Published in final edited form as:

Clin Breast Cancer. 2012 December ; 12(6): 445–449. doi:10.1016/j.clbc.2012.07.010.

Complete Radiologic Response and Long-Term Survival With Use of Systemic High-Dose Methotrexate for Breast Cancer–Associated Leptomeningeal Disease

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Keywords

Blood brain barrier; HER2 positive breast cancer; Leptomeningeal disease; Metastatic breast cancer; High-dose methotrexate

Case Report

A 56-year-old postmenopausal woman presented with a 3-month history of weight loss, nausea, vomiting, polyuria, and polydipsia. On examination, she was mildly hypotensive, had dry mucus membranes, and appeared chronically ill. A 2-cm mass was palpated in the left breast. Laboratory evaluation revealed a sodium level of 163 mEq/L, and further workup was consistent with central diabetes insipidus. She also was found to have evidence of hypopituitarism, with an undetectable adrenocorticotrophic hormone and low-normal serum cortisol level, a low free thyroxine level in the setting of a normal thyroid stimulating hormone level, and a low follicle-stimulating hormone level despite postmenopausal status. Gadolinium-enhanced magnetic resonance imaging (MRI) of her brain revealed a bilobed sellar-suprasellar mass. Staging positron emission tomography (PET) revealed fluorodeoxyglucose uptake in the left breast and in the left supraclavicular, bilateral axillary, and inguinal lymph nodes; a sellar-suprasellar mass; and widespread bony metastases. Microscopic examination of a breast core biopsy revealed large epithelioid cells that infiltrated benign breast lobules in both single-file configuration as well as in sheets (Figure

1A). The atypical cells displayed round nuclei, focally prominent nucleoli, and abundant cytoplasm with intracytoplasmic vacuoles. Immunohistochemistry showed the tumor cells to be negative for E-cadherin, which supports the diagnosis of infiltrating lobular carcinoma. The tumor cells were negative for the estrogen and progesterone receptors but were positive for human epidermal growth factor receptor 2 (HER2/*neu*) (Figure 1B). She was started on levothyroxine, hydrocortisone, and desmopressin nasal spray for her central hypothyroidism, central adrenal insufficiency, and diabetes insipidus, respectively, as well as bisphosphonates for her bony metastasis.

She underwent transsphenoidal resection of the sellar mass followed by fractionated stereotactic radiation therapy to the sellar region. Intraoperative frozen section examination of the sellar mass revealed tissue fragments composed of atypical, discohesive cells with epithelial features, including intracytoplasmic vacuoles (Figure 1C). Immunohistochemistry performed on the permanent sections of the pituitary mass showed the tumor cells to be positive for gross fluid cystic disease protein (Figure 1D), consistent with a metastasis of breast origin. Systemic therapy with weekly paclitaxel and lapatinib was started and tolerated well for 8 months. Paclitaxel was subsequently discontinued due to toxicity, and single-agent lapatinib was continued for an additional 6 months.

New onset of headaches and disequilibrium a few months later prompted an MRI of the brain, which revealed new diffuse fine nodular enhancement in the subarachnoid space lining the posterior fossa and extending supratentorially as well as into the superior cervical spinal, consistent with meningeal coating. Baseline coronal T1 with postgadolinium images (Figure 2A) showed a bright signal throughout the cerebellar folia, with a large nodular lesion in the left cerebellar hemisphere. Cerebrospinal fluid (CSF) sampling revealed an elevated protein level, and cytopathology was positive for signet ring cells consistent with metastatic adenocarcinoma. Restaging PET indicated excellent control of systemic disease. Based on the distribution of the central nervous system (CNS) disease, it was thought unlikely that intrathecal (IT) chemotherapy would penetrate the sites of disease. High-dose methotrexate (MTX), at a dose of 8 mg/m², was administered every 2 weeks for 6 cycles, by which time she had resolution of her neurologic symptoms. MRI with identical technique performed at 3 months after treatment (Figure 2B) and 12 months after the last high-dose MTX (Figure 2C) indicated complete resolution of the prior changes. Of note, intravenous trastuzumab was also administered every 3 weeks during this time. High-dose MTX was administered monthly thereafter for 5 additional cycles, at which time, it was discontinued due to intolerance. Our patient continues to receive trastuzumab 18 months after the diagnosis of leptomeningeal disease (LMD). She has an excellent quality of life, and no neurologic sequelae or evidence of CNS recurrence.

Discussion

Breast cancer is one of the most common malignancies that metastasizes to the leptomeninges and accounts for approximately 27% of all LMD cases.¹ Although only approximately 8% of locally advanced breast cancers will metastasize to the CNS (including parenchymal metastasis and LMD), this confers a poor prognosis, with an estimated median survival of 8.1 months.² Furthermore, untreated LMD of any tumor origin confers a median

survival of 4 to 6 weeks, with a median survival for treated LMD being <6 months.³ Of patients with CNS metastasis, however, analysis of the data suggests that those with HER2⁺ tumors live longer than those with HER2⁻ tumors (11 vs. 6 months).⁴

Patients with LMD who have good performance status, an absence of significant neurologic symptoms, and low systemic disease burden are considered to have favorable prognostic features.⁵⁻⁷ For these patients, the current treatment approach involves the use of whole-brain irradiation and/or radiation to bulky sites of disease as well as IT chemotherapy administration.⁸⁻¹⁰ For patients with unfavorable features, palliation may include radiation therapy, but IT therapy is generally not recommended. IT administration of chemotherapy is an invasive procedure, with adverse effects, including nausea, vomiting, aseptic meningitis, and seizures.^{11,12} The technique itself is also highly variable and may be associated with procedural complications such as subdural leakage, which can result in variable CSF concentrations.¹³ IT chemotherapy is also not recommended in the setting of multiple sites of bulky disease or where obstruction to CSF flow is present.¹³

Systemic treatment approaches have also been evaluated in the treatment of LMD. High-dose systemic MTX crosses the blood-brain barrier (BBB) and has been shown to have excellent penetration into CNS tissues.^{14,15} High-dose MTX has been used in various solid tumors to treat LMD, with disease responses and improved survival observed when compared with historical data on IT therapy.^{16,17} A retrospective study of 32 patients (29 with breast cancer) with parenchymal metastasis or LMD treated with systemic MTX (3.5 g/m² every 2 weeks) has been reported. Eighteen of these patients had disease stabilization (either partial response or stable disease). However, of the 32 patients, 9 patients were treated concurrently with other CNS-directed therapy, including radiation, IT chemotherapy, or CNS penetrating chemotherapy. Of the 23 patients treated with intravenous MTX monotherapy, 5 of 14 with LMD had disease control (partial response or stable disease). In patients with parenchymal metastasis alone who received intravenous MTX monotherapy (n = 9), 8 experienced disease control. The median overall survival for the entire cohort (n = 32) from the time of diagnosis was 13.4 months, with 1 patient alive at 33.9 months. Of note, no patients achieved a complete response to therapy.

Other systemic treatment approaches may provide benefit to patients with LMD. Capecitabine penetrates the BBB and has been shown to have activity against CNS metastasis in breast cancer.¹⁸⁻²⁰ Patients with HER2⁺ metastatic breast cancer have a higher rate of CNS disease (approximately 40% incidence) when compared with other breast cancer subtypes.²¹ However, the median survival for these women far exceeds the median for other subtypes,²² and a number of targeted agents used to treat this population have been shown to cross the BBB. The small molecule endothelial growth factor receptor/HER2 inhibitor, lapatinib, is known to cross the BBB and has been associated with disease responses in the CNS.^{23,24} Other investigational approaches to managing HER2⁺ tumors with CNS involvement include new small molecule inhibitors such as neratinib and afatinib, as well as IT trastuzumab.^{25,26}

We have described a case of a patient with breast cancer-associated LMD treated with high-dose systemic MTX concurrent with anti-HER2 therapy, who experienced a complete

radiological response after 6 cycles of therapy as well as survival beyond the reported median for her disease. Important features to note that relate to this case include low systemic disease burden, which was well controlled with trastuzumab, and lobular histology, which typically has a more favorable prognosis compared with other breast cancer histologies.²⁷ An additional feature of this approach is avoidance of radiation therapy, which saves it as a potential salvage therapy in the event of progression and minimizes the potential risk of cognitive decline that can be associated with whole-brain radiotherapy.

In summary, IT chemotherapy has poor penetration to CNS tissues, and its use may be further hampered by the location and bulk of disease sites as well as technical variation. Systemic chemotherapy that penetrates the BBB may have better CNS penetration and more uniform distribution than the IT approach,¹⁴ although no prospective data support this. Clearly, prospective studies that use chemotherapy that penetrates the BBB, such as MTX, are warranted to examine more carefully chemotherapy's role in the management of LMD. Issues that require clarification that relate to this treatment approach include the optimal duration of therapy, the optimal dose of chemotherapy, and the role of concurrent or adjunct CNS-directed therapies. Quality of life during such treatment should also be considered, given that high-dose MTX requires frequent hospitalization. Future studies, in addition, may involve comparisons of the available treatment strategies, eg, a randomized trial that compares IT chemotherapy and radiation therapy vs. high-dose MTX. Until further data are available, patients with LMD should be managed in a center with experienced personnel in treating this rare manifestation of malignancy in a multidisciplinary fashion that involves neurosurgeons, neurooncologists, and radiation oncologists.

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Clinical Practice Points

- Breast cancer is one of the most common malignancies that metastasizes to the leptomeninges, with human epidermal growth factor receptor 2 (HER2)⁺ tumors having a higher incidence of central nervous system involvement than other breast cancer subtypes. Conventional treatment for leptomeningeal disease includes radiation therapy and intrathecal chemotherapy, the latter requiring an invasive procedure for administration, with the potential for significant adverse effects. Despite standard treatment approaches, patients with leptomeningeal disease usually have a poor prognosis, with a median survival of <6 months. High-dose methotrexate is one of the few chemotherapeutic agents known to cross the blood-brain barrier; however, data are limited as to its clinical efficacy.
- We present the case of a patient with advanced HER2⁺ breast cancer who developed new onset headaches and disequilibrium secondary to both intracerebral and leptomeningeal disease. Treatment with high-dose systemic methotrexate concurrent with trastuzumab resulted in resolution of her symptoms as well as a long-lasting clinical and radiologic remission that exceeded that expected with conventional therapies.
- Prospective studies that evaluate the role of agents that penetrate the blood-brain barrier, including high-dose methotrexate, are clearly warranted in patients with leptomeningeal disease. In addition, this patient population should ideally be managed in a center with personnel experienced in treating this rare manifestation of malignancy in a multidisciplinary fashion.

Figure 1.

Histologic Examination of Invasive Lobular Carcinoma Primary to the Breast and Metastatic to the Sellar Fossa. The Primary Breast Carcinoma Consisted of Atypical, Plump Cells with Abundant Cytoplasm and Intracytoplasmic Vacuoles (A, H&E, Magnification $\times 100$), That Were Negative for E-cadherin and Displayed Strong Circumferential Membranous Staining for HER2/neu (B, H&E, Magnification $\times 100$). The Sellar Mass Consisted of Discohesive Atypical Cells with Intracytoplasmic Mucin (C, H&E, Magnification $\times 100$), That Were Positive for Gross Fluid Cystic Disease Protein (GCDFP) (D, H&E, Magnification $\times 100$)

Figure 2.

Brain MRI T1 Post-gadolinium Images at Baseline (A), Post-treatment at 3 Months (B), and 12 Months (C) Showing Complete Resolution of Cerebellar and Leptomeningeal Enhancement