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ORIGINAL RESEARCH REPORT

High-dose intravenous methotrexate in the management of breast cancer with leptomeningeal disease: Case series and review of the literature

Jonathan T. Kapke [a,*], Robert J. Schneidewend [a], Zeeshan A. Jawa [a], Chiang-Ching Huang [b], Jennifer M. Connelly [a], Christopher R. Chitambar [a]

[a] Medical College of Wisconsin, Milwaukee, WI, USA
[b] University of Wisconsin—Milwaukee, Milwaukee, WI, USA

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Abstract
Leptomeningeal metastasis (LM) in breast cancer is associated with significant morbidity and mortality. While there is currently no standard therapy, treatment options include craniospinal radiotherapy, intrathecal chemotherapy and systemic chemotherapy. Craniospinal radiotherapy has not demonstrated improved survival and intrathecal chemotherapy is often poorly tolerated due to associated neurotoxicity. The use of systemic chemotherapy can be limited by inadequate central nervous system penetration. High-dose systemic methotrexate administered intravenously (HD-MTX), has been reported to improve quality of life and provide durable remissions for LM in breast cancer. We present three cases of metastatic breast cancer and LM with prolonged survival after administration of HD-MTX. Based on our observations and review of the literature, HD-MTX seems to be a viable treatment option for patients with LM in breast cancer, and in select cases, the use of HD-MTX, as part of a multimodality treatment plan, may be associated with prolonged survival.

* Corresponding author at: Division of Hematology and Oncology, Medical College of Wisconsin and Froedtert Clinical Cancer Center, Medical College of Wisconsin, 9200 W. Wisconsin Avenue, Milwaukee, WI 53226, USA. Fax: 414-805-4606.
E-mail address: jonathan.kapke@phci.org (J.T. Kapke).

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Introduction

Breast cancer is the most common malignancy among females worldwide, and in the USA, it affects approximately one in eight women [1,2]. Breast cancer commonly spreads to the central nervous system (CNS), and when compared to other solid tumor malignancies, only lung cancer is more commonly associated with CNS metastasis [3]. Leptomeningeal metastasis (LM), where deposits of malignant cells occupy the lining of the CNS, has an estimated incidence of less than 5% in metastatic breast cancer and is associated with significant morbidity and mortality [4]. Risk factors for developing LM include triple-negative and human epidermal growth factor receptor 2 (HER-2) positive disease, as well as invasive lobular histology [5,6]. Estimated survival after diagnosis of LM ranges from 6 to 8 weeks in those left untreated to 8–30 weeks in those who receive therapy, and in general, less than 10–20% of breast cancer patients live more than 1 year after LM diagnosis [7,8].

There is no standard treatment for LM in breast cancer. Current treatment options include craniospinal radiotherapy, intrathecal chemotherapy, and systemic chemotherapy. Although radiotherapy seems to alleviate signs and symptoms of LM, it has not been shown to prolong survival [8,9]. In addition, although commonly used in clinical practice, the efficacy of intrathecal chemotherapy is not well established, and it is often poorly tolerated because of significant neurotoxicity [10]. Data supporting the use of systemic chemotherapy for LM are limited to case reports and small case series as most patients with LM are excluded from larger clinical trials. Observed efficacy has been seen in a limited number of regimens that have adequate CNS penetration. High-dose intravenous methotrexate (HD-MTX) has been shown in retrospective studies and case reports to have significant efficacy when compared to other therapies for patients with LM [10–12].

Methotrexate is a folate antimetabolite that inhibits DNA synthesis, repair, and cellular replication. When dosed at 3.5–16 g/m^2, HD-MTX has been shown to achieve CNS drug levels necessary for antitumor effect [11,13]. The use of HD-MTX has been well established for prophylaxis and treatment of CNS disease in lymphoma and leukemia. Although there are less data on its use for leptomeningeal carcinomatosis in solid tumor malignancies, HD-MTX has been reported to improve quality of life and provide disease remissions far beyond the estimated averages for breast cancer patients with LM [7,12,14,15].

We present three cases of metastatic breast cancer with LM that achieved prolonged survival after treatment with HD-MTX and provide a review of the literature.

Case reports

Case 1

LH is a 71-year-old female with a history of ulcerative colitis who initially presented in December 2014 with progressive lower extremity weakness. She was admitted for further management and magnetic resonance imaging (MRI) of the spine showed multiple focal metastatic lesions throughout the cervical and lumbar spine, as well as, extensive leptomeningeal carcinomatosis. Of note, MRI brain was negative for parenchymal brain lesions. Initial staging computed tomography (CT) demonstrated a large lobulated enhancing heterogeneous left breast mass, measuring approximately 3.2 × 3.2 cm, with left axillary lymphadenopathy. The patient underwent a left breast biopsy with pathology significant for invasive ductal carcinoma that was estrogen receptor (ER)-positive, progesterone receptor (PR)-positive, and HER2-negative. She underwent lumbar puncture with cerebrospinal fluid (CSF) cytology analysis positive for metastatic breast cancer. The patient was started on dexamethasone and treated with palliative radiation therapy to the cervical and lumbar spine. Her lower extremity strength improved, and she was discharged home.

The patient subsequently received systemic chemotherapy using intravenous HD-MTX with leucovorin rescue until plasma methotrexate levels were <0.1 μM. She received a total of seven cycles of therapy, and treatment was repeated every 14 days. Cycle one was dosed at 3.5 g/m^2, cycle two was dosed at 4 g/m^2, and cycles three to seven were dosed at 8 g/m^2. Anastrozole 1 mg daily was added with cycle seven. Treatment was tolerated relatively well without significant complications. After completing seven cycles of therapy, the patient's palpable breast mass dramatically decreased in size with only a 1-cm scar remaining on physical exam, and CSF cytology became negative for malignancy. Restaging imaging demonstrated improvement in epidural soft tissue enhancement, regression of spinal metastatic disease, and decreasing leptomeningeal carcinomatosis.

It was felt that the patient had achieved a maximum benefit after seven cycles of HD-MTX, and the decision was made to transition to capecitabine. The patient was maintained on capecitabine for approximately 18 months, but then she developed posterior reversible encephalopathy syndrome that was attributed to capecitabine as her symptoms resolved with drug discontinuation. She was continued on anastrozole alone for 7 months until restaging imaging demonstrated worsening osseous metastasis and new pulmonary nodules consistent with progressive metastatic disease. Palbociclib was added to anastrozole for about 5 months, but the patient developed altered mental status, and restaging MRI demonstrated an enlarging left parasagittal falx lesion with stable leptomeningeal disease. Anastrozole was switched to exemestane and palbociclib was continued for several months. The patient then developed progressive pulmonary, hepatic, and CNS disease and subsequently transitioned to abemaciclib plus fulvestrant. While on abemaciclib, the patient experienced progressive diarrhea that was difficult to control. She ultimately elected to stop this agent for quality of life reasons after being on treatment for approximately 7 months. Fulvestrant was continued alone for 7 additional months. Restaging imaging then demonstrated progressive disease in the liver, but stable osseous, CNS, and leptomeningeal disease. The patient was started on paclitaxel chemotherapy, which she continues to date.

At the time of this writing, the patient is alive and tolerating systemic therapy without significant dose limiting toxicity. Her leptomeningeal disease is radiographically and

clinically stable. Despite being diagnosed with leptomeningeal disease at initial presentation, the patient has survived 54 months with systemic therapy, including first line HD-MTX, and she has maintained an excellent quality of life.

Case 2

MY is a 63-year-old female who was initially diagnosed with left breast cancer in May 2006. She was treated with left mastectomy and bilateral salpingo-oophorectomy. Final pathology demonstrated stage IIA, T2N0 invasive lobular carcinoma, ER-positive, PR-positive, HER2-negative. She was subsequently treated with six cycles of docetaxel, doxorubicin, and cyclophosphamide (TAC) chemotherapy followed by adjuvant radiation. She was offered adjuvant hormone therapy but declined treatment at that time.

The patient was in remission until July 2015, when she presented with progressive weakness and vision changes. Restaging imaging demonstrated leptomeningeal carcinomatosis with associated optic nerve compression, pathologic L5 compression fracture, and extensive bony disease. The patient underwent L5 laminectomy. Surgical pathology was positive for metastatic invasive lobular carcinoma of the breast, ER-positive, PR-positive, and HER2-negative. She was started on anastrozole and subsequently received six cycles of HD-MTX at a dose of 8 g/m^2, which was completed in October 2015. Restaging imaging at that time demonstrated regression of leptomeningeal carcinomatosis and bony disease. She was subsequently started on palbociclib and letrozole.

At the time of this writing, the patient is alive and well. She remains on palbociclib and letrozole without dose limiting toxicity. Her leptomeningeal disease remains stable, and to date the patient's disease has been controlled for 44 months since the initial diagnosis of leptomeningeal carcinomatosis.

Case 3

CB is a 45-year-old female who was diagnosed with right breast cancer in 2010. Initial treatment included lumpectomy plus sentinel lymph node biopsy. Pathology demonstrated a 2.0 cm invasive ductal carcinoma with negative sentinel lymph node sampling, ER-positive, PR-positive, HER2-negative. The Oncotype DX Recurrence Score was 30. She subsequently received four cycles of dose-dense doxorubicin and cyclophosphamide (DDAC) followed by postoperative radiation therapy. The patient started tamoxifen after completing radiation in March 2011.

In September 2013, the patient presented with progressive hip pain and headaches. She underwent a positron emission tomography (PET)/CT that demonstrated a bilobed suprahilar right-sided mass measuring 1.7 $\times$ 1.2 cm, as well as, a lytic lesion in L5 and the right iliac wing. Biopsy of the right iliac wing lesion demonstrated metastatic breast cancer, ER-positive, PR-positive, and HER2-negative. MRI of the brain demonstrated dural enhancement highly suspicious for leptomeningeal carcinomatosis without parenchymal brain metastasis. Of note, the patient had been amenorrhoeic since receiving chemotherapy 2 years earlier, and laboratory assessment suggested post menopausal status. She was started on anastrozole 1 mg daily in July 2013.

In October 2013, restaging PET/CT demonstrated extensive progression of disease within the liver, bones, and lungs. Worsening leptomeningeal disease was also seen, but no parenchymal brain lesions were observed. It was at that time that she elected to transfer her care to our institution. Liver biopsy was performed with pathology positive for metastatic breast cancer that was ER-positive, PR-positive, and HER2-negative. Reassessment of menopausal status with laboratory testing demonstrated a premenopausal state. Ovarian function suppression with leuprolide was added to anastrozole, and palliative radiation therapy to the whole brain and to an L5 compression fracture was administered.

The patient subsequently received weekly paclitaxel and bevacizumab, administered on Day 1 and Day 15 of a 21-day cycle, for a total of three cycles. Restaging imaging demonstrated disease progression in the liver, and treatment was switched to eribulin administered on Day 1 and Day 8 of a 21-day cycle. She received eight cycles of eribulin, and then elected to take a treatment break for bilateral salpingo-opherectomy. Anastrozole was changed to letrozole. Restaging scans 5 months later demonstrated progressive disease in the liver and bone. She resumed eribulin for an additional six cycles. Restaging imaging in March 2015 demonstrated disease progression in the liver and bone, as well as progressive leptomeningeal carcinomatosis.

In light of significant worsening leptomeningeal disease, the patient received five cycles of HD-MTX dosed at 8 g/m^2. Restaging imaging demonstrated stable leptomeningeal disease, but disease progression in the liver. She was then treated with carboplatin and gemcitabine for three cycles with stable leptomeningeal disease but ongoing progression in the liver. Treatment was changed to capecitabine. After six cycles of capecitabine, oligometastatic progression of disease was noted in the thoracic spine. The patient received palliative radiation therapy to the thoracic lesion, and capecitabine was administered for three more cycles. Restaging imaging subsequently demonstrated stable leptomeningeal disease; however, significant progression was noted in the liver and throughout the skeleton. The patient transitioned to end-of-life care and died in August 2016. The patient lived a total of 17 months after the initial diagnosis of leptomeningeal disease.

Discussion

Treatment of metastatic breast cancer with LM remains a significant therapeutic challenge. Prognosis is very poor, and there are no standard treatments. Potential treatment options include radiotherapy, intrathecal chemotherapy, and systemic chemotherapy, but limited data are available to guide optimal treatment selection [16].

Available data suggests that radiation therapy for LM is often associated with an initial improvement in neurologic signs and symptoms; however, the clinical improvement from radiation therapy is often short-lived [8,9,17]. Furthermore, despite the symptomatic improvement, radiation therapy for LM in breast cancer has not been associated with an overall survival benefit [8]. Craniospinal and whole brain

radiation therapy have also been associated with a variety of neurocognitive side effects that may significantly impact quality of life, particularly in patients who achieve a relatively long-term survival with LM [18]. Finally, the use of craniospinal and whole brain radiotherapy may decrease the ability for systemic therapy to penetrate the blood–brain barrier and potentially limit the effect of systemic therapy on the management of LM.

Although commonly used in clinical practice, the efficacy of intrathecal chemotherapy is not well established, and it is often poorly tolerated because of significant neurotoxicity [10]. Commonly used intrathecal agents for the treatment of LM include methotrexate, cytarabine, and thiotepa. Intrathecal chemotherapy administration typically requires frequent lumbar punctures, which often adds additional logistical challenges and exposes the patient to additional procedure related risks. Various studies have evaluated intrathecal chemotherapy for LM with disappointing results.

In a study by Niwinska et al., outcomes were measured for 149 patients with breast cancer and LM who received a variety of treatment modalities. In addition, the efficacy of intrathecal methotrexate was compared to intrathecal liposomal cytarabine. Median survival from LM diagnosis for study patients receiving intrathecal methotrexate was 4.2 months compared to 4.6 months for those receiving intrathecal liposomal cytarabine. The study concluded that intrathecal chemotherapy was not associated with an overall survival benefit. Significant neurologic toxicities were observed for patients receiving intrathecal chemotherapy. Specifically, 47% of patients receiving intrathecal chemotherapy had neurologic complications compared to only 6% in patients who did not receive intrathecal chemotherapy ($p = .007$). Finally, in a planned analysis of the effect of radiation therapy and systemic therapy on survival, only systemic therapy was associated with an improvement in overall survival for the study population [16].

The combination of intrathecal chemotherapy with radiation therapy has also been evaluated. In a Phase II single-arm study by Pan et al., the efficacy and safety of combining intrathecal chemotherapy with involved field radiotherapy for treating LM in advanced solid tumors was studied. A total of 59 patients with various solid tumors were enrolled. Only 11 patients (19%) had breast cancer. The overall clinical response rate was 86%; however, the median overall survival was only 6.5 months with a 1-year survival rate of 21%. Furthermore, neurotoxicity was observed in 26% of patients, with 5% of patients suffering severe neurotoxicity and two patients died from treatment-related neurotoxicity [19]. They concluded that a combination of intrathecal chemotherapy and radiation therapy is a possible treatment option for LM in metastatic solid tumors. However, this treatment approach is associated with significant neurotoxicity and does not appear to demonstrate a significant survival advantage.

Data supporting the use of systemic chemotherapy for LM are limited to case reports and small case series as most patients with LM are excluded from larger clinical trials. Observed efficacy has been seen in a limited number of regimens that have adequate CNS penetration. HD-MTX has been shown in retrospective studies and case reports to have significant efficacy when compared to other therapies for patients with LM [10–12].

Glantz et al. [12] reported on 16 patients with solid tumor LM who were treated with HD-MTX dosed at 8 g/m^2. Toxicity, response, and survival were compared to a reference group of 15 patients who received standard intrathecal methotrexate. The median overall survival for those who received HD-MTX was 13.8 months compared to 2.3 months for the intrathecal methotrexate group ($p = .003$) [12]. The toxicity of the HD-MTX was minimal, and adequate CSF drug concentrations were measured. This study supports the use of HD-MTX as a viable treatment option for LM in metastatic solid tumors including breast cancer; the survival observations suggest superiority of this therapy to intrathecal chemotherapy.

Researchers have also studied the combination of HD-MTX with intrathecal chemotherapy. In a Phase II study by Mrugala et al. [20] that closed early because of poor accrual, patients with breast cancer and LM were treated with HD-MTX in combination with intrathecal liposomal cytarabine. The three patients reported in this study had an overall survival of 11.3, 8.2, and 5.5 months at time of data extraction [20]. The small sample size makes it difficult to interpret these data; however, the reported survival does suggest that HD-MTX with or without intrathecal chemotherapy may be a viable option for LM in breast cancer.

Overall, the data reviewed, including our report, suggest that HD-MTX is a viable treatment option for LM in breast cancer. Our observations suggest that integrating HD-MTX into a multimodality treatment plan can be associated with prolonged survival in select cases of breast cancer with LM. Currently, there are limited data available to help predict which patients with LM might respond to therapy. Further study is necessary to better understand the underlying pharmacogenomics of responders compared to nonresponders to better guide treatment selection and predict patient outcomes. In the future, genomic analysis for methotrexate targets in malignant cells in the CSF may be of value in identifying patients most likely to response to HD-MTX [21].

Conclusion

HD-MTX is a viable treatment option for patients with LM in breast cancer, and in select cases, the use of HD-MTX may be associated with prolonged survival. Incorporating HD-MTX as part of a multimodality treatment plan for breast cancer with LM may be the best approach to therapy. Additional prospective studies are needed to better clarify the role of HD-MTX for breast cancer patients with LM.

Declaration of Competing Interest

The authors declared that there is no conflict of interest.

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