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Review Article

Leptomeningeal metastases in breast cancer

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Abstract: Central nervous system (CNS) metastasis from breast cancer may be characterized as either parenchymal brain metastasis (BM) or leptomeningeal (LM) metastasis. BM are much more common (about 80% of all CNS metastases), and have been more extensively studied than LM. CNS metastasis in breast cancer has been associated with reduced overall survival, with the shortest survival generally observed in cases of LM. Here, we review the epidemiology, prognostic factors, diagnostic tools, currently available treatments, and potential future therapies for LM from breast cancer.

Keywords: Leptomeningeal metastases, intrathecal chemotherapy, breast cancer

Epidemiology

With improved systemic therapies successfully resulting in more long-term survivors with advanced cancers, the incidence of central nervous system (CNS) metastasis is increasing [1, 2]. There were an estimated 69,325 cases of brain metastasis (BM) from the 15 most common primary sites in 2007, a projected 5% increase from 2003, with breast cancer BM comprising 15.4% of these [3].

In breast cancer, aggressive chemotherapy has resulted in improved outcomes for individuals with advanced disease [4]. Along with increased survival, late-onset metastatic spread has become an increasing clinical problem. Although less frequent than solid organ and bone metastasis, central nervous system (CNS) metastasis occur somewhat commonly in breast cancer, and may present long after treatment of the primary cancer [5]. Individuals diagnosed with early stage breast cancer have a 5% long-term risk of developing CNS metastasis [6, 7]. Although CNS metastasis most commonly occurs in those with known systemic metastasis, the overall risk of CNS recurrence as the initial site of metastatic spread is 1.3% [7]. The median overall survival in those with breast cancer and CNS metastasis is 9 months, with a one-year survival rate of 20% [7]. BM occur most commonly (10%) in the young adults (20-39 years-old), and are more common in African Americans compared to white patients (7.4% versus 4.6%) [6].

Certain breast cancer subtypes have been associated with an increased risk of CNS metastasis. For example, those that are hormone receptor negative are 4 times more likely to have CNS metastasis than those that are hormone receptor positive, and individuals with lung metastasis as a first site of relapse are also 4 times more likely to develop CNS metastasis [8]. A 24-month metastasis-free interval following the diagnosis of breast cancer is associated with a reduced overall risk of CNS metastasis [8].

The majority of CNS metastasis is due to parenchymal BM, with leptomeningeal metastasis (LM) comprising a much smaller number. The precise incidence is difficult to estimate, in part because of the infrequency of LM, and in part because of variability in the detection of LM, and some instances of minimally or asymptomatic disease. There are also regional differences in patient populations, and the potential for referral bias at large centers. As a result, the actual incidence is likely higher than what has

Table 1. Prognostic Factors in Leptomeningeal Breast Cancer

Prognostic factor	Favorable (reference #)	Unfavorable (reference #)	Nonsignificant (reference #)
Clinical			
Good Initial Performance Status	14, 36, 37, 56		34, 38
Histology			56
Histological Grade			56
Active systemic disease		34, 36	38
Concurrent Brain Metastasis			36
Increased ICP at Diagnosis			14
HR Receptor Positivity	56		14, 34, 36
HER 2 Receptor Positivity			34, 56
Triple Negative Receptor Status		14	
Diagnostic			
Positive Initial CSF cytology			36
Normal Initial CSF Protein	14		36, 38
Low CSF glucose			36, 38
Elevated CSF Cyfra 21-1 level		56	
Therapeutic			
Any chemo	14, 34		
IT Chemo	37		36
IV Chemo	37		36
Combined Modality Tx	34		
> 3 prior chemotherapy regimens	56		
WBRT	14, 37		
Spine RT			37
Response			
Clinical Response	14, 37		
CSF Cytologic Clearance	34, 38		

ICP=intracranial pressure; HR=hormone receptor; HER 2=human epidermal growth factor receptor 2; CSF=cerebrospinal fluid; cyfra=cytokeratin fragment; IT=intrathecal; IV=intravenous; Tx=treatment; WBRT=whole-brain radiation therapy; RT=radiation therapy.

been reported. Overall, LM likely comprises about 11-20% of CNS metastasis [9, 10]. Prospective studies have found a median overall survival (OS) of 9-30.3 weeks in those with breast cancer following the diagnosis of LM [11-13] (**Table 1**). Compared to lung cancer LM, studies have shown mixed results, with some favoring a longer survival for breast cancer LM [12] and others demonstrating no difference [13].

Clinical features

Presenting symptoms in breast cancer LM likely occur at frequencies similar to what has been observed in trials that have included multiple solid tumor histologies, although direct comparisons have not been made. Headache is among the most common symptoms, likely due to infiltration of the meninges by tumor cells, or elevation in intracranial pressure (ICP). Any new headache syndrome in a patient with cancer, and especially headaches that are worse upon awakening or when recumbent, and headaches that awaken a person from sleep should heighten suspicion for LM and potentially elevated ICP. In extreme cases, ICP elevation may result in severe headaches, papilledema or a depressed level of consciousness. In breast cancer LM, up to 46% of cases have confirmed ICP elevation at diagnosis [14]. Cranial neuropathies or back pain due to involvement of spinal nerve roots is also common. Seizures and focal neurological deficits localizing to brain parenchyma are more frequently seen with BM [15]. Up to 1/3 of cases with LM are asymptomatic.

The interval between initial cancer diagnosis and the development of LM is longer for breast cancer than in other solid tumors. Median time

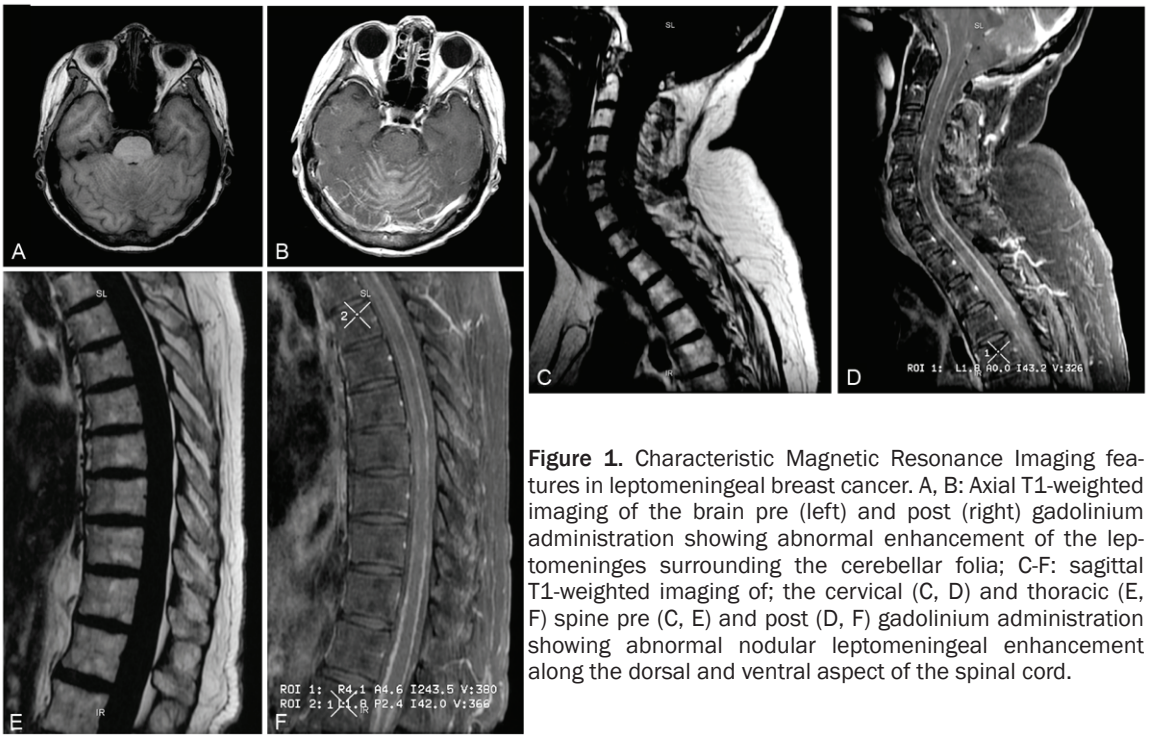

Figure 1. Characteristic Magnetic Resonance Imaging features in leptomeningeal breast cancer. A, B: Axial T1-weighted imaging of the brain pre (left) and post (right) gadolinium administration showing abnormal enhancement of the leptomeninges surrounding the cerebellar folia; C-F: sagittal T1-weighted imaging of; the cervical (C, D) and thoracic (E, F) spine pre (C, E) and post (D, F) gadolinium administration showing abnormal nodular leptomeningeal enhancement along the dorsal and ventral aspect of the spinal cord.

from initial breast cancer diagnosis to LM diagnosis is 3 ½ years [14, 16, 17] compared to one year or less for lung cancer LM [16-18].

Breast cancer LM may occur as an isolated CNS metastatic site, or may occur with concurrent BM at variable frequencies (37-63%) [9, 10, 19]. Concurrent active cancer outside the CNS occurs in 60-80% at LM diagnosis [19, 20].

Diagnostics

Traditionally, the combination of clinical symptomatology and demonstration of malignant cells in cerebrospinal fluid (CSF) have been required to establish a diagnosis of LM. However, the sensitivity of CSF cytology in solid tumors is somewhat limited and may be adversely impacted by limited sample size, or delays in processing [21]. Repeating the CSF cytology up to 3 times increases the sensitivity in solid tumors from 75% to above 90% [21]. Ambiguous CSF cytology, often reported as 'cytological atypia' is suggestive of LM, but makes diagnosis of LM and assessment of cytologic response challenging.

Contrast-enhanced magnetic resonance imaging (MRI) has emerged as a reliable diagnostic tool in LM [22]. Leptomeningeal enhancement, nodular enhancement or cranial/spinal nerve enhancement are all characteristic (**Figure 1**). In the appropriate clinical context, findings suggestive of LM on MRI are adequate to initiate treatment of LM even in the absence of a positive CSF cytology [22]. Survival in solid tumor LM is similar between individuals with positive versus negative CSF cytology [23].

Breast cancer molecular subtypes and LM

Measurement of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER-2) expression levels in breast cancer gives prognostic information, and helps to guide systemic chemotherapy. Overall survival and proclivity to develop metastatic spread including CNS metastasis differs depending on hormone receptor (ER/PR) and HER-2 status at diagnosis.

Overexpression of HER-2 has been associated with an increased incidence of CNS metastasis compared to other molecular subtypes [24-26]. Late occurrence of CNS metastasis in spite of good systemic disease control in HER2 positive breast cancer has led to the postulation that treatment with the anti-HER2 monoclonal antibody trastuzumab may have a causative role.

However, the incidence of brain metastasis appears similar between trastuzumab treated and non-treated individuals [27-29], making it more likely that brain metastasis occur more commonly as part of the intrinsic biology of HER2 positive breast cancer. Large studies in HER2 positive breast cancer have demonstrated improved overall survival, longer time to the development of CNS metastasis [30] and improved survival following the diagnosis of BM in those who received trastuzumab [4]. One possible explanation for the benefit with trastuzumab is that even though it does not appear to readily cross the blood-brain barrier (BBB) and produce therapeutic levels in CSF [31, 32], the antibody may prevent circulating tumor cells from entering the CNS, or it may reach the tumor regionally in sites where tumor infiltration has disrupted BBB integrity [33].

In long-term follow-up of individuals with early-stage breast cancer, those with ER/PR negative HER-2 positive tumors were most likely to develop CNS metastasis (14.3%), while CNS metastasis were less common in ER/PR/HER-2 positive breast cancers (7.9%) [5]. Luminal A (ER +, low grade) breast cancer was associated with the least frequent development of CNS metastasis (2.2%) [5].

Initial hormone receptor positivity is associated with a higher incidence of bone metastasis and a longer median time to the development of LM when compared to triple-negative breast cancer [34]. Triple negative breast cancer is more likely than receptor positive breast cancer to present with isolated LM and has been associated with a shorter median overall survival following the development of distant metastases. In 3 year median follow-up, of individuals with triple negative breast cancer who experienced a recurrence, 13% recurred initially in the CNS, and 36% had CNS involvement overall in their clinical course [25].

As a prognostic indicator in breast cancer LM, however, investigations looking at hormone receptor and HER-2 status have produced variable results. Some series have found that hormone receptor positivity is associated with longer survival [35], while others have found no association [34, 36]. HER-2 status does not appear to impact overall survival from LM, but treatment with trastuzumab was associated with a significantly longer time to the development of LM (15.2 versus 9.9 months) [34, 36].

Other prognostic factors

Institutional series have found a variety of factors that impact survival in breast cancer LM beyond hormone receptor status (**Table 1**). Better initial performance status is generally associated with improved survival both in LM from all cancers [20], and from breast cancer LM specifically [35-37]. The cytologic conversion of CSF from positive to negative during the course of treatment (cytologic response) [34, 38] and clinical improvement following treatment (clinical response) [37] have also been associated with improved survival. Histology and histological grade are significant in some studies [36], but not in others [35]. Treatment with radiation and/or chemotherapy is consistently associated with better overall survival [34, 35, 37]. However, given that these are non-randomized, retrospectively collected observations, treatment bias cannot be excluded. It is likely that in some cases, those treated with more aggressive chemotherapy and radiation were younger and had a better initial performance status, two factors that also impact prognosis.

Current therapies

There is currently no generally accepted standard of care in the treatment of breast cancer LM. Surgery (for hydrocephalus), radiation therapy (RT), and chemotherapy (systemic or intra-CSF) may be considered. Treatment decisions are influenced by the individual's functional status, ability and willingness to receive additional treatment, and extent of active systemic disease. In some cases, the diagnosis of LM compels providers and patients to pursue palliative care, especially when LM is accompanied by a dramatic clinical decline.

One caveat to consider when assessing functional status in LM patients is whether or not an individual has elevated ICP. CSF outflow obstruction that occurs when the arachnoid villi are no longer able to effectively reabsorb CSF is often associated with a progressive headache syndrome and depressed level of consciousness. Relief of CSF outflow obstruction by CSF diversion has been shown to improve functional status, and is likely to prolong survival in

Table 2. Leptomeningeal Metastasis Randomized Controlled Trial Survival Data

Study	LM Cancer Types	Treatment Arms	n (Br/Total)	Median OS Breast	Median OS Total
Boogerd et al. [11]	Breast Only	IT	17/17	18.3	n/a
		IV	18/18	30.3	n/a
Grossman et al. [12]	Br, Lu, Ly, Other	IT T	24	NR	14.14
		IT MTX	28	NR	15.86
		Both Groups	25/52	15.14	
Hitchins et al. [13]	Lu, Br, GI, CUP,	IT MTX	23	NR	12
	Ly, Other	IT MTX + Ara C	20	NR	7
		Both Groups	11/43	9	8
Glantz et al. [43]	Br, Lu, Mel, GI	IT liposomal cytarabine	11/31	NR	15
		IT MTX	11/30	NR	11.14

LM=leptomeningeal metastasis; n=number of LM cases; OS=overall survival. Br=breast; Lu=lung; Ly=lymphoma; GI=gastrointestinal; CUP=cancer of unknown primary; Mel=melanoma. Ara C= cytosine arabinoside; T=thiotepa; MTX=methotrexate. NR=not reported.

these cases [39]. A ventriculoperitoneal shunt (VPS) procedure carries a small risk of hemorrhage, infection or shunt malfunction. However, placement of a VPS is a definitive treatment for elevated ICP, and may be combined with a reversible on/off valve to facilitate administration of intrathecal (IT) chemotherapy [39]. For those in whom a surgical procedure is not desired or tolerable, palliative RT is also effective in relieving CSF outflow obstruction, although the duration of benefit is variable [40].

RT is a palliative treatment or adjunctive therapy with IT or IV chemotherapy (see below). A short course of fractionated RT may be delivered that is generally tolerable, and may be useful to relieve pain in sites of nerve root compression. RT is especially important to consider in cases with bulky leptomeningeal disease, as the penetration of IT chemotherapy is poor in these instances [41].

IV chemotherapy with high-dose methotrexate likely improves survival over radiation alone, and has shown a trend toward improved overall survival compared to IT chemotherapy with improved tolerability [11]. The main advantage of IV chemotherapy is that it does not cause chemical meningitis and has a lower risk of leukoencephalopathy compared to IT treatment. However, IV methotrexate may produce systemic side-effects such as mucositis, bone-marrow suppression and nephrotoxicity. IV methotrexate requires inpatient monitoring to ensure adequate clearance, which may adversely impact quality of life.

IT chemotherapy is an alternative to IV methotrexate. One advantage over IV administration is that IT treatments may be given in the ambulatory setting, typically every 2 weeks. Liposomal cytarabine, methotrexate and thiotepa are the most commonly administered IT chemotherapeutic agents. IT chemotherapy is mechanistically attractive, because it circumvents the pharmacologic challenges of drug delivery beyond the blood-brain barrier, and it is less myelotoxic than systemic chemotherapy. This makes it an attractive option for heavily pretreated individuals or those receiving IV chemotherapy for concurrent active systemic disease.

However, IT chemotherapy still has limitations related to distribution and toxicity. The distribution of IT chemotherapy is dependent on normal CSF circulation. As mentioned above, up to 46% of LM patients have evidence of CSF outflow obstruction. Therefore, prior to administration, individuals receiving IT chemotherapy should have no clinical evidence of CSF outflow obstruction or elevated ICP. The most common toxicity of IT chemotherapy is ventriculitis/arachnoiditis, occurring in 10-23% of cases [13, 42, 43]. This is a non-infectious 'chemical meningitis' that occurs in response to IT chemotherapy. It can be extremely uncomfortable, resulting in severe headaches, nausea and

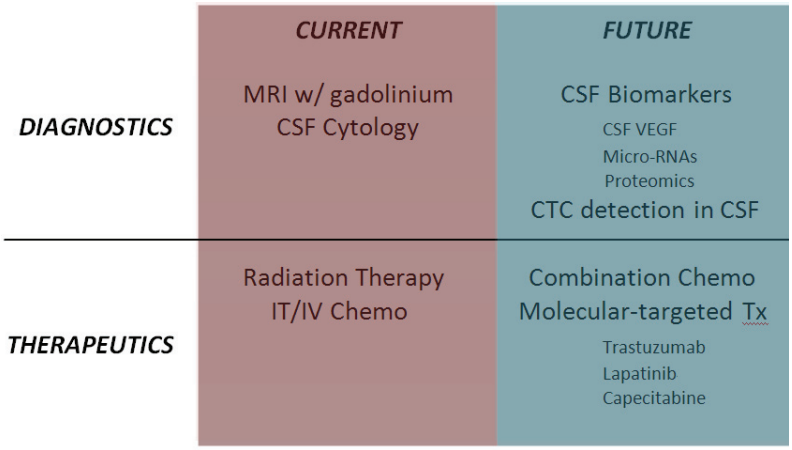

Figure 2. Current and future technologies to advance the diagnosis and treatment of leptomeningeal breast cancer.

vomiting. Pretreatment with dexamethasone substantially reduces the incidence of chemical meningitis. Other rare but serious toxicities of IT therapy include: leukoencephalopathy (7.5%), and bacterial meningitis (3.75%) associated with the presence of an intraventricular reservoir [42].

A handful of randomized clinical trials are available to guide treatment of breast cancer LM. These are summarized in **Table 2**. The trials that have compared IT treatments (methotrexate versus thiotepa [12], methotrexate versus combination methotrexate plus cytosine arabinoside [13], and methotrexate versus liposomal cytarabine [43]) for LM from multiple different cancers found no significant differences in survival between the treatment arms.

Future directions

Molecular diagnostic and therapeutic strategies will provide a means for earlier detection of LM, and more effective treatments than are currently in use (**Figure 2**).

Diagnostics

Serum or CSF biomarkers with higher sensitivity than CSF cytology and MRI could allow for earlier and more definitive diagnosis of LM. Abnormalities on MRI or in CSF require a substantial volume of disease, and it is possible that treatment delay due to the insensitivity of current technologies contributes to the poor prognosis in LM. CSF vascular endothelial growth factor (VEGF) has 75% sensitivity, 97% specificity, and 94% negative predictive value in the diagnosis of breast cancer LM using CSF cytology as a gold standard [44].

Validation early in high-risk individuals is required to assess whether elevation in CSF VEGF may be used as a method for early LM detection or screening.

Proteomic analysis of CSF has identified a number of peptides that are differentially expressed in individuals with breast cancer LM compared to breast cancer non-LM individuals and those without breast cancer [45]. Micro-RNA studies have investigated the ability to detect abnormal levels of micro-RNAs in the CSF of cancer versus non-neoplastic conditions. Using 7 micro-RNAs, metastasis versus non-neoplastic controls were correctly identified in 98.9% of cases, and CNS breast versus lung metastasis were discerned correctly in 68.9% [46].

Another potential for early identification is analysis of circulating tumor cells (CTC). Used frequently in serum, CTCs may also be detected in the CSF of individuals with LM [47]. Molecular tumor cell markers may be chosen to identify specific CTCs. Metastatic cells in CSF express epithelial cell adhesion molecule (EPCAM), unlike cells of glial origin that do not. In addition to its diagnostic potential, CTC methods capture individual live tumor cells, which will add to the current understanding of the biology of CNS metastasis and the natural history of LM.

Treatment

Survival following a diagnosis of LM is unacceptably short. Working with currently available therapies, aggressive ICP management and combination IT chemotherapy may afford some survival benefit over previously studied IV or IT monotherapies [48]. Molecular therapeutic strategies are likely to play an increasingly important role in the treatment of breast cancer LM. Individual case reports and case series have shown that IT trastuzumab may have some activity in HER-2 positive breast cancer

LM and is potentially well-tolerated [49-52]. Response to treatment following capecitabine [53, 54] or lapatinib [55] have also been reported in limited numbers of breast cancer LM.

Trial design

Five prospective randomized trials, 3 of which provide breast cancer specific survival data (**Table 2**), and a number of institutional retrospective case series (**Table 1**) provide the evidence base of breast cancer specific LM information to date. Additional prospective clinical trials are required to evaluate the impact of specific treatments on survival and quality of life. Going forward, breast cancer LM trials should be considered in order to answer questions about the impact of treatment interventions and receptor status on survival. Multicenter collaboration is likely to be necessary to execute disease-specific LM trials in a timely manner.

Conclusions

In spite of an increased incidence of breast cancer LM, overall survival with current treatments remains limited to less than 6 months on average. An improved understanding of the mechanisms of CNS metastasis and development of screening and earlier detection methods will lead to more effective therapies. Combination chemotherapy and radiation may be considered in breast cancer LM, especially those without active systemic disease or concurrent brain metastasis. There remain great clinical research opportunities to improve on molecular diagnostic testing and to complete prospective randomized trials. These will undoubtedly lead to innovative therapies for LM and better inform treatment decisions in this challenging and increasing neurological complication of breast cancer.

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