Endocrine Therapy for Leptomeningeal Metastases from ER-Positive Breast Cancer: Case Report and a Review of the Literature

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Abstract: Leptomeningeal disease is an uncommon complication of estrogen receptor positive breast cancer. While there is little consensus on the standard of care, recommendations from current clinical practice guidelines are to treat with intrathecal chemotherapy, necessitating invasive procedures and potentially resulting in a substantial incidence of serious complications and side effects. Here, we review all published evidence of the effectiveness of systemic hormonal therapy alone in treating this condition, with the advantage of requiring no invasive procedures and having virtually no serious complications or side effects. Evidence indicates that most hormonal therapies can penetrate the central nervous system and can be an effective treatment of endocrine sensitive breast cancer that is widely metastatic to the leptomeninges.

Key Words: breast cancer, endocrine therapy, ER-positive, leptomeningeal

Clinically, leptomeningeal disease (LMD) occurs in about 1–2% of all breast cancer. It most often occurs in patients with high grade estrogen receptor (ER)-negative infiltrating ductal carcinoma or low grade ER-positive infiltrating lobular carcinoma (1), though it can occur with any subtype. Whether this predisposition is due to factors related to cell shape, density, deformability, adhesion or other physical properties, or is related to the intrinsic molecular workings of the cell is unknown. Parsimony would favor a single, unifying explanation, but, since the known molecular biology of lobular and high grade ER-negative ductal tumors is disparate and cell morphology seen under the microscope for these two breast cancer types is also quite different, a unifying link remains a mystery. Whatever the underlying drivers, it remains challenging to treat. Here, we show an illustrative example of ER-positive LMD that responded dramatically to hormonal therapy, review all the published literature on the subject, and offer insights and implications from this experience.

A 46-year-old premenopausal woman initially experienced radicular lower back pain and then weakness in her lower extremities. This progressed over 2 weeks and she could no longer stand and then had loss of urinary and bowel control. She was previously healthy.

Neurologic exam showed that she could not stand or walk and there were no patellar or Achilles reflexes. The breast exam was normal, as was the remainder of the physical exam. A lumbar puncture showed a protein of 1552 mg/dL, glucose 21 mg/dL and nucleated cells 388/dL with 98% being identified as lymphocytes. Cytology was not performed since a neoplasm was not initially suspected. Magnetic resonance imaging of the cervical, thoracic, and lumbar spine showed diffuse leptomeningeal enhancement of the cerebellar hemispheres, brainstem, spine, and cauda equina nerve roots (Fig. 1a). A presumptive diagnosis of infectious meningitis was made and intravenous antibiotics were started. All cultures and serologic tests remained negative however, and she did not clinically improve.

Computerized tomography of the chest, abdomen, and pelvis was unremarkable. A mammogram showed an area of architectural distribution in the left breast.
Magnetic resonance of the breasts showed two areas of enhancement along the 3:00 axis in the left breast. A core needle biopsy of one area showed low grade infiltrating lobular carcinoma, Allred score for ER was 8/8, for PR 8/8, HER-2 by immunohistochemistry was 0/3, and Ki-67 was 1%.

A repeat lumbar puncture done 17 days after initial presentation demonstrated malignant cells by cytology. Protein had risen to 1,976 mg/dL. Tamoxifen 20 mg once a day was initiated. One week latter, her leg strength had improved and her bowel control returned, though she could not walk and a urinary catheter remained in place. Leuprolide was added. She then received 2,000 cGy of radiation to the cauda equina beginning 7 days after tamoxifen was started. After 2 months of tamoxifen and leuprolide, bowel and bladder control returned to normal, she could stand and walk, and her cerebral spinal fluid protein decreased to 528 mg/dL from a pretreatment level of 1,926 mg/dL. Repeat magnetic resonance of the spine and brain two and a half months after starting systemic therapy showed near resolution of leptomeningeal enhancement over the entire neuroaxis (Fig. 1b). Five months later, she had returned to normal activities of daily living with normal bowel and bladder function. Protein had decreased further to 469 mg/dL. Though cytology has remained positive, nucleated blood cell count decreased from 388/dL to 71/dL, possibly reflecting a quantitative drop in the amount of nucleated cancer cells in the cerebral spinal fluid. Clinical response was sustained for 10 months, when leg weakness and constipation recurred. Her disease then did not respond to letrozole, everolimus and leuprolide, and she died of progressive disease 1 year after initial diagnosis.

**Figure 1.** (a) Diffuse leptomeningeal enhancement of the thoracic and lumbar spinal cord as well as the conus medullaris and cauda equina nerve roots. Upper arrows show thoracic meningeal enhancement, lower arrow, cauda equina involvement. (b) Magnetic resonance imaging of the thoracic and lumbar spine 2.5 months after treatment. Near complete resolution of enhancement is seen.

**REVIEW AND DISCUSSION**

The Ommaya reservoir first came into use in the early 1960s, initially to treat central nervous system (CNS) infections such as cryptococcal meningitis (2). It was soon used in the treatment of acute leukemia in the CNS, and then, on the supposition that all systemic anticancer agents penetrated poorly into normal or diseased meninges, its use was extrapolated to solid tumors. This strategy has achieved little therapeutic success, with median survivals remaining in the 3- to 4-month range for at least 40 years. Reported complication rates remain high, with death from catheter related causes of 1–8% (3), chemical leukoencephalopathy rates of 20% (4), CNS infection rates of 15% (5), and an overall complication rate of 50% (6). There are no randomized trials of intrathecal (IT) therapy compared to best supportive care to directly determine what effect, if any, IT chemotherapy has on the natural history of the disease in breast cancer. Given the known average life expectancy with this management, median improvement in survival could not exceed 1–2 months.

Metastatic, ER-positive breast cancer can be a relatively indolent disease and about 50% of patients benefit from hormonal manipulation. Trials have demonstrated that initial chemotherapy, either alone or in combination with hormonal therapy, does not improve survival, compared to initial hormonal therapy alone (7,8). Hormonal therapy has fewer side effects and a portion of patients experience long-term, sustained responses. For those reasons, hormonal therapy alone is the strategy of choice to initially treat most women with ER-positive metastatic breast cancer. Thus, the use of IT chemotherapy via a brain
reservoir, with or without hormonal therapy, contradicts this well-established, evidenced-based paradigm of breast oncology. Moreover, methotrexate and cytosine arabinoside have modest or no activity, respectively, as systemic therapeutic agents for metastatic breast cancer, and neither currently play an important role in the management of systemic disease. Recent data also indicate that high dose systemic methotrexate has disappointing activity in the treatment of carcinomatous meningitis for breast cancer, with no improvement compared to historical results (9). Possibly, these drugs were simply borrowed from leukemia management as a matter of convenience as their main rationale for use in breast cancer LMD.

In addition, more direct evidence does not support any benefit from IT chemotherapy added to systemic therapy for the treatment of LMD. Bokstein analyzed and compared results from two prospective trials from the same institution (4). One study used systemic therapy and radiation therapy and one used systemic therapy, radiation therapy and IT chemotherapy. This comparison found no difference in survival, but a higher treatment complication rate with IT therapy versus without IT therapy, approximately 60 versus 13%, respectively. Boogerd conducted a randomized, prospective trial of systemically treated breast cancer patients with LMD, with or without IT methotrexate (10), n = 35. No difference was seen in time to progression in the two groups, and median survival was longer, 30 weeks in the no IT group compared to 18 weeks in the IT group, p = 0.3. Survival without IT therapy was thus double that expected from historical controls. Treatment-related complications were 42% in the IT group versus 6% in the no IT group. The trial was closed early because of difficulty in obtaining consent to be randomized to IT therapy. Supporting these findings, inspection of all trials in the published literature on the subject noted that survival has not changed significantly in over 30 years for intrathecally treated LMD (11), leading one to reasonably conclude that efficacy is limited at best, with no strategic way forward with this approach.

No prospective trials exist examining the use of hormonal therapy alone or with radiation therapy for the treatment of ER-positive LMD. Here, we present an example of a woman with LMD as the initial presentation of a clinically undetectable breast cancer, a rare but reported phenomenon (12). More importantly, when she was treated with tamoxifen, leupolide and local radiation therapy, she had rapid resolution of bowel and bladder incontinence, was able to walk from a paraplegic state, cerebral spinal fluid protein level dropped from 1,976 to 460 mg/dL, and enhancement throughout the meninges on magnetic resonance imaging resolved. These last two findings and the lack of further neurologic progression elsewhere definitively prove a systemic effect and penetration of systemic therapy into the CNS. Table 1 lists all reported cases of ER-positive LMD, extending this proof of principle to other situations and breast tumors. Because this is a collection of case reports, and subject to significant selection bias and an unknown denominator, the specific probability of benefit cannot be ascertained, but it provides proof of principle, over time and multiple different clinical contexts, of this approach. In addition, successful hormon-al treatment of LMD for prostate cancer has been reported several times, making this strategy generalizable to other malignant tumor types (21,22).

There may be concern that hormonal therapies will not penetrate the blood–brain barrier. Evidence does not support this concern, and indeed clearly indicates that hormonal therapies or their downstream therapeutic effect penetrate effectively through the normal or abnormal blood–brain barrier. Hot flashes are mediated centrally by a mechanism in the brain, and while the specifics have not been fully worked out, evidence indicates neurons in the hypothalamus or brain stem are responsible for mediating this phenomenon (23,24). Most, if not all, hormonal therapies for breast cancer cause hot flashes; therefore the molecule, or the downstream therapeutic effect of these molecules, must penetrate the CNS to produce hot flashes. The only possible exception to this may be fulvestrant, which does not clearly increase the risk of hot flashes.

CONCLUSION AND FUTURE DIRECTIONS

Leptomeningeal disease is a devastating complication of breast cancer. Treatment with chemotherapy via an Ommaya reservoir is fraught with complications, is marginally effective, and can often make a difficult situation worse. Hormone therapy has long been the treatment of choice for endocrine sensitive, ER-positive breast cancer that has metastasized diffusely to distant sites. Consistent with this established principle of breast oncology, and because of its ease of use, advantageous side effect profile, low cost, and relative efficacy, it is indicated as a treatment option for LMD caused by endocrine sensitive breast cancer.
Further insight and improvement into the treatment of endocrine resistance in breast cancer is needed. HER-2 kinase (25–27), mTOR (28,29), PI3 kinase (30), and CDK4/6 (31) small molecule inhibitors in combination with hormonal therapies may be useful in addressing this problem and should be explored in the treatment of LMD. Laptanib, a HER-2 kinase inhibitor, enters the CNS and has shown modest activity alone in HER-2 positive brain metastases. A newer, irreversible inhibitor of HER-2 kinase action, neratinib, may be laptanib more potent than laptanib and deserves attention, though its CNS penetration has been less well studied. ONT 380 is another such in-class molecule, but that penetrates the CNS in preclinical models. Everolimus, an mTOR inhibitor, clearly penetrates the blood–brain barrier and could therefore be added to existing hormonal therapy (32). There are currently two oral, selective receptor down-regulators, SERDS, now in early development that show promise, and might penetrate the central nervous system (33). Lastly, heat shock protein 90 inhibitors, in combination with hormonal therapy, have demonstrated potential in abrogating resistance to therapy (34).

Current predictors of endocrine sensitivity in ER-positive breast cancer, such as quantitative ER and PR, Ki-67, bcl-2 expression, Oncotype DX assay score and other luminal A subtype genomic classifiers could be useful for optimally selecting patients for hormonal LMD therapy. Markers of early response or progression, such as a change in Ki-67 score, could be assessed on tumor cells from the CSF, 1–2 weeks following initiation of hormonal therapy, after a similar fashion that is already been proven to be predictive in pre-operative models of systemic hormonal agents for breast cancer (35). Fluorescence-activated cell sorting analysis could give objective, reproducible measures of changes in low abundance cell populations in cerebral spinal fluid, and has sometimes been used in leukemic studies. CSF sampling after drug exposure could allow for drug level quantitation.

Given the present state of knowledge and outcomes, a simple prospective multicenter study of physician’s
hormonal therapy of choice with time to neurologic progression and survival as end points as well as central collection of cerebral spinal fluid and tumor blocks for exploratory molecular analyses would be illuminating and a step forward. Last, grouping together of LMDs across disparate anatomic and molecular tumor types can dilute potentially relevant therapeutic and biologic signals and should be avoided in future efforts.

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CONFLICTS OF INTEREST

All authors have no conflict of interest to disclose.

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