



A view on the landscape of breast cancer brain metastases

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“Ultimately, it is necessary to not view breast cancer as a single disease but as a group of diseases”

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Introduction to breast cancer & brain metastases & why subtypes matter

Metastases to the central nervous system (CNS) are an unfortunate complication of breast cancer, second only to lung cancer [1–4]. The incidence of breast cancer brain metastases (BCBM) are approximated to be 5–16% in studies [1,5–7]; however, at autopsy the incidence is in fact much higher [1,6,8]. The development of BCBM can be associated with neurologic morbidity and augurs an inferior prognosis [9–11]. Moreover, BCBM are not limited to advanced stage disease, as the CNS is a site for relapse even in early stage breast cancer [5]. Presently, routine screening is not recommended, thus there is no precise understanding of CNS disease burden at diagnosis as typically BCBMs are captured due to symptoms and/or examination findings [6,8]. Steadily, this incidence has been increasing, in part due to advancements in systemic therapies which have improved survival; patients are living longer so as to develop BCBM as well as progress in radiographic techniques which have led to enhanced detection [1,2,5,7,9,12]. Certain patient and tumor characteristics have been shown to be associated with a higher risk of developing BCBM and these include younger age (<35 years), positive nodal status, ethnicity, presence of visceral metastases, estrogen receptor negative disease, HER2 disease, grade III tumors and tumor size [1,5,6]. In addition, the number of BCBM has prognostic relevance [6] as does the size of the BCBM and the patient’s performance status [4].

Ultimately, it is necessary to not view breast cancer as a single disease but as a group of diseases [2,12,13], as its subtypes are associated with varying patterns of metastatic spread and prognosis [8,14–16]. The different subtypes based on hormone receptor status and HER2 status are associated with a difference in incidence [11,17,18]. The time from diagnosis of the initial breast cancer to the development of BCBM is longer in patients with estrogen receptor positive (ER+) disease versus those with triple-negative breast cancer (TNBC) or HER2-positive cancer [11].

Triple-negative breast cancer

Patients with TNBC have a 25–46% of BCBM and tend to have simultaneous systemic progression, leading to a poorer survival [5,6]. Patients tend to have earlier CNS relapse which is inclined to involve new sites within the brain [19].

HER2-positive breast cancer

HER2-positive breast cancer is considered to be a particularly aggressive subtype and is associated with a poorer prognosis [1,7,20,21]. Around 20–25% of all breast cancers are HER2-positive [1,7,21]. It is associated with an increased risk of BCBM [1,3,5,7,14,21], and incidence rates in this population range from 30.7–53% [1,5,6]. Around 50% of patients succumb due to intracranial progression as ultimately there are poorer local control rates of disease [5,19]. Though it is not clear what predisposes HER2+ patients to the development of BCBM, hypotheses have included the prolonged survival of patients with anti-HER2 therapy and their limited intracranial efficacy as well as biologic tropism [7,11].

ER+ breast cancer

Those with estrogen receptor negative disease, in contrast to those who are ER+, have at least twice the incidence of BCBM [6]. Those patients with ER+/HER2-negative disease, have a BCBM incidence of 5–10% [17].

Therapeutic limitations

BCBM not only pose a clinical challenge but also a therapeutic challenge [9]. The blood–brain barrier (BBB) is a particular impediment [5,6,9,13,19]. It is comprised of a layer of endothelial cells and astrocyte foot processes which in turn form a selective barrier with drug efflux mechanisms leading to the limited efficacy of systemic treatment [5–7,12,13]. Most traditional antineoplastic therapies cross the BBB poorly [5,17]. Furthermore, there is increasing research into the blood–tumor barrier which is formed once metastases have breached the BBB and this in turn may also impact drug delivery [7,13]. There is increasing knowledge to suggest that different subtypes of BCBM may also lead to various disruption of the BBB [7]; there appears to be increased disruption in TNBC as opposed to HER2-positive disease. It is not known how this directly impacts drug delivery [9].

Another emerging therapeutic limitation has emerged from our understanding that BCBM may differ from their primary in regards to hormone receptor status as well as HER2 status [5].

Historical/current treatment strategies

A multidisciplinary approach to treatment is best as patients with BCBM have complicated needs that require the care from multiple oncologic providers [5,11,22,23]. The appropriate treatment strategy is formed among systemic treatment options, surgical modalities and radiotherapeutics and needs to be tailored to each individual patient [22]. A detailed review of systemic, surgical and radiation treatment plans is outside of the scope of this article.

In the past, most patients with BCBM were treated with whole brain radiation therapy and in certain cases with or without the addition of stereotactic radiosurgery as well as surgical resection if clinically warranted [1,5,6]. The ultimate treatment plan depends upon multiple variables, such as the number, size and location of the BCBM [4,5,7,12,13,24,25]. In the setting of high disease burden, the conventional treatment has been whole brain radiation therapy [6,26]; however, this carries with it concerns of decreased quality of life and cognitive decline [6]. Overtime, the trend has been toward the use of stereotactic radiosurgery which typically better serves patients with small BCBM and a limited number of lesions [6]. However, this modality is associated with intracranial progression, especially in previously disease-free sites of the brain [19]. Surgical modalities are typically reserved for patients who have a high performance status and a single lesion; it portends a survival benefit [6,13].

There are a range of systemic treatment regimens that have been used to varying efficacy for BCBM [5,6]. This includes drugs such as methotrexate [27], cisplatin with etoposide [6,11,24], topotecan [6,24], temozolomide [6] and capecitabine [28]. Targeted therapies with potential therapeutic utility in BCBM include the tyrosine kinase inhibitor neratinib [3,6,11], lapatinib [5–7,11,20,24] and eribulin [6,21].

Emerging treatment strategies

The emerging treatment landscape for treatment of BCBM is diverse, utilizing different strategies to improve delivery into the CNS [17].

An agnostic approach to treatment is the use of tumor treating fields, which utilize alternating electric fields that interfere with mitosis thus resulting in apoptosis and are currently being investigated [13]. In addition, combining modalities and therapeutic strategies has shown promise [29]. By combining modalities and therapies, there is the potential to target key pathways synergistically or additively [29]. For example, combining radiotherapeutics which disrupt the BBB with targeted agents and immunotherapeutics may offer future multimodality treatment strategies for patients with BCBM [13,17,29–31].

Focusing on subtypes of BCBM also yields different therapeutic strategies.

Triple-negative breast cancer

One agent under evaluation for BCBM is the use of PARP inhibitors, which are expected to impair DNA repair mechanisms [5]. Drugs of this class have been used in patient with *BRCA1* and *BRCA2* mutated breast and ovarian cancer [5,11,13]. *BRCA1* mutations have been noted in TNBC [32], and there are ongoing studies to evaluate the utility of these drugs in BCBM.

There has been a shift in cancer care toward the use of immunotherapeutics and there have been data to show that the CNS is not as immunologically privileged as once thought [5,7] and there may be a role for immunotherapy

in the treatment of BCBM [13]. Tumor-infiltrating lymphocytes have been noted to be prognostic in TNBC [13]. A Phase III study of atezolizumab (a PD-L1 inhibitor) with nab-paclitaxel demonstrated prolonged progression-free survival in patients with metastatic TNBC [33] and a monotherapy study of atezolizumab also demonstrated some efficacy in metastatic TNBC [34]. Future trial work should evaluate patients with BCBMs.

HER2-positive breast cancer

The development of tucatinib, which is a tyrosine kinase inhibitor with more selectivity against HER2, has demonstrates some efficacy in BCBM [11,35]. A Phase I study utilizing both tucatinib and ado-trastuzumab found an objective response rate of 12% in the brain with prolonged stable disease [11,36]. A Phase Ib trial of tucatinib with trastuzumab and capecitabine showed that in 12 patients with BCBM at baseline, 42% achieved an objective response in the brain [11,35,37].

ER+ breast cancer

As discussed above, PARP inhibitors are being evaluated in patients with BCBM and *BRCA2* mutations are seen in hormone receptor-positive breast cancer [32].

The cyclin D-CDK4/6/INK4-Rb pathway plays a key role in cell cycle division and dysregulation of this pathway is seen in several malignancies, including breast cancer [7,21]. Currently available CDK4/6 inhibitors include abemaciclib, which is thought to be more CNS penetrant [5,7], ribociclib and palbociclib [7,11,21]. These drugs have shown some efficacy in the management of ER+ metastatic breast cancer and there is interest in understanding their potential role in ER+ BCBM [7].

Another pathway of interest is the PI3K/Akt/mTOR pathway which is dysregulated in many cancers, including breast cancer [7]. The *PIK3CA* mutation and deletion of *PTEN* are two of the most common aberrations in this pathway [7]. In hormone positive breast cancer, 28–47% of tumors have a *PIK3CA* mutation and *PTEN* deletion is seen in 29–44% [7]. There is interest in exploring mTOR inhibitors with endocrine therapy in BCBM [7,13].

Hurdles on the horizon

BCBM are a major cause of morbidity and mortality for which we are in desperate need of better therapies [17]. The treatment landscape is changing with newer modalities and therapeutics being introduced; one key barrier is the exclusion of patients of BCBM from clinical trials [7,12,38]. The design of clinical trials needs to not only incorporate untreated BCBM but also there is a need to encourage diversity as well as patient advocacy through the use of patient reported outcomes [39].

There is also a need for deepening our understanding of genomic evolution of BCBM [29,40–42]. Studies have demonstrated that matched BCBM and primary tissue can be discordant in around 20% of patients, predominantly demonstrating loss of hormone receptor expression and gain of HER2 [12,13]. By improving our understanding into molecular mechanisms, we will be better able to develop therapeutic strategies [40].

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