased neurotoxicity with the combined approach, some of the side effects presented by the authors could have alternate explanations. The combination of systemic cytarabine with IT formulation and the schedule of IT administration in relation to systemic therapy might have also contributed to the postulated neurotoxic effect.

Study Design and Treatments

A single arm, phase II study was designed to include patients with LC from breast cancer (planned accrual, N = 22). Patients had to have MRI imaging and/or CSF confirmation of LC and were allowed to have parenchymal (brain) metastatic disease, but controlled systemic disease. The primary endpoint of the study was progression-free survival (PFS). If all patients were evaluable, a study with 2-sided Type I error of 0.05 would have 0.85 power to detect an increase in median PFS from 7 weeks to 12 weeks. The null rate of 7 weeks was estimated from 2 studies of patients with solid tumor cancers and parenchymal and leptomeningeal metastases. A study by Jaeckle et al examined 42 patients undergoing treatment of LC with liposomal cytarabine and found a median PFS of 7 weeks and a median OS of 12.6 weeks.[30] A study by Lassman et al[17] did not report PFS but also found a median OS of 12.6 weeks. Secondary objectives included OS and safety of the combination therapy.

The study population was patients with metastatic breast cancer involvement of brain parenchyma and leptomeninges, naive to whole brain radiotherapy. Eligible, enrolled patients underwent restaging and CSF flow study prior to administration of IT chemotherapy. All study patients received an Ommaya reservoir for CSF sampling and administration of chemotherapy.

The treatment regimen consisted of intravenous HD-MTX at 8 g/m^2 and IT liposomal cyatarabine (IT Depocyt) at 50 mg per dose with permissible dose modification based on creatine clearance. IT Depocyt was commenced 7 days before the first dose of HD-MTX. Patients received 50 mg of IT Depocyt every 14 days for 3 doses (weeks 1-6, induction phase) during MTX "off weeks" until completion or off-study. Responding patients received 2 additional doses of IT Depocyt (weeks 7-11, consolidation phase). Patients showing response after completion of the consolidation phase demonstrated by MRI (complete response [CR], partial response [PR], stable disease [SD]) and negative CSF analysis continued on the study and entered the maintenance phase (weeks 13-37). Patients in the maintenance phase received IT Depocyt every 4 weeks for a maximum of 5 doses with a 14-day interval between administration of intravenous HD-MTX and IT Depocyt. The total number of doses of IT Depocyt allowed for the study was 10. Non-responders were taken off the study but were followed for progressive disease (PD) and survival (See study Schema, Figure 1).

Table 2 Patient Outcomes

Patient	Therapy		PFS, mos	OS, mos	Comments
	Doses MTX	Doses Cytarabine			
1	3	3	1.4	8.2	PD at end of induction
2	2	1	1.3	5.5	PD at end of induction
3	5	4	8.2	11.3	PD at end of consolidation

Abbreviations: MTX = methotrexate; OS = overall survival; PD = progressive disease; PFS = progression-free survival.

HD-MTX was administered on inpatient basis every 14 days for 3 doses (duration of induction phase, 6 weeks). At the completion of induction therapy, disease assessment with MRI and CSF analysis was performed. Patients responding in brain parenchyma (CR or PR or SD) and who had CSF negative for malignant cells continued on therapy. Non-responders were taken off the study and were followed for PD and survival. Responding patients received HD-MTX at 8 grams/m^2 every 2 weeks for 2 additional doses (duration of consolidation phase, 4 weeks). MRI and CSF analysis were done after completion of this stage of the study. If MRI results showed CR, PR, or SD, and CSF was negative for malignant cells, patients continued on therapy. Non-responders were taken off study therapy and followed for PD and survival. Responding patients proceeded to the final stage of the study (maintenance). Patients received HD-MTX at 8 grams/m^2 monthly for the maximum of 6 doses. Assessments of response were completed every 4 weeks for CSF and every 6 weeks for parenchymal disease by MRI during this phase of the study. If CSF become positive at any time during this phase of the study or MRI showed signs of progression (PD) or there was clinical progression, patients were taken off the study (see Figure 1 for study schema).

Regulatory Considerations

All patients provided written informed consent to study treatment after being informed of alternative therapies and of potential risks of IT Depocyt and HD-MTX. The study was approved by the Fred Hutchinson Cancer Consortium Institutional Review Board and the University of Washington Human Subjects Division and funded by Sigma Tau Pharmaceuticals, Inc (currently Leadiant Biosciences).

Results

The study was closed 32 months after the first patient was enrolled owing to low accrual. Three patients have been enrolled and treated (13.6% of planned accrual). All patients were female, with a median age of 50 years (range, 46-60 years). The median Karnofsky performance status at the time of enrollment was 70%. The mean interval between the diagnosis of leptomeningeal disease and initiation of therapy was 1.2 months. One patient had human epidermal growth factor receptor 2-positive disease, but all 3 patients had estrogen receptor-positive disease (Table 1). The median PFS was 1.4 months (range, 1.3-8.2 months), and the OS was 8.2 months (range, 5.5-11.3 months) (Figure 2, Table 2). The median number of HD-MTX and IT liposomal cytarabine doses administered per patient was 3 for each drug. The longest surviving patient received 5 doses of HD-MTX and 4 doses of IT liposomal cytarabine. The regimen was well-tolerated, with no significant hematologic toxicity except for grade 4 lymphopenia in 1 patient, and no signs of neurotoxicity. Transient grade 3 transaminitis was noted in all 3 patients.

Discussion

Breast cancer with leptomeningeal metastases presents a therapeutic challenge. Radiotherapy and standard chemotherapy provide limited benefit. Maximizing cytotoxic concentrations of chemotherapeutics in the CSF is desirable and may offer a therapeutic advantage. Our preliminary results demonstrate the feasibility of this approach on a limited number of patients with encouraging survival data. Combination of systemic therapy with an IT approach appears to be very feasible, especially in patients who have intraventricular catheter (Ommya). Although systemic HD-MTC administration requires in-patient stay and may be limiting for some patients owing to comorbidities or quality of life issues, IT therapy administration is done outpatient and does not typically require significant time commitment. There were several limitations to our study that ultimately resulted in poor accrual and premature study closure. Patient identification and eligibility criteria were the major obstacles in successful enrollment. Many patients were in advanced stages of their systemic cancer or had prior whole brain radiation when LC was identified. Several patients were not able to commit to the therapy plan owing to social circumstances and quality of life concerns. Given the nature of the condition, there were also challenges in establishing the diagnosis of LC promptly, and delays in initiation of therapy were significant (on average, it took 1.2 months from the diagnosis to treatment start). Our accrual limitations highlight the challenges of conducting studies in "orphan diseases" such as LC and underscore the importance of multi-center collaboration.[18]

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Disclosure

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