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Review

Treatment of leptomeningeal carcinomatosis: Current challenges and future opportunities

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ABSTRACT

Leptomeningeal metastasis (LM) in breast cancer patients confers a uniformly poor prognosis and decreased quality of life. Treatment options are limited and often ineffective, due in large part to limitations imposed by the blood–brain barrier and the very aggressive nature of this disease. The majority of studies investigating the treatment of LM are not specific to site of origin. Conducting randomized, disease-specific clinical trials in LM is challenging, and much clinical outcomes data are based on case reports or retrospective case series. Multiple studies have suggested that chemo-radiotherapy is superior to either chemotherapy or radiation therapy alone. Attempts to overcome current obstacles in the treatment of breast cancer LM hold promise for the future. We review the epidemiology, diagnosis, and prognosis of LM in breast cancer, and discuss the treatment options currently available as well as those under investigation.

1. Epidemiology

Breast cancer affects one in eight women. It is estimated that ~230,000 women in the USA will be diagnosed with breast cancer in 2014 [1]. Leptomeningeal metastasis (LM) can complicate virtually any malignancy, and breast carcinoma is the most common solid tumor associated with it [2,3]. Estimates of the incidence of LM in breast cancer patients in clinical series range from 1–8% [4,5], with autopsy series revealing an incidence as high as 16% [6]. Triple-negative breast cancer appears to have a higher likelihood of LM [7], and a shorter interval between initial diagnosis and development of LM [8].

2. Diagnosis

The clinical presentation of LM is highly variable, as any level of the neuro-axis may be affected. The gold standard for diagnosis of LM is demonstration of malignant cells in cerebrospinal fluid (CSF), although the false negative rate may be substantial and improved sensitivity may rely on repeated sampling of the CSF [2]. Several studies have examined the diagnostic usefulness of other CSF measurements with mixed results. Hypoglycorrhachia (<50% of LM) [2,4,5,9–11], lymphocytic pleocytosis (25–64% of LM), and elevated opening pressures (~50% of LM) are non-specific, but raise suspicion for LM in the proper clinical setting [11]. Also non-specific, elevated CSF protein was more sensitive in some studies [11,12], correlating with the diagnosis in ~60–90% of cases. Other CSF biomarkers investigated include lactate dehydrogenase, carcinoembryonic antigen, lactate, oligoclonal bands, B-glucuronidase, beta-2 microglobulins, vascular endothelial growth factor, and cancer antigen 15-3 [2,13,14–16], but are not routinely used due to similarly suboptimal sensitivity and specificity.

Neuroradiologic criteria for the diagnosis of LM have played a growing role since the advent of MRI [17]. The characteristic finding on MRI is meningeal enhancement, best noted at the skull base between cerebellar folia, along cranial nerves, and around the spinal cord and nerve roots (Fig. 1). MRI findings are abnormal in 75–90% of patients with cytology-positive CSF [11,18]. One retrospective review of 187 LM patients showed that 53% of patients were diagnosed by imaging, 23% by cytology, and 24% by both [30]. Most experts agree that typical MRI findings in conjunction with a consistent clinical picture fulfill diagnostic criteria for LM [19].

3. Prognosis

Unfortunately, outcomes for breast cancer patients with LM remain dismal: rates of response to therapy and overall survival

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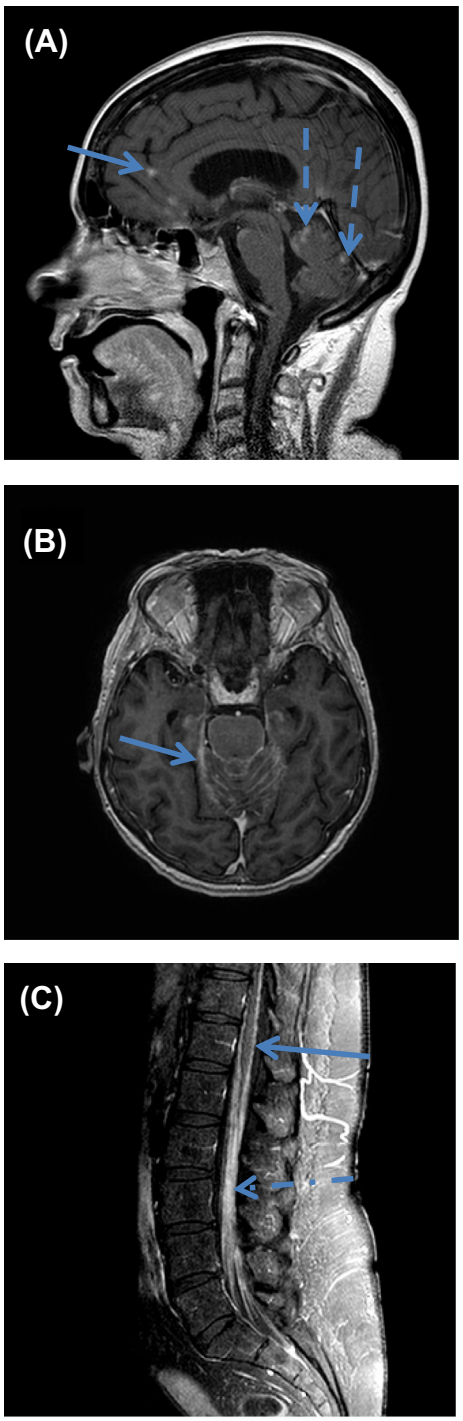

Fig. 1. (A) Sagittal T1-weighted post-contrast MRI of the brain revealing enhancing lesions deep within the sulci supratentorially (solid arrow), on the cerebellar surface (dashed arrow), and at the anterior surface of the fourth ventricle (dashed arrow). (B) Axial T1-weighted post-contrast MRI of the brain showing enhancing lesions on the cerebellar surfaces (arrow). (C) Sagittal T1-weighted post-contrast MRI of the lumbosacral spine revealing "sugar coating" of the surface of the spinal cord (solid arrow) and bulkier enhancement of the cauda equina (dashed arrow).

(OS) have not markedly changed, despite dramatic improvement in outcomes for those with visceral disease. Outside of performance status (PS), no consistent set of prognostic or predictive indicators have been elucidated to guide management. PS has demonstrated prognostic significance in a number of studies [7,10,11,20,21]. Pre-treatment CSF markers for prognostication have not definitively been shown to correlate with outcomes [2,4,5,7,11,12]. Other potential prognostic factors include age [5,7,12], control of systemic disease [12], histological grade [11], presence of cranial neuropathies [5], presence of lung metastases [5,11], no response to systemic or intrathecal therapy [10], and number of prior chemotherapy regimens [10,11,21].

Evaluation of tumor tissue for the presence of estrogen receptors, progesterone receptors, and human epithelial receptor 2 (HER2) is standard practice in breast cancer as these are both prognostic and predictive markers influencing management. The importance of receptor status in breast cancer LM mirrors its importance in breast cancer in both systemic disease as well as brain metastases [22]. Some studies show that HER2+ LM has a better OS while triple-negative patients have poorer OS [20]. However, other studies suggest that patients with triple-negative disease may only appear to have worse outcomes because they have shorter time until diagnosis of LM [8]. Suggestion has been made for serial evaluation of receptor status on these cells to guide clinical management [23].

Median survival in patients with LM from solid tumors ranges from 6–8 weeks in untreated patients, and 8–30 weeks in treated patients. Early studies combining patients with various primary tumors suggested that those with LM and breast cancer primaries have a higher response to treatment (up to 60% improving or stabilizing with chemotherapy and/or radiation therapy) and longer median survivals than those with other primaries (7 months *versus* 8–30 weeks) [2,4,11,20,24].

4. Treatment

Therapeutic trials for solid tumor LM are small and include heterogeneous patient populations. Accrual is challenging because of the relatively low incidence and rapidly progressive nature of the disease. The majority of data available on efficacy and outcomes are from non-randomized or observational studies in patients who were not uniformly treated and have a wide range of tumor types. Additionally, endpoints have varied between trials, making it challenging to determine the optimal management of patients with LM. Modalities used in patients with LM to date include radiation therapy (RT), systemic therapy, and intrathecal therapy.

4.1. RT

Craniospinal RT plays an important role in the treatment of central nervous system (CNS) metastases because it addresses the entire CSF space. However, it is often not used to treat LM due to significant toxicity, particularly in patients who may have overlapping RT fields from prior chest wall RT. A more focal approach is often employed to limit toxicity. Whole brain RT, alone or followed by chemotherapy, is used to treat a substantial portion of the CSF space, palliate symptoms, and improve quality of life [5,10]. Focal RT is frequently used to treat bulky disease as other treatment modalities may have limited effect on regions of large CSF tumor burden. Focal RT can be administered either in a fractionated manner or as a single dose via stereotactic radiosurgery. No broad guidelines exist and decisions are made on a case by case basis.

In turn, it is unclear whether increased doses or alternate dosing schedules of radiation may be appropriate in certain tumor subtypes. Studies have suggested that tumors arising in patients with deleterious germline BRCA1/2 mutations are more sensitive to the DNA-damaging effects of RT [19]. There exists mixed data regarding the role of receptor status on sensitivity to RT. Triple negative patients with intracranial metastases (not LM specifically) have high objective response rates to RT but shorter OS [25]. Other studies have not demonstrated receptor status to be predictive of outcome to hypofractionated RT [26].