

Brain Metastasis from Breast Cancer

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Published Date: October 12, 2016

ABSTRACT

Brain metastases are less common than bone or visceral metastases in patients with breast cancer but the incidence is on the rise. The overall prognosis of breast cancer patients with brain metastases is poor and less treatment effective. Brain metastasis also leads to progressive neurologic impairments and therefore compromised quality of life. The increased incidence is most attributed to the use of sensitive detection methods such as contrast-enhanced magnetic resonance imaging and increased awareness of brain metastasis among patients and clinicians. Adjuvant and systemic therapy with drugs that have less blood-brain barrier penetrance might cause an increased risk of brain metastases. Molecular subtype is a crucial predictive factor for overall survival after developing brain metastases. Patients who do not have a poor prognosis based on previously identified prognostic factors should be treated with radiation therapy to control symptoms. Whole-brain radiation therapy, stereotactic irradiation and surgery are tools for the local treatment of brain metastases. Novel molecular target therapy, including HER2-targeted therapy, has demonstrated an antitumor effect in brain metastases. This review provides an overview of the incidence, risk factors, diagnosis, prognostic factors, treatments, and current and potential future management strategies of breast cancer brain metastases.

Keywords: Brain Metastases; Breast Cancer; Prognostic Factor; Subtype; Treatment

INTRODUCTION

A major challenge and obstacle in management of recurrent or advanced Breast Cancer (**BC**) is its tendency for distant metastasis to liver, bone, lung and brain. Breast cancer is the second most common cause of metastatic brain disease [1]. The incidence of developing Brain Metastasis (**BM**) has been previously reported to range from 10 to 16 %among living, advanced breast cancer patients [2] and as high as 30 % in autopsy series [3]. It has been observed that Brain Metastases From Breast Cancer (**BMBC**) occur more frequently among younger women, those with larger tumors, higher nuclear grade, highly proliferative activity, in certain subtypes such as Estrogen-Receptor (**ER**) - negative, triple negative, HER2 - amplified tumors, and those with extensive nodal metastases [1,4]. In recent years, overall prognosis of patients with BMBC has improved and it is now more favorable than that of patients with brain metastasis from lung cancer [5].

INCREASING BREAST CANCER BRAIN METASTASIS

It has been previously reported that the incidence of central nervous system metastasis from BC is 10-16% [6,7]. In a more recent retrospective review of 60,794 BC patients [8] with 24% (14,599 patients) had brain metastases. This could be attributed to the increased general awareness, early detection and recognition of related symptoms, improved systemic therapy, and more therapeutic options for intra-cranial disease. Autopsy studies have shown brain metastases in up to 36% of BC patients [9] and, another prospective trial CEREBEL discovered almost 20% of screened asymptomatic metastatic BC patients presented with brain metastases [10]. The underestimation of BM incidence is probably inmost occasions of clinical practice CNS metastases are mostly being detected only when symptomatic [11].

Among symptoms recorded, those most frequently associated with BM included headache (35%), vomiting (26%), nausea (23%), and hemi paresis (22%) [8]. Other neurological symptoms included, visual changes (13%), seizures (12%) and altered mental status (7%)cases, are less commonly seen but still need clinical attention.

The mean age of the patients at the time of diagnosis of BC was 50.3 years, while the mean patient age at the time of diagnosis of BMBC was 48.8 years. 12 % of patients with first relapsed in brain metastasis [12]. The median interval between the diagnoses of BC to identification of BM was 34 months (varied from 1to 97 months). The median interval from identification of BM to death was 15 months (ranged from 1 to 55 months) [8]. Among the 9057 patients with known menopausal status recorded, 2685 (30%) were premenopausal at the time of breast cancer diagnosis, while 4186 (46%) were postmenopausal. The majority (79%) of the types of BCBM was ductal carcinoma and most of the patients (68%) had nodal positive at the time of initial BC diagnosis.

PATHOGENESIS OF CNS DISSEMINATION FROM BREAST CANCER

The mechanism underlying cancerous brain spreading is still unclear and many preclinical studies have been conducted to investigate the biological behavior of CNS metastasis in BC. Brain metastasis formation constitutes several critical steps, such as cell migration, vascular dissemination, tumor cells extravasation, and metastasis growth [13]. The major determinants in the cell-to-cell and cell-to-Extracellular Matrix (**ECM**) interactions are the disintegrin and metalloproteinase domain-containing protein 8 (**ADAM8**) and the β 1-integrin, mediating cell-to-cell and cell-to-ECM interactions as well as ligand and receptor shedding. The β 1-integrin has been identified as a potential mediator of invasion in glioma by promoting signal transduction at various receptors among which the Tyrosine Kinases Receptors (**TRKR**) [14]. In addition, integrin activity also affects cell-to-ECM interaction, essential for cell migration through the Blood-Brain Barrier (**BBB**) [15].

The BBB remains a significant impediment for cancer cells to gain access to the brain. It has been proposed that endothelial expression of Cyclooxygenase-2 (**COX-2**) raises metalloproteinases expression in BC cells, overcoming and promoting their migration through the BBB [16]. The interaction between endothelial cells and BC cells is determined by several factors, essential for brain invasion. For example, the enhanced expression of the molecular chaperone α B-crystallin was shown to promote BC cells adhesion to human brain microvasculature endothelial cells [17] and a preclinical study in mice showed that COX-2, the EGFR ligand HBEGF, and the α 2,6-sialyltransferase ST6GALNAC5 were also related to BC extravasation into brain tissue [18].

Once tumor cells have penetrated the BBB, another important step for metastatic growth is acquisition of adequate supply of oxygen and nutrients through angiogenesis promotion. This is evident by highly vascularized and Vascular Endothelial Growth Factor (**VEGF**) - driven angiogenesis in brain metastatic lesions. Studies also showed that ADAM8 stimulates both transendothelial cell migration via β 1-integrin activation and angiogenesis through VEGFA release. Once across the BBB, BC cells are surrounded by reactive astrocytes which upregulate plasmin production, leading to paracrine secretion of death signals such as Fas Ligand (**FasL**) [19]. In response to this insult, BC cells are able to produce anti-plasminogen activators, such as neuroserpin and serpin B2 to against astrocytes activity [20].

An organ-specific brain metastasis gene expression profiling detected 37 essential proteins with a differential expression between primary BC which develop brain metastases and those do not [21]. In this analysis, the overexpression of the Glucose-Regulated Protein 94 (**GRP 94**), the fibroblast growth Factor-Inducible14 (**FN14**), the Tumor-Necrosis Factor (**TNF**) Tumor-Receptor-Associated Factor 2 (**TRAF2**), and HER2 were significantly associated with brain metastasis formation ($p < 0.001$). The over expression of HER2 was the best predictor of subsequent development of brain metastasis, with a positive likelihood ratio (**LR**) of 6.7 ($p < 0.0001$), followed by FN14 (positive LR = 3.01; $P = 0.001$), GRP94 (positive LR = 1.89 $p = 0.003$), and TRAF2 (positive LR = 1.67; $p = 0.055$) [21].

PROGNOSIS OF BREAST CANCER PATIENTS WITH BRAIN METASTASES

In clinical practice, patients overall general condition is commonly defined using either the Karnofsky Performance Status Score (**KPS**) or the Eastern Cooperative Oncology Group (**ECOG**) system.

In the early 2000's, new prognostic systems have been approved for the prognostic stratification of patients with newly diagnosed brain metastases: the Radiation Therapy Oncology Group (**RTOG**) Recursive Partitioning Analysis (**RPA**), combining KPS, age, and disease extension [22] and the Graded Prognostic Assessment (**GPA**), combining age, KPS, number of central nervous system lesions and presence or absence of extra-cranial metastases [23].

A more specific GPA for patients with BC has been proposed in 2012 adding also the BC molecular subtype to the prognostic factors [24]. Patients with a breast-GPA score of 0-1.0 have a median survival time (**mST**) of 3.4 months, a score of 1.5-2.0 have a mST of 7.7 months, a score of 2.5-3.0 have a mST of 15.1 months, and a score of 3.5-4.0 have a mST of 25.3 months. In 2015, the breast-GPA was further modified by incorporating the number of brain metastatic lesions into the prognostic factors (Table 1). The analysis was conducted in a cohort of 1552 patients with newly diagnosed brain involvement and showed concordance index between the observed OS and the OS estimated by the score was 0.78 (95% CI 0.77-0.80) for breast-GPA and 0.84 (95% CI 0.83-0.85) for modified breast-GPA (P < 0.001) [25].

Table 1: Modified Breast-GPA Index for Women with Breast Cancer and Brain.

Factor	0	0.5	1.0	1.5	2.0
KPS	≤50	60	70-80	90-100	-
Subtype	TNBC	ER or PR+ /HER2-	ER and PR- /HER2+	ER or PR+ /HER2+	-
Age, years	>50	≤50	-	-	-
No of brain metastasis	>3	1-3	-	-	-

Abbreviations: **GPA:** Graded prognostic assessment; **HER2:** Human epidermal growth factor receptor 2; **KPS:** Karnofsky performance score; **TNBC:** Triple-negative breast cancer

TREATMENT TOWARD THE INTRA-CRANIAL SANCTUARY AND OVERCOMING BLOOD-BRAIN-BARRIER

The anti-HER2 antibody trastuzumab, one of the most widely used targeted therapies, is an essential component in the treatment of HER2-overexpressed breast cancer. Although trastuzumab is effective for extra-cranial systemic disease, its efficacy against BM remains controversial. Differential sensitivity to trastuzumab between BM and mammary fat pad tumors is unambiguous [26]. Meta-analysis of the phase-III adjuvant trials NSABP B31, NCCTG N9831, HERA and PACS 04 had shown a higher incidence of cerebral metastasis after adjuvant trastuzumab treatment [27]. This is correlated with controlled systemic, extra-cranial disease [28], supporting the

hypothesis that the increased risk for BM after adjuvant trastuzumab treatment is attributed to better systemic control. Clinical evidence for the efficacy of trastuzumab against established BM is limited because of the lack of prospective data in this setting.

Main therapeutic strategies of BMBC include surgery (usually for solitary lesion and less than 4 cm), whole brain radiation or Stereotactic Radio Surgery (**SRS**), chemotherapy, and biological therapies. With the exception of chemotherapy that has shown only a modest effect on survival due to the poor capacity of chemotherapeutic drugs to penetrate Blood-Brain-Barrier (**BBB**), advances in other therapeutic approaches have resulted in longer survival of patients. The goals of radiation therapy are to alleviate neurological symptoms by lesion shrinkage and to prolong survival.

Palliative radiation therapy in patients with symptomatic intracranial metastases led to a 63% reduction in symptoms [29] thus justifying the use of WBRT as the standard of therapy for brain metastases. WBRT remains the standard treatment for patients with poor prognosis, diffusely disseminated brain metastases, poor performance status and uncontrolled extracranial metastatic disease [30]. Acute toxicity related to WBRT is usually mild and self-limiting and includes fatigue, alopecia, dermatitis, nausea, vomiting, headache and decreased appetite; cerebral edema is generally common, but is usually manageable by corticosteroids treatment. Late and long-term side effects after 90 days of radiation therapy are not self-limiting and may have significant and lasting consequences. The risk for late complications is related to the total radiation dose, fraction size, patient age, extent of disease, and neurological impairment before radiotherapy. They include radiation necrosis, neuro-endocrine impairments, cerebrovascular diseases, and leuko-encephalopathy/dystrophy, leading to neuro-cognitive deterioration and dementia.

Patients with a favorable prognosis, GPA class-1 and even class-2 in selected cases, with a single brain lesion or oligometastasis should be evaluated for eligibility for surgical metastectomy; in these cases aggressive treatment is indicated to achieve long-term control of CNS relapse. For patients with a single, large metastasis in a surgically accessible location, resection may provide the best choice for rapid symptoms control. Surgery is also used in some patients with a limited number of metastases, particularly when there is one dominant, symptomatic lesion in a suitable position. The major risks associated with surgical resection include peri-operative anesthesia, stroke, postoperative neurologic deterioration, infection, and intracranial hemorrhage. Three randomized clinical trials have compared surgery plus WBRT to WBRT alone in patients with a single brain metastasis, demonstrating a survival benefit from the combined approach [31]. This indicated that multi-disciplinary approach in BCBM might achieve better survival if the patient is tolerable.

Stereotactic Radio-Surgery (**SRS**) is a non-surgical radiation therapy used to deliver targeted high dose radiation in a single or few sessions precisely. It allows maximum dose delivery within the target, minimizing the irradiation of healthy surrounding tissues and limiting the potential

side effects of radiotherapy. There are three different types of radiation beams available for SRS: high energy X-rays produced by linear accelerators, gamma rays, and charged particles such as protons produced by cyclotrons. Stereotactic radio surgery with gamma knife is now often used as the initial approach instead of whole brain radiation when there are 1-4 metastatic foci [32]. No prospectively randomized trials have been conducted to compare SRS (with or without WBRT) to surgery, but an observational study suggests that SRS is at least equal to neurosurgery in selected BM patients, with local control rates of 80-90% when added to adjuvant WBRT [33]. SRS significantly improved or maintained KPS at 6 months with a less steroid dose but there was a higher incidence of both acute and delayed grade 3 or 4 toxicity in patients received SRS after WBRT. Therefore, for patients with single metastasis who undergo WBRT, SRS boost is considered standard of care. Most of the trials included all BM patients instead of specific BCBM patients and therefore the results need to be interpreted cautiously when applying to BC patients. The increased use of radio-surgical techniques has shown a potential impact on survival. As an example, a recent report has demonstrated the median survival was 33 months for 50 patients who had radio-surgery for treatment of brain metastasis secondary to breast cancer [34].

The role of systemic therapy in the management of patients with brain metastases is not settled and remains controversial. The development of new therapeutic strategies with a better control of extra-cranial BC disease has determined an increased incidence of brain metastases. Preliminary data supporting the efficacy of systemic therapies in the management of BCBM are available from several published trials, with the evidence that chemotherapy and targeted therapies after WBRT may improve survival in BC patients with brain metastasis [35]. CNS relapse remains a critical turning point in the management of metastatic BC treatment, so that the emergence of new therapeutic strategies active on brain metastases represents an unmet medical need and a major clinical challenge. Previously, trastuzumab was used for HER2-overexpressed metastasis and hormonal therapy (34 %) for ER+ and/or PR+ tumors. Several retrospective studies have shown a survival benefit of trastuzumab-based therapies for HER2-positive metastatic BC patients with CNS metastases. In particular, the improvement of survival seems to be mainly attributed to the activity of active anti-HER2 treatments on extra-cranial disease rather than control of brain lesions [36]. The limited efficacy of trastuzumab against BM is often related to inadequate penetration through the BBB. Based on its presumed ability to better penetrate the BBB than trastuzumab, lapatinib, a small molecule kinase inhibitor of EGFR and HER2, was evaluated in BCBM. Lapatinib was recently established as systemic therapy option and the only brain permeable targeted agent for HER2-positive cancer, has demonstrated limited intracranial response rates and some improvement in progression free survival for HER2+ BCBM patients. Molecular size constraints are believed to limit larger monoclonal antibodies, such as pertuzumab and trastuzumab, from crossing the BBB. However, emerging evidence reveals that the BBB is disrupted in the setting of metastases or post-radiotherapy, allowing for improved penetrance of these larger targeted agents because of perturbed BBB. An increasing body of evidence shows

that the combination of trastuzumab and lapatinib, either concomitantly or sequentially, leads to a longer survival in mBC patients with brain metastases. Ado-trastuzumab emtansine (**T-DM1**) shows clinical efficacy against brain metastasis in preclinical models [37] and clinical activity in BCBM patients [38]. More recently, a retrospective exploratory analysis of the EMILIA trial showed a significant overall survival advantage for patients with brain metastases treated with T-DM1 (26.8 months) compared with patients treated with lapatinib and capecitabine (12.9 months) [39]. Therefore, these results support the combination of lapatinib and capecitabine, but also the use of mono-therapy with TDM-1 for patients with HER2-positive BC with brain metastases. CNS relapse is still a challenging turning point in the management of metastatic BC treatment, so that the development of new therapeutic strategies active on brain metastases represents a major clinical demanding. Neratinib, an irreversible inhibitor of both EGFR and HER2, is under investigation as single agent or combined with capecitabine in BC patients with progressive brain metastases (NCT01494662). Recent published study showed that Neratinib, given after chemotherapy and trastuzumab-based adjuvant therapy for 12 months, significantly improved 2-year invasive disease-free survival [40]. Taken together, these data suggest that the addition of chemotherapy after completion of WBRT as well as the development of different formulations of anti-HER2 therapies could have a more advantageous therapeutic profile.

The systemic treatment of patients with TNBC is represented by chemotherapy in both metastatic and early setting. Therefore, for patients diagnosed with TNBC the integrity of the BBB is essential and may limit the delivery of drugs to the site of brain metastases. Brain objective response rate with conventional chemotherapy combinations ranges from 0% to 55% [41]. Over the last 15 years, platinum (cisplatin or carboplatin) with different combinations have shown response rates of 34-40%. In particular, 13% of intra-cranial complete response and 25% partial response were achieved with the combination of cisplatin and etoposide [42].

In preclinical models, BMBC exhibits higher microvascular density than their respective primary tumors [43]. These data endorse the essential role of the microenvironment in shaping and defining biological properties of the tumor and suggest that BM may be more dependent on blood vessels than primary tumors. Indeed, angiogenesis is required for effective colonization and growth of breast cancer cells in the brain, as inhibiting Vascular Endothelial Growth Factor (**VEGF**) receptor activation reduces brain metastatic growth of brain-tropic breast cancer cell variants through a reduction in angiogenesis [44]. These observations raise the issues of whether BM is more reliant on angiogenesis than extra-cranial tumors and/or if the brain endothelium is more reliant on VEGF than the systemic vasculature. Recently, it has been proposed that the combination of anti-angiogenesis prime and followed chemotherapy might lead to vascular normalization and better drug delivery to the intra-cranial tumor [45-48]. Moreover, both hematologic and non-hematologic toxicities were generally mild and manageable; in particular, only 1 patient experienced grade 3-4 hypertension and no grade 3-4 hemorrhage nor proteinuria were recorded [48].

Brain metastasis in luminal-like BC tends to be a relatively rare and late event, with a median time to development of BM of about 55 months [49]. In a retrospective study, patients with metastatic luminal-like subtype had a median survival from primary BC diagnosis consistently longer than patients with TNBC (72.7 months versus 39.6 months; $p<0.01$), although shorter in median survival after BM diagnosis (10.0 months versus 7.6 months, respectively; $p<0.01$) [50]. Previous data demonstrates reliable activity of endocrine treatment strategies, such as tamoxifen, megestrol acetate, or aromatase inhibitors, remain active in BM and prolong survival [51,52].

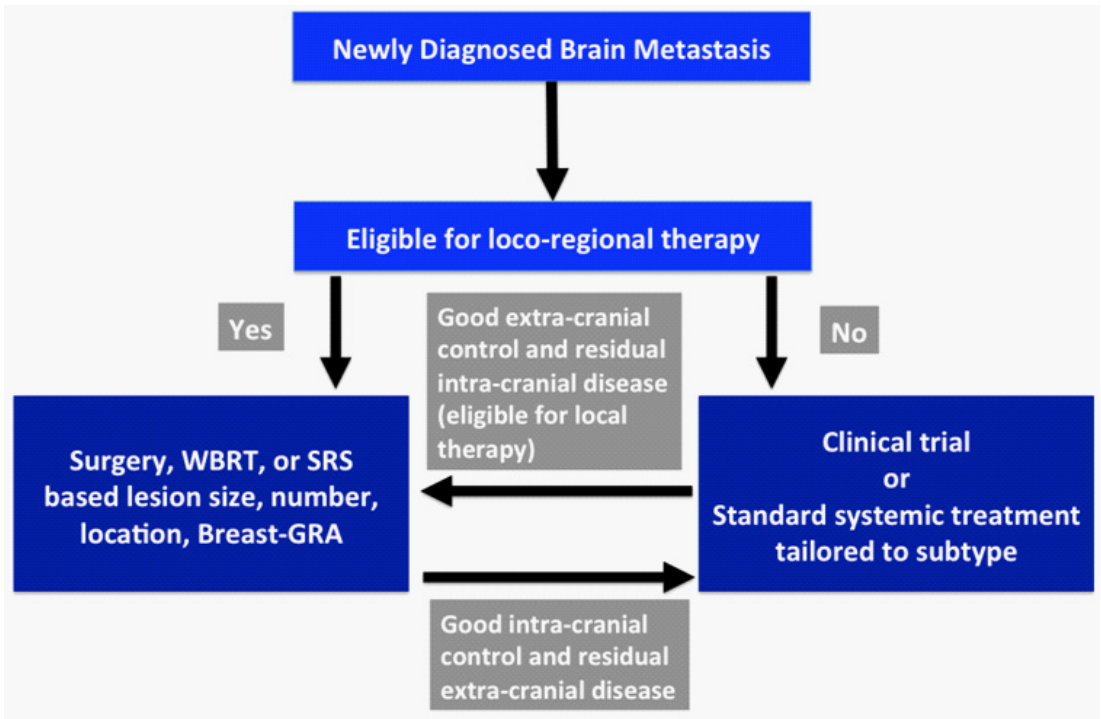


Figure 1: An algorithm for the treatment of brain metastases.

PALLIATION OF NEUROLOGICAL SYMPTOMS

As reported above, patients with brain metastases experience important and troublesome symptoms [11], therefore palliation of neurological symptoms has to be applied the first step of a multidisciplinary therapeutic approach.

The majority of symptoms are due to growing CNS lesions compression the normal brain parenchyma and increasing intracranial pressure. The administration of corticosteroids has been routinely implemented in the management of intracranial hypertension, leading to BBB stabilization with improved cerebral blood flow. The use of osmotic-agent such as intravenous mannitol at a 20% solution is also commonly implemented to treat severe neurological symptoms or when a rapid reduction of intracranial pressure is needed. However, the optimal dose of mannitol is still unclear and a pooled analysis of 18 studies failed to found significant

correspondence between change in clinical symptoms, intracranial pressure and mannitol dose [53].

Seizures are frequent encountered manifestations of brain metastases, and symptomatic epilepsy should be promptly treated by anticonvulsants at the earliest instance. However, the choice of antiepileptic drugs is challenging for this patients because brain tumor-related epilepsy is often drug-resistant. New generation drugs, such as lacosamide and levetiracetam, are commonly used because of their superior safety profile and their limited drug interactions. In particular, levetiracetam showed improved rate of seizure-control from 48% to 88% [54]. Notably, anticonvulsants for seizure prophylaxis in BM is not necessary in patients without history of seizures [55].

IS IT FEASIBLE TO PREVENT BRAIN METASTASES FROM BREAST CANCER?

Animal models of BM have provided insights into processes of the brain-metastatic cascade: dissemination of metastatic cells from the primary tumor, intra-vasation into the blood circulation, evasion the immune surveillance, active or passive migration towards the target organ, embedding into a capillary bed and attachment to the endothelium, extravasation through the BBB, and expansion in the brain microenvironment [56]. Despite major preclinical studies and advances, the clinical role of prophylactic treatments for BCBM is neither investigated nor clinically justified, and clinical features alone may not identify high-risk patients for BM to justify the toxicity associated with prophylactic approaches. Prophylactic Cranial Irradiation (**PCI**) slowed disease progression resulting in survival benefit in Small-Cell Lung Cancer (**SCLC**), providing the rationale for application in BC. Currently, a randomized phase-III trial is investigating the potential of a prophylactic taxane/trastuzumab treatment alone or in combination with PCI [NCT00639366]. Published case series and retrospective analyses, however, indicate that PCI and its benefit-to-risk ratio in BC patients at high risk for BM should be cautiously approached [57]. Addition of the Receptor Tyrosine Kinase (**RTK**) inhibitor to chemotherapy might have chance to improve the prevention of brain metastases [40]. BCBM can be diagnosed certain years after the primary diagnosis of the disease. This should be taken into consideration when applying prophylactic therapies. Recent studies revealed that single cells or clusters of disseminated breast cancer cells might remain quiescent for a long period of time. The long latency for BM makes the determination of the optimal time point for applying PCI or prophylaxis using drugs more difficult. This must be taken into account when designing prophylactic clinical trials.

FUTURE APPROACHES FOR TREATING BCBM

The prospective phase-III trial EMILIA revealed that T-DM1 was superior to lapatinib/capecitabine combination in patients with disease progression after trastuzumab [58]. If reduced efficacy of trastuzumab in BM is not due solely to inefficient delivery, but instead due to acquired or microenvironment-mediated activation of alternative signaling pathways, T-DM1 would be

expected to be effective in these patients. This hypothesis is supported by preclinical findings [37], case reports [59] and a subgroup analysis (asymptomatic brain metastases) in a randomized, open-label, phase-III trial of previously treated (physician's choice) metastatic HER2-positive patients [60]. Furthermore, new generation EGFR family inhibitors, more potent and specific than lapatinib (neratinib and afatinib), showed significant responses in single cases of BCBM [61]. The investigation of mechanisms of de novo or acquired resistance to anti-HER2 therapy in systemic disease led to the elucidation of downstream HER2 signaling inhibitors in BM, including the PI3K inhibitor BKM120 and the mTOR inhibitor everolimus, either alone or in combination with trastuzumab. The role of immunotherapy in cancer treatment is a major interest in recent years, but not much is known with regard to BCBM. Evidence from other malignancies, such as the activity of ipilimumab in patients with brain metastases from malignant melanoma [62], suggests that immune system modulation might be feasible. The impact of microenvironment of the host tissue to the metastatic tumor cells is another important aspect for future research. In the brain, glial and micro-glial reaction to the colonized tumor cells may be correlated with elaboration of factors that help the colonization process. It has also been suggested that metastatic tumor cells could potentially affect the glia in a novel way resulting in a cross talk between the tumor cells and the micro environment [63]. Blocking flow of such factors from both directions could be another way to prevent intra-cranial dissemination.

CONCLUSION

The improvement of patient survival in recent years greatly attributed to earlier detection, advancement of the surgical techniques such as introduction of radio-surgery, systemic therapies, treatment based on presence of certain biomarkers, and supportive treatments. Systemic therapeutic approach is an evolving field and its true impact on the survival of patients with brain metastasis remains to be determined. Additionally, over the last few years, our understanding and discoveries of molecular drivers of brain metastases, the blood-brain barrier, and CNS penetration of drugs has improved tremendously. Improved understanding of biology, multimodality treatment, and innovative drug development can lead to improvement in the management of brain metastases. In the near future, increasingly targeted therapies will have a significant role in the treatment of patients with brain metastases with actionable mutations. There are numerous unanswered questions that need to be solved: Is treatment resistance of BM due to a lack of drug penetration into the brain lesion? Has the brain metastatic cancer cell evolved to evade the same therapy to which its predecessors are sensitive? Does the brain microenvironment provide factors that modulate cancer cells to become resistant, and if so, what are these mechanisms of resistance? What is the role of intra-tumoral heterogeneity? How can microenvironment-targeted therapies, such as anti-angiogenic or immunotherapy, improve the treatment efficacy? [64] Although there are currently no definitive answers to these questions, recent data provide some insight that could direct future approaches. The reduced clinical efficacy of antibody-based therapies in the brain has been attributed to the decreased BBB permeation; however the clinical

benefit of bevacizumab or T-DM1 treatment suggests adequate penetration of antibodies into BBB and encourages the investigation of other large molecule therapies in the BM setting. Despite major preclinical and clinical advancement in the characterization, prevention and treatment of BM, the multitude and complexity of the unresolving questions to be answered will require a tighter integration and translational research between bench and bedside.

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