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Treatment of Leptomeningeal Metastases from Breast Cancer: A Literature Review

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Abstract

Breast cancer (BC), owing to its high prevalence, represents one of the leading causes of women's death worldwide. Due to remarkable progress in therapy directed against this malignant neoplasm, there was an increase in the survival of affected patients and, therefore, a rise in the number of central nervous system metastases (CNSM) – up to twenty percent, located in the leptomeninges. There is not enough evidence of the therapeutic options for treating leptomeningeal metastases (LM) from breast cancer in the medical literature, and the management of these patients is complex. Even with an aggressive approach, therapeutic outcomes are uniformly disappointing due to the relentless growth of the central nervous system and systemic cancer or their lethal complications. The development of management strategies for CNSM constitutes an important clinical challenge and more prospective trials are needed to better address the impact of the available treatment on overall survival and quality of life. This article aims to provide an overview of the current established treatment for LM from BC, a rare complication of metastatic breast cancer (MBC), with high morbidity and mortality rates.

Keywords : Breast Neoplasms, neoplasm metastasis, central nervous system, methotrexate, palliative care.

Background

Female breast cancer (BC) incidence rates have slowly increased by about 0.5% annually since the mid-2000s. For women, breast, lung, and colorectal cancers represent 51% of all new diagnoses, with breast cancer alone being responsible for almost one-third; and the main cause of death of females in several countries [1]. Directly linked to these expressive numbers, the incidence of central nervous system (CNS) metastasis, a feared complication that often leads to a worse prognosis and a steep functional decline, has increased [2] due to advances in both imaging technologies leading to earlier detection of brain metastasis and introduction of improved systemic therapies in longer survival in individuals with advanced primary breast cancer.

CNS involvement rarely occurs as an initial manifestation of BC, usually manifesting itself in an advanced stage of the disease, with metastasis in multiple organs. It is estimated that 30-50% of patients with metastatic breast cancer (MBC) will develop CNS metastasis during the disease [3], and 5% leptomeningeal metastases (LM) [4]. Most CNS metastasis occurs in the brain parenchyma, reaching about 80% of cases [6], and the leptomeningeal involvement, which is distinguished by the dissemination of malignant cells in the leptomeninges and in the subarachnoid space, corresponds to the remaining cases. Although LM from breast cancer has the best prognosis when compared to LM secondary to other malignancies, it still carries a poor prognosis, with a median overall survival (OS) of approximately 4 weeks, which can be prolonged to 4 months in some patients with aggressive multimodal treatment [7].

As a result of the lower number of cases of LM, there is not enough evidence of the therapeutic options available, formulated mainly through retrospective studies. Another crucial factor in the quality of the information available so far is that the data are from studies carried out with different types of cancer, the evolution of neoplasms, and therapeutic response different from those found in breast cancer, limiting their use for this disease [6].

Review and Discussion

The treatment plan and sequencing it is to improve the quality of life, stabilizing or improving neurologic function and palliate symptoms. The choice for MBC must be personalized to target specific molecular characteristics and patterns of metastatic spread. Currently, there is no commonly accepted standard treatment for LM from breast cancer. The present management of LM consists of a combination of intrathecal (IT) chemotherapy, systemic therapy, radiation therapy (RT), and best-supportive care [9].

CNS metastasis occurs in about 5% of those with early-stage breast cancer at some point during illness [6,7,10]. Most often, CNS metastasis occurs as a late manifestation of breast cancer in association with metastatic spread in other organs. CNS metastasis is rarely an early presenting feature of breast cancer. Understanding and improving upon currently available therapies for CNS metastasis is crucial mostly because this pattern of dissemination relates to the worst prognosis, impairs functional status, and loss of overall quality of life (QoL). Parenchymal brain metastasis (BM) accounts for most CNS metastasis. Prospective trials have helped to guide treatment decisions for brain metastasis [7]. Retrospective reviews have identified factors such as the number of metastases, the presence or absence of active systemic disease, and hormone receptor status impacting survival [11, 12]. LM represents a minority of CNS metastasis (11-20%) [6, 13] and less data is available to inform therapy decisions; most of the data is obtained retrospectively. Most studies do not examine breast cancer exclusively but rather include other solid tumors, hematologic malignancies, and primary brain tumors. The direct application of these results to breast cancer is limited. Since each type of cancer treatment, prognosis, and systemic involvement is diverse, it is logical to consider that LM from breast cancer may have a different natural history and respond differently to treatment than LM from other neoplasms [14].

Remarkably, there has been an association between lobular histology and CNS metastasis, and there is some evidence for an increased incidence of brain metastasis in human epidermal growth receptor 2 positive (HER2+) breast cancer [10, 15]. The impact of HER2 and hormone receptor status in LM is less well-defined. However, for patients with HER2+ metastatic disease, the treatment scenery is continually changing, and patient subgroups with specific clinical needs, such as those with CNS involvement, are taking place; numerous anti-HER2 targeted drugs, including trastuzumab, pertuzumab, trastuzumab-emtansine (TDM-1), lapatinib, neratinib, trastuzumab deruxtecan, and tucatinib, have proven antitumor activity in the brain by growing time-to-brain metastasis evolution and time-to-brain progression in patients with CNS metastasis [16].

Patients with a long history of survival, without complete remission, and in need of multiple lines of treatment are at greater risk of LM. More prolonged survival and exposure of tumor cells to genotoxic chemotherapy may select for increasingly chemoresistant cell clones making LM even more resistant to therapy over time [17]. Even though IT chemotherapy is widely used in the United States of America for solid tumor LM, proof of its benefit has not been established in randomized controlled trials (RCT) [18]. RCTs suggest modest improvements with long-acting over standard IT chemotherapies [19, 20], and some retrospective studies suggest IT chemotherapy prolongs survival [21], but it is largely inconclusive. In a small, randomized study, Boogerd et al [22] demonstrated that the addition of IT chemotherapy to systemic treatment and involved field RT did not lead to a survival benefit or improved neurologic response. The IT regimen of choice adopted by most institutions consists of methotrexate (MTX) monotherapy or combined with RT [23].

RT does not represent the first-line treatment in LM, but it is used to alleviates radicular pain, sometimes improves focal neurologic deficits and may also delay or prevent progression of neurologic deficits. Focal RT, such as involved field or stereotactic radiosurgery (SRS), may be considered in patients with local, circumscribed, and symptomatic lesions, or in those with cerebrospinal fluid (CSF) flow obstructions due to spinal or intracranial blocks to improve the distribution of intra-CSF therapy [4]. Wolf et al. [24] retrospectively analyzed 16 patients with LM from solid tumors (five from BC), treated with SRS, reporting a disease control of 57.1% with a six-month and one-year OS of 60% and 26%, respectively. The study suggests that SRS could be added to treat bulky LM in patients also eligible for systemic therapy, including immune and targeted therapies, to prolong OS. Whole brain radiation therapy (WBRT) is not recommended for the treatment of LM due to the poor benefit and the significant risk of developing severe adverse effects [4]. However, some studies investigated the effect of WBRT in unfit patients for systemic treatment and low-performance status, limited in maximum of 30 Gy in 10 daily fractions. Brower et al. [25] retrospectively analyzed 124 patients with LM from solid tumors (22 BC) and showed a median OS of 9.2 months when WBRT was associated with systemic chemotherapy, with a major benefit in patients with a good Karnofsky performance status scale.

IT therapy is employed in patients with tumor cells in the CSF and/or with linear diffuse enhancing leptomeningeal disease, while is not effective to treat nodular lesions due to the limited penetration into the tumoral tissue. The drugs commonly used are MTX, liposomal cytarabine (Ara-C), and thiotepa. High-dose MTX has been reported to have some efficacy in treating LM [26, 27]. Tetef et al. [27] reported a non-RCT of 13 patients with LM from breast, lung, or osteosarcoma. This dose-escalation study aimed to determine if a level of 1 uM could be achieved in the CNS. No patient had cleared the tumor cells from the CSF, but five of the nine breast cancer patients had already been exposed to MTX and were resistant to this drug. The finally recommended regimen was a loading dose of 700 mg/m2 [27] and a 23-hour infusion of 2,800 mg/m2, with leucovorin starting 6 hours after the MTX infusion. Glant et al. [26] retrospectively reviewed patients who had received MTX 8 g/m2 over 4 hours for LM. Thirteen of the 16 patients treated with high-dose MTX had a complete cytologic

response at one month. Median survival for the patients treated with high-dose MTX was 13.8 months, with six patients alive at 23–52 months. Among a comparison group treated at their institution with IT MTX, the median survival was 2.3 months. This comparison suggests that high-dose MTX could be more effective, However, the patients had a variety of tumors, with more melanoma in the IT group and more chemosensitive tumors in the high-dose MTX group. Another possible factor impacting survival is that the high-dose systemic MTX regimen would also treat systemic disease, whereas IT treatment would not. A more recent trial of high-dose MTX for patients primarily with parenchymal and leptomeningeal breast cancer, or both, seemed to show a higher response rate for parenchymal lesions (33%) versus leptomeningeal disease (29%). Although the criteria of response in leptomeningeal disease were less clearly defined [28]. Boogerd et al. [22] compared intraventricular chemotherapy with non-intrathecal treatment, including systemic chemotherapy and involved-field RT, in patients with LM from BC. A neurological improvement was observed in 59% of the IT and 67% of the non-intrathecal group, with a median progression-free survival (PFS) of 5.7 months and 6 months, respectively. The median OS of patients receiving IT therapy was of 4.6 months and 7.6 months for patients treated with non-intrathecal therapy. Le Rhun et al. [23] investigated the activity of the addition of liposomal Ara-C to systemic therapy in 69 patients with LM from BC. Patients treated with systemic therapy alone achieved a median PFS and OS of 2.0 and 4.0 months, respectively, while those receiving liposomal Ara-C plus systemic therapy reported a median PFS and OS of 4.3 and 7.3 months, respectively.

Furthermore, hormonal therapy for LM from BC has been described in case reports. Boogerd et al. [29] reported on two breast cancer patients treated for LM with primarily spinal column involvement. Both patients responded to tamoxifen and, possibly, other hormonal agents. The response was defined by neurologic improvement, but at least one of the patients had a clearance of the malignant cells from the CSF. The prolonged control of the disease in these patients might reflect their estrogen-receptor status or the fact that patients with spinal involvement alone have a more favorable prognosis [29]. Ozdogan et al. [31] described a breast cancer patient with primary brain involvement who had progressive neurologic signs despite prior brain radiation and IT MTX. The patient experienced a progression-free survival of 16 months when treated with letrozole [31]. Peroukides et al. [32] described a patient with estrogen-receptor breast cancer who had progressed on tamoxifen and developed LM. She responded to letrozole therapy with a continuation of IT MTX. Her survival was 36 months from the start of letrozole therapy. In prostate cancer, there has been a single case report of a patient with leptomeningeal prostate cancer who survived for more than five years with leuprolide therapy [33]. There were several letters to the editor regarding hormonal therapy of leptomeningeal breast cancer, with Chamberlain [34] suggesting that IT therapy is standard; however, one-third of treatment cycles of IT MTX is associated with aseptic meningitis, and Boogerd et al. [29] indicating that, in his experience, half of the longer-term survivors who have had IT MTX may develop encephalopathy. Studies are also more difficult to evaluate when the numbers of patients are small, and a variety of tumors is included.

In two prospective studies phase II, patients with solid tumors LM and immunotherapy naïve, median survival demonstrated was short. Of the twenty patients, that received Pembrolizumab - 17 with breast cancer, two with lung cancer and one with ovarian cancer -, about 50 percent of patients achieved stable disease, 60 percent were alive at three months and the median overall survival remained limited at 3.6 months [35,36]. In the combination of ipilimumab plus nivolumab in 18 patients with LM, about 39 percent had stable disease, one had complete response and the median overall survival was 2.9 months [37].

Conclusion

The prolonged control of the disease in these patients might reflect their estrogen-receptor status or the fact that patients with spinal involvement and isolated brain metastasis have a more favorable prognosis, moreover shorter exposure of tumor cells to genotoxic chemotherapy before the LM may not select chemoresistant cell clones making LM less resistant to therapy that time.

LM metastasis remains a neurologically devastating and fatal complication of cancer. The fact that most of the current data regarding the treatment of LM comes from retrospective series and there is limited high-quality evidence regarding the standard treatment of LM related to breast cancer makes it difficult to determine if the longer survival described for patients who underwent treatment is indeed the result of the treatment itself or due to the good initial clinical characteristic of the patients able to tolerate such therapy. The development of management strategies for CNSM constitutes an important clinical challenge and more prospective trials are urgently needed to better address the impact of the available treatment modalities on OS and quality of life. Furthermore, systemic high-dose MTX has been pointed out in several studies as a drug capable of improving survival and cytological response in patients with CNS metastasis originating from solid tumors, especially breast cancer; still, the regimen has not yet been validated by large clinical trials.

Author Contributions

The authors confirm their contribution to the paper as follows: study conception and design: JCS; data collection: JCS; analysis and interpretation of results: JCS and ADCJ; draft manuscript preparation: JCS, JBC, and FMS. All authors reviewed the results and approved the final version of the manuscript.

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Conflicts of Interest

The authors declare that they have no conflicts of interest to report regarding the present study.

Ethics Approval and Informed Consent Statement

Not applicable.

Availability of Data and Materials

All data presented in this study are available from the corresponding author upon reasonable request.

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