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Current Treatment Options for Breast Cancer Brain Metastases

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Opinion statement

In the past, the standard of care for treatment of BM was whole brain radiation therapy (WBRT), stereotactic radiosurgery (SRS), and surgery. There has been a greater role for medical therapies in the last two decades due to the discovery of driver mutations and corresponding targeted therapies. These innovations have dramatically altered the approach to treating these patients. Some of the important mutations include epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) mutations in small cell lung cancer, human epidermal growth factor receptor (HER2) mutation in breast cancer, and BRAF mutation in melanoma. Disease-specific graded prognostic assessments have identified prognostic factors for each of the major tumor types associated with BM. These reflect the increased treatment sensitivity of these tumors to specific agents. Furthermore, there is a difference in the genetic makeup of BM compared to their primary tumor. Genomic studies of BM patients comparing somatic point mutations and copy number variations with their primary tumor have demonstrated that while both the primary tumor and BM share a number of common mutations, BM can often develop distinct mutations. Therefore, there is a need to individualize systemic therapies in BM. Several organizations including the Food and Drug Administration and the American Society of Clinical Oncology now emphasize the inclusion of BM patients in various phases of clinical drug development.

Introduction

Brain metastases (BM) are the most common intracranial tumors in adults and are associated with poorer outcomes in advanced malignancies. The incidence of BM varies by cancer type: 20% of lung cancer patients, 7% of melanoma, 7% of renal cell carcinoma, and 5% of breast cancer develop BM. Approximately 10–16% of patients with metastatic breast cancer develop symptomatic brain metastases and an additional 10% of patients have asymptomatic brain involvement that is discovered upon postmortem autopsy [1]. The number of breast cancer patients with brain metastases (BCBM) is increasing due to improved survival rates and greater use of imaging modalities. Luminal A breast cancer is hormone-receptor positive (estrogen-receptor and/or progesterone-receptor positive) and human epidermal growth factor receptor 2 (HER2) negative and has low levels of the protein Ki-67, which helps control how fast cancer cells grow. Luminal A cancers are low-grade, tend to grow slower, and have the best prognosis. Luminal B breast cancer is hormone-receptor positive (estrogen-receptor and/or progesterone-receptor positive) and either HER2-positive or HER2-negative with high levels of Ki-67. Luminal B cancers generally grow faster than luminal A cancers and their prognosis is worse. Among breast cancer patients, the HER2-enriched and triple negative (TN) molecular subtypes are associated with higher incidences of BM compared to luminal A and B molecular subtypes. This neurotropism may be due to upregulation of signaling pathways such as WNT/beta-catenin [2].

Given that the median overall survival (OS) for BCBM patients ranges widely from 3 to 25 months, there has been significant efforts made to define prognostic factors and indices [3]. Established prognostic factors include age, tumor subtype (TN vs. HER2 vs. luminal), Karnofsky Performance Status (KPS), the number of brain metastases, and the presence of extracranial metastases [4, 5•]. The three major treatment modalities for BCBM include surgery, whole brain radiation therapy (WBRT), and stereotactic radiosurgery (SRS). Surgery is usually used for solitary BM and provides prompt symptomatic relief and resolution of peritumoral edema. Intracranial disease control can further be achieved by postoperative radiation therapy that includes either WBRT or SRS. This strategy has been shown to improve survival in patients with well controlled extracranial disease [6]. Patients with four or fewer intracranial metastases can be treated with SRS. WBRT provides better CNS control but is associated with neuro-cognitive decline [7•]. Conventional chemotherapy has historically played a limited role in the management of BCBM. This is due to the blood brain barrier (BBB) which limits passage of large molecules into the brain parenchyma [8]. It also harbors various efflux transporters such P-glycoprotein and breast cancer resistance protein (BCRP). P-glycoprotein has shown to play a role in efflux of chemotherapy agents and BCRP renders drugs ineffective by binding to them [9]. The various targeted therapies developed for breast cancer act by disrupting key signaling pathways. The majority of early drug trials in breast cancer excluded patients with BM thereby hindering the development of specific treatments for BCBM. An emerging area of research is the integration of radiation therapy (both WBRT and SRS) with targeted therapy or immunotherapy. The rationale for the combination of radiation and immunotherapy is the abscopal effect whereby radiation at one site leads to regression of metastases at other sites. Radiation at one site induces immunogenic cell death which may release tumor-cell derived antigens. These antigens may prime cytotoxic T cells with the help of antigen-presenting cells (APC). Cytotoxic T cells then circulate through the bloodstream and attack remaining tumor cells in other non-irradiated organs and cause tumor cell death. This effect is augmented with use of checkpoint inhibitors which cause an enhanced immune response. Studies have validated this phenomenon and have demonstrated reduced regional recurrence with improved OS [10–12]. There are several ongoing trials to investigate this effect (NCT03340129, NCT02696993). Further studies are required to study the role of targeted therapies as salvage therapy in recurrent post-SRS patients.

Surgery and stereotactic radiosurgery

In patients with a single BM, three phase III trials have compared surgery followed by WBRT to WBRT alone [13, 14•, 15]. The combination treatment compared to

radiotherapy alone showed greater survival ($p = 0.04$) and a longer functionally independent survival (FIS, defined as World Health Organization Performance Status less than or equal to 1 and neurological function less than or equal to 1, $p = 0.06$). Patients who received the prior combination therapy had a longer survival (10 months) compared to those who received WBRT alone (6 months). Improvement in functional status was seen more rapidly and for longer periods of time after neurosurgical excision and WBRT compared to WBRT alone. Total resection in patients with two or three BM produced results that are comparable to those with single lesions [16]. The European Association of Neuro-Oncology has published guidelines for the management of BCBM [17•]. They recommend that surgical resection be considered in patients with one to three newly diagnosed BM, especially for lesions that are greater than or equal to 3 cm in diameter regardless of symptoms, necrotic or cystic appearance with edema/mass effect, in the posterior fossa with associated hydrocephalus and those located in symptomatic eloquent areas [17•]. Surgery is also recommended as it extends survival in patients in whom systemic disease is absent or controlled and the KPS is greater than 60. BCBM patients do not routinely undergo surgical resection unlike primary brain tumors. In cases that they do, systemic therapy is usually withheld prior to a major surgical procedure. This makes assessing drug concentrations and comparing pre- versus post-procedure concentrations in BCBM tissue more challenging mainly due to lack of pretreatment (control) tissue. Given biological heterogeneity in breast cancer patients, additional phase 0 trials may be considered to investigate the distribution and activity in tumor tissue of novel molecular compounds given prior to surgical resection of BM and assess if these concentrations are influenced by disruption of the blood-tumor barrier with surgery [18].

SRS for up to three or four BM is effective with local control of 80–90% tumor volume at 1 year and a median OS of 6–12 months [19]. The addition of SRS to WBRT leads to an improvement in local control, prognosis, and survival in patients with a single BM with a high Graded Prognostic Assessment (GPA) score of 3.5–4 regardless of one, two, or three BM [20]. Graded Prognostic Assessment takes into account factors such as KPS, tumor subtype, and age. GPA of 3.5–4 portends a poor prognosis compared to GPA of 0–1 [21]. In recent years, SRS has been increasingly used for patients with five to ten BM with OS and treatment complication rates similar to those with fewer BM [22]. Studies comparing SRS to surgery show similar outcomes but are rarely randomized and are likely to be affected by selection bias [23, 24]. Leptomeningeal relapse can be a significant complication following treatment of BM. The risk is significantly higher with posterior fossa metastases undergoing a "piecemeal" resection as opposed to an "en bloc" resection [25, 26]. The risk is also higher in postoperative SRS when compared to either SRS or WBRT alone [27, 28]. Acute neurologic complications of SRS include seizures, headache, and hemorrhage [29]. Approximately 10% of patients who receive tumor bed radiosurgery have radiation-related edema seen as increased T2 signal changes around the resection site [30]. Radiation necrosis is an additional complication whose incidence has been underestimated and is in need of further study [31]. Corticosteroids with or without hyperbaric oxygen are commonly used in the management of radiation necrosis. The VEGF inhibitor bevacizumab has been shown to decrease maximum bidirectional measurements for post-contrast T1 and FLAIR images by 48% and 60% respectively. Bevacizumab can stabilize the vascular permeability in the site of necrosis [32].

Role of WBRT

Traditionally, WBRT has been recommended in patients with multiple BM (greater than 4) due to breast cancer. A major concern with this approach in patients who survive more than 6–12 months is cognitive dysfunction, especially if they are HER2-positive. These patients are living longer when compared with HER2 negative BCBM due to improved systemic disease control (2.1 years 95% CI 1.6–2.6 vs. 0.65 years 95% CI 0.4–1.3, $p = 0.001$) [33]. WBRT following surgery or SRS is no longer routinely recommended in the guidelines as it improves local control but does not extend OS [14•, 34, 35]. The Alliance trial was a randomized phase III trial that compared SRS alone to SRS + WBRT in BM from multiple primary tumor types with a primary neurocognitive endpoint [20]. It demonstrated that neurocognitive decline was more frequent after SRS + WBRT versus SRS alone (88% vs. 62%; $p = 0.002$), with greater deterioration in immediate recall, delayed recall, and verbal fluency [36]. Another recent phase III study compared SRS to WBRT following surgery. It showed that SRS had lower rates of cognitive deterioration at 6 months when compared to WBRT (52% vs. 85%; $p < 0.00031$) [37]. Thus, SRS is a less toxic alternative to WBRT in the postoperative setting to WBRT.

Patients with advanced age, hypertension, and diabetes are at an increased risk of developing cognitive dysfunction following WBRT. This is due to injury of the endothelium of small vessels that results in accelerated atherosclerosis and chronic ischemia. This clinically resembles vascular dementia and it was thus hypothesized that drugs used for vascular dementia may prevent cognitive decline due to radiation therapy. RTOG-0614 was a double-blind, placebo-controlled phase II trial in which memantine showed a modest improvement of cognitive function when given during and after WBRT [38]. The acetylcholinesterase inhibitor donepezil has shown a modest impact on cognitive function [39]. RTOG 0933 is a single-arm phase II trial that reported that the conformational avoidance of the hippocampus during WBRT is associated with memory protection [40].

Medical therapy

The role of conventional chemotherapy has been limited in the past for patients with BCBM due to various mechanisms of inactivation and resistance. Active agents include capecitabine, high-dose methotrexate, cisplatin plus etoposide, and temozolomide. In a phase III study (EMBRACE), a microtubule dynamic inhibitor eribulin mesylate synthesized from halichondrin B, a natural marine product, improved OS in patients who were pretreated with surgical resection and WBRT [41]. In another phase III study (BEACON) etirinotecan pegol (EP), a novel long-acting topoisomerase-1 inhibitor demonstrated an improved OS [42]. This trial compared EP with treatment of physician's choice (TPC) which included eribulin, vinorelbine, gemcitabine, nab-paclitaxel, ixabepilone, or docetaxel in patients who were pretreated with anthracycline, taxane, and capecitabine, including those with treated, stable BM. EP was associated with a significant reduction in the risk of death (HR 0.51, $p < 0.01$) when compared to TPC. Median OS was 10.0 and 4.8 months for EP and TPC respectively. Survival

rates were 44.4% for EP versus 19.4% for TPC. Fifty percent of patients on EP experienced grade 3 or higher toxicity versus 70% in the TPC group. A confirmatory phase III trial in patients with BM is ongoing (NCT02915744) and is estimated to be completed by February 2020. The tubulin targeting drug paclitaxel is prevented from reaching its target by the P-glycoprotein efflux pump at the BBB. ANG1005 is a conjugate of paclitaxel and Angiopep-2 (a brain peptide vector) and was developed and tested in brain tumors. ANG1005 enters the brain to a greater extent than paclitaxel and further bypasses the efflux pump at the BBB. It was also demonstrated that ANG1005 caused a more potent inhibition of human tumor xenografts than the parent drug paclitaxel, with an increase in survival of mice with intracerebral implantation of U87 MG glioblastoma cells or NCI-H460 lung cancer cells [43]. Intrathecal chemotherapy with methotrexate or depot cytosine arabinoside or thiotepa has been shown to be of palliative value in leptomeningeal metastases [44].

Targeting HER2 in BCBM

HER2 is a membrane tyrosine kinase and part of the epidermal growth factor receptor family (HER/EGFR/ERBB). It is an oncogene that is overexpressed in approximately 20% of breast cancers [45] and is one of the most heavily researched and targeted pathways in breast cancer. HER2-positive tumors are associated with an aggressive disease course and have a higher incidence of BM up to 50% in some cases [46]. The high propensity of HER2-positive breast cancer to metastasize to the brain is postulated to be due to limited intracranial activity of anti-HER2 therapy and the inherent tropism of this subtype to the brain [47]. HER2 targeting agents can be classified into monoclonal antibodies (trastuzumab, pertuzumab), antibody-drug conjugates (T-DM1), and small molecule tyrosine kinase inhibitors (lapatinib, neratinib). An important consideration is trastuzumab's enhanced CNS penetration following pre-treatment with radiation or surgery, both of which disrupt the BBB. Studies show that the CSF concentration of trastuzumab in BM patients is 1:420 without pretreatment and improves to 1:79 after being treated with radiation or surgery [48,49].

There have been few retrospective studies on trastuzumab-based therapies to show improved survival in HER2-positive BCBM. These studies have been almost always due to extracranial disease control [50, 51]. In the CLEOPATRA trial, the addition of pertuzumab (which acts against a different epitope of the HER2 receptor) to the combination of trastuzumab and docetaxel was compared to trastuzumab with docetaxel alone [52]. This randomized, double-blind, placebo-controlled, phase III trial enrolled patients with locally recurrent, unresectable, or metastatic HER2-positive breast cancer while excluding those with CNS metastases, LVEF less than 50% during or after previous trastuzumab therapy, those who have received other anticancer therapy, or those with a cumulative exposure of more than 360 mg of doxorubicin per square meter of body surface area or its equivalent. Patients received either the pertuzumab, trastuzumab, and docetaxel combination or the placebo, trastuzumab, and docetaxel combination. Median OS was 56.5 months (95% CI, 49.3—not reached) in the pertuzumab combination group as compared with 40.8 months (95% CI, 35.8 to 48.3) in the placebo combination group showing a difference of 15.7 months. Median PFS improved by 6.3 months in the pertuzumab group (HR, 0.68; 95% CI, 0.58 to 0.80). Median time to

development of CNS metastases as a first site of disease progression was prolonged at 15 months with pertuzumab compared to 11.9 months in the placebo group as demonstrated by a post hoc analysis [53]. Leptomeningeal carcinomatosis, which is a rare but fatal manifestation of BCBM seen in 3.5% of all breast cancer patients, has an increasing incidence in recent years [54, 55]. This is possibly due to widespread use of adjuvant trastuzumab, a drug that has poor CNS penetration and increased systemic relapse-free survival without affecting the propensity for CNS metastases [56, 57]. In patients with leptomeningeal metastases, it has been shown that intrathecal administration of these monoclonal antibodies could result in better outcomes [58]. There are studies investigating this effect by comparing trastuzumab monotherapy to trastuzumab in combination with pertuzumab [59].

Trastuzumab emtansine (T-DM1) is a novel drug whose trastuzumab subunit binds to the HER2/neu receptor and the DM1 subunit binds to tubulin inside cells [60]. The EMILIA trial recruited patients with locally advanced or metastatic breast cancer (with 95% of initially enrolled patients having CNS metastases at time of enrollment) and compared lapatinib plus capecitabine versus T-DM1 [61]. This was a randomized, open-label, international trial in which HER2-positive, unresectable, locally advanced, or metastatic breast cancer patients who were previously treated with trastuzumab and a taxane were enrolled. The primary end points were PFS, OS, and safety. Secondary endpoints included progression-free survival (PFS), objective response rate (ORR), and time to symptom progression. A total of 991 patients were randomly assigned, and median PFS as assessed by independent review was 9.6 months with T-DM1 versus 6.4 months with lapatinib plus capecitabine (HR for progression or death from any cause, 0.65; 95% CI, 0.55 to 0.77; $p < 0.001$). Median OS at the second interim analysis crossed the stopping boundary for efficacy (30.9 months vs. 25.1 months, HR for all-cause mortality, 0.68; 95% CI, 0.55 to 0.85; $p < 0.001$). The ORR was higher with T-DM1 (43.6% vs. 30.8% with lapatinib plus capecitabine; $p < 0.001$) and results of all additional secondary end points favored T-DM1. Rates of adverse events of grade 3 or above were higher with lapatinib plus capecitabine at 57% compared to 41% for T-DM1. The incidence of thrombocytopenia and elevated serum aminotransferase levels were higher with T-DM1. Patients treated with lapatinib plus capecitabine had a higher incidence of gastrointestinal adverse effects such as diarrhea, nausea, vomiting, and palmar-planter erythrodysesthesia. Similar PFS was seen in both groups (5.9 vs. 5.7 months respectively). Patients treated with T-DM1 demonstrated significant improvement in OS with 26.8 versus 12.9 months seen in the capecitabine plus lapatinib arm in a retrospective analysis [62]. PFS by independent review was similar in the two treatment arms (HR = 1.00, $p = 1.00$; median PFS, 5.9 vs. 5.7 months). Similar results were obtained by multivariate analyses and it was concluded that in patients with treated, asymptomatic BCBM at baseline, T-DM1 was associated with significantly improved OS as compared with lapatinib-capecitabine. This improvement in OS is attributed to improved systemic disease control.

At the 2016 American Society of Clinical Oncology (ASCO) Annual Meeting, the combination of trastuzumab with tucatinib (ONT-380), a small molecule tyrosine kinase inhibitor (TKI) against the HER2 receptor with minor activity against the EGFR receptor, demonstrated favorable, sustained CNS responses [63]. This was a non-randomized, open-label, phase Ib trial done at

five US sites that recruited patients 18 years or older with HER2-positive progressive breast cancer pre-treated with trastuzumab, pertuzumab, and TDM-1. Patients were required to be positive for HER2 assessed locally, evaluable lesions as defined per RECISTversion 1.1, and an ECOG performance status of 0 or 1. Patients received either tucatinib twice a day in conjunction with capecitabine 1000 mg/m^2 orally twice daily for 14 days of a 21-day cycle in one arm and trastuzumab 6 mg/kg intravenously once every 21 days, or both treatments. The primary endpoint was determination of maximum tolerated and recommended phase II dose of tucatinib (300 mg orally twice daily). All patients who had received at least one dose of study treatment were analyzed. A modified 3+3 dose-escalation design was used to determine the recommended phase II dose, starting with tucatinib in combination with capecitabine or trastuzumab, with subsequent evaluation of the triplet combination. The tucatinib phase II dose was determined to be 300 mg orally twice daily, equivalent to single-agent maximum tolerated dose (MTD). There was no drug-drug interaction with capecitabine on pharmacokinetic analysis. Reported adverse events for the drug included diarrhea in 67% of patients, nausea in 60% of patients, palmar-plantar erythrodysesthesia syndrome in 44% of patients, and fatigue in 38% of patients. The proportion of patients with measurable disease achieving objective response was 83% in the combination of tucatinib and capecitabine, 40% in the combination of tucatinib, and trastuzumab and 61% in the combination of tucatinib with both capecitabine and trastuzumab. Validation of the current study results will be determined by the double-blinded randomized study HER2CLIMB with an expected completion date of July 2021 [63].

Lapatinib, a novel TKI with activity against both the HER2 and EGFR receptors, can cross the BBB. The CNS penetrability of lapatinib increases with BM, with up to 26% detected in the CNS as opposed to 2.8% in the normal brain although it is susceptible to the activity of efflux pumps in the BBB [64, 65]. There were two phase I trials conducted in order to determine the safety and tolerability of lapatinib in healthy individuals. In a dose escalation study of 67 heavily pretreated patients with HER2 and/or HER1-overexpressing metastatic cancers, lapatinib was well tolerated with clinical activity seen in the 650–1600 mg daily dose range and most commonly between 900 and 1200 mg. This dose escalation study was the first to show clinical activity of lapatinib [66]. Lapatinib was studied in another phase I study that recruited $N = 33$ patients with HER2 and/or EGFR overexpressing metastatic cancers. Heavily pretreated patients with metastatic cancers overexpressing ErbB2 (HER2) and/or expressing ErbB1 (EGFR) were randomly assigned to one of five dose cohorts of lapatinib. The biologic effects of lapatinib on tumor growth and survival pathways were assessed in tumor biopsies obtained before and after 21 days of therapy. Partial responses were seen in 4 patients with breast cancer out of 33 tumor biopsies examined [67].

Lapatinib was used in a single-arm, open-label, multicenter phase II trial with HER2-positive metastatic breast cancer with brain metastases not previously treated with WBRT, capecitabine, or lapatinib. Among 45 patients enrolled in the trial, 44 (98%) were assessable for efficacy and had a median follow up of 21.2 months (range 2.2–27.6). Patients received lapatinib 1250 mg orally daily and capecitabine 2000 mg/m^2 orally from days 1 to 14. The primary endpoint was the proportion of patients with an objective CNS

response, defined as a 50% of greater reduction in volume of CNS lesions in the setting of no steroid use, progressive neurological symptoms, and progressive extracranial disease. The results showed that 29 patients had an objective CNS response (65.9%, 95% CI 50.1–79.5), all of which were partial. Forty-nine percent of patients had grade 3–4 treatment-related adverse events, the most common being diarrhea (20%) and hand-foot syndrome (20%) [68••].

A multicentered phase II study of lapatinib in HER2-positive BCBM patients with 242 enrolled patients was performed to further evaluate CNS activity of lapatinib after a small phase II trial showed regression of CNS lesions with this agent. In the larger phase II trial, CNS objective responses were seen in 6% of patients and 21% experienced a > 20% volumetric reduction of CNS lesions in the absence of increasing steroid use, progressive neurologic signs and symptoms, or progressive extra-CNS disease in an exploratory analysis [69]. There was an association that was observed between volumetric reduction and improvement in PFS and neurologic signs and symptoms. Although the intracranial response rates for lapatinib were low, they improved when capecitabine was added in the single-arm phase II LANDSCAPE trial. The intracranial response rate was 66% with a median time of 5.5 months to intracranial progression [68••, 69, 70]. Finally, a phase II trial that compared lapatinib plus capecitabine ($N = 13$) to lapatinib plus topotecan ($N = 9$) in HER2-positive BCBM patients previously treated with trastuzumab and cranial radiotherapy was stopped early due to excess toxicity and lack of efficacy in the lapatinib plus topotecan arm. However, the lapatinib plus capecitabine arm showed an encouraging CNS objective response (≥ 50% volumetric reduction) rate of 38% (95% CI 13.9–68.4) [71•]. No responses were observed in the lapatinib plus topotecan arm. This arm was also associated with excess toxicity.

Neratinib is another novel TKI which is an irreversible inhibitor of HER2, erbB4, and EGFR. Preclinical data has demonstrated that neratinib can penetrate the BBB. Neratinib can reverse ATP-binding cassette subfamily B member 1 (ABCB1)-mediated chemoresistance [72] and may be able to target activating HER2 mutations in HER2-negative breast cancer and overcome resistance to trastuzumab or lapatinib [73, 74]. Neratinib decreased the activation of the four HER receptors and inhibited downstream pathways. Neratinib also reduced phosphorylated HER2 (pHER2) and pHER3 in acquired trastuzumab resistant cells. Trastuzumab plus neratinib had a greater growth inhibition than either drug alone in four HER2-positive cell lines. The combination inhibited SKBR3 and BT474 cells that had acquired resistance to trastuzumab as well as in a BT474 xenograft model. The results from this study showed that combined treatment with trastuzumab and neratinib is likely to be more effective than either treatment alone for both trastuzumab-sensitive breast cancer as well as trastuzumab-resistant HER2-positive tumors. In a multicenter, phase II open-label trial, the efficacy of neratinib was evaluated in patients with HER2-BCBM. Patients with HER2-positive BCBM (more than or equal to 1 cm in longest dimension) who experienced CNS progression after one or more lines of CNS-directed therapy such as WBRT, SRS, and/or surgery were eligible for this study. Patients received 240 mg orally once daily and tumors were assessed every 2 cycles. Forty patients enrolled in the study between February 2012 and June 2013 of which 78% had prior WBRT. Three women achieved partial response (CNS ORR of 8%, 95% CI 2–22%). The median number of cycles was 2 with a median PFS of 1.9 months. Patients in this study reportedly

experienced a decreased quality of life over time. In this study, neratinib had low activity and did not meet the investigator's threshold for success [75] with a CNS ORR of 8% (95% CI 2–22%). In order to enhance CNS activity, this trial was extended to a two-drug combination neratinib and capecitabine. Patients with measurable BCBM (> 1 cm in longest dimension) and no prior lapatinib or capecitabine were eligible. Capecitabine 750 mg/m^2 twice daily for 14 days followed by 7 days off plus neratinib 240 mg orally once daily was given to patients in this study. Brain MRI and non-CNS imaging were done every 2 cycles for 18 weeks, then every 3 cycles. The primary endpoint was composite CNS ORR requiring reduction in volumetric sum of target CNS lesions, no progression of non-target or non-CNS lesions, no new lesions, no escalating steroids, and no progressive neurologic signs or symptoms. Overall survival at 12 months was 63% (95% CI 43–77%). Grade 4 toxicity was not observed with 49% experiencing grade 3 toxicities. Diarrhea was seen in 32% patients even after loperamide prophylaxis was recommended during cycle 1. This trial is still ongoing with final results expected after December 2019.

A phase II trial of neratinib and capecitabine for patients with HER2-positive BCBM was reported at the ASCO 2017 meeting by Freedman et al. The trial consisted of a cohort 1 ($N = 40$) in which patients with progressive BCBM received neratinib 240 mg/day, cohort 2 ($N = 5$) which consisted of craniotomy candidates who received neratinib 240 mg/day until surgical resection and the same was continued after surgery, and cohort 3A ($N = 37$) and 3B ($N = 11$) which included patients with progressive BCBM with no prior lapatinib and with prior lapatinib respectively who received neratinib 240 mg/day and capecitabine 750 mg/square meter on day 1 to 14 of a 3 week cycle. Patients with HER2-positive BCBM with signs of CNS progression in a new or previously treated site after one or more lines of local CNS therapies were administered were eligible for this study. Patients also needed to have a measurable disease of more than 1 CNS lesion greater than or equal to 10 mm, ECOG performance status of 0–2, adequate end-organ function, and a normal ejection fraction. Patients with prior capecitabine and lapatinib were excluded as were patients with only leptomeningeal disease, significant diarrhea, or active escalation of steroids. Patients were followed every 3 weeks with brain MRI and body CT re-imaging at week 6. CNS ORR per volumetric criteria was the primary endpoint of this study. The secondary endpoints were toxicity, site of first progression, PFS, OS, and CNS response by Response Assessment in Neuro-Oncology (RANO) BM criteria. A CNS ORR of 49% (95% CI 32–66%) in terms of volumetric response and 24% in terms of sum of longest diameters was observed. Median time of CNS progression was 5.5 months and 6-month PFS was 38%. Overall survival was 13.5 months with 51% experiencing grade 3 toxicity [76].

Another study involving neratinib was the phase I/II trial of neratinib and capecitabine for 33 patients with HER2-positive BCBM [77]. This study was conducted in two parts. Part 1 was a 3+3 dose-escalation study in patients with advanced solid tumors who received oral neratinib once daily plus capecitabine twice daily on days 1 to 14 of a 21-day cycle at predefined doses. In part 2, neratinib plus capecitabine was administered at the MTD in patients with trastuzumab-pretreated HER2-positive BCBM with the ORR being the primary endpoint. In part one ($N = 33$), the combination of neratinib 240 mg per day plus capecitabine 1500/m^2 per day was defined as the MTD. This was further

evaluated in part 2 with a larger sample size ($N = 72$) which showed an ORR of 64% (39 of 61) in patients with no prior lapatinib exposure (median PFS of 40.3 weeks) and 57% (4 of 7) in patients who were previously treated with lapatinib (median PFS of 35.9 weeks).

Tucatinib (ONT-380), a potent and highly selective small molecule inhibitor of HER2, was tested in a single-agent phase I study in HER2-positive metastatic breast cancer. As discussed above, tucatinib is being evaluated in combination with capecitabine and trastuzumab in HER2-positive metastatic breast cancer following prior treatment with trastuzumab and T-DM1. Tucatinib 300 mg orally twice daily is currently being studied in combination with both capecitabine and trastuzumab as triple therapy. In a 3+3 dose escalation phase Ib study of tucatinib, the drug was administered in combination with capecitabine (1000 mg/m^2 orally twice daily 14 days of a 21 day cycle) and trastuzumab (8 mg/kg IV loading then 6 mg/kg IV once every 21 days) to HER2-positive metastatic breast cancer patients with prior pertuzumab, lapatinib, or neratinib and asymptomatic brain metastases (treated or untreated). A total of eight patients (with 2–6 prior treatments) have completed 2–8 cycles of triplet therapy while six patients remain active. In one patient with brain metastases, a dose-limiting toxicity of reversible cerebral edema with grade 3 dysarthria and visual field deficit was observed. Another grade 3 treatment-related event of reversible increase in serum aminotransferases was reported. To date, patients with at least one follow-up scan have been shown to have partial response (4 patients), stable disease (2 patients) and progressive disease (2 patients). Of note, the two patients with partial response and the two patients with stable disease had previously received pertuzumab. The estimated study completion date is July 2019 [78].

Another phase Ib open-label, multicentered trial enrolled 57 ERBB2/HER2-positive metastatic breast cancer patients previously treated with trastuzumab and a taxane. The objective was to determine the MTD of tucatinib in combination with T-DM1 in treatment of HER2-positive metastatic breast cancer with and without brain metastases. Tucatinib 300 mg or 350 mg was administered orally twice daily for 21 days and T-DM1 3.6 mg/kg was administered intravenously once every 21 days. The main outcomes were safety assessments, pharmacokinetics, and responses assessed using RECIST 1.1 every 2 cycles for 6 cycles, followed by every 3 cycles. A total of 57 T-DM1 naïve patients who had undergone a median of two earlier HER2 therapies (range 1–3) were treated. The MTD for tucatinib was determined to be 300 mg administered twice daily with dose-limiting toxic reactions observed at 350 mg twice daily with pharmacokinetic analysis showing no drug-drug interactions with T-DM1. Adverse reactions in patients treated at the maximum tolerated dosage included nausea (72%), diarrhea (60%), fatigue (56%), epistaxis (44%), headache (44%), emesis (42%), constipation (42%), and decreased appetite (40%). Toxic reactions related to tucatinib that were grade 3 or higher included thrombocytopenia (14%) and hepatic transaminitis (12%) [79] (Table 1).

Targeting the PI3K/Akt/mTOR pathway in BCBM

The phosphatidylinositol3 kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway is targeted by various drugs which have been used in the treatment of BCBM. The two most common aberrations in this pathway are the

Table 1. Newer targeted agents against the HER2 receptor developed for BCBM

Study	Targeted therapy	Trial	Patients	Local control	Progression-free survival (months)	Overall survival (months)
Verma et al. [61]	TDM1 vs. lapatinib-capecitabine	Retrospective analysis of BM in EMILIA	TDM1: 45 L+C: 50	Not reported Not reported	5.9 5.7	26.8 12.9
Baselga et al. [81]	Placebo + trastuzumab + docetaxel Pertuzumab + trastuzumab + docetaxel	Randomized, double-blind, phase 3 trial	808	Not reported	12.4 18.5	Not reported Not reported
Borges et al. [79]	TDM1+ tucatinib	Phase 1b, open-label	57	Not reported	8.2	Not reported
Bachelot et al. [68••]	Lapatinib + capecitabine	Phase II study for new BM	45	65.9%	5.5	17
Freedman et al. [75]	Neratinib	Single-arm phase II study	40	Not reported	1.9	8.7
Lin et al. [95]	Lapatinib	Phase II study of progressive BM with prior trastuzumab	39	Not reported	18% at 4 months	Not reported
Lin et al. [69]	Lapatinib	Multicenter phase II trial	242	> 20% in 21% patients	2.4	6.4
Saura et al. [77]	Neratinib + capecitabine	Phase II trial	39	Not reported	Not reported	63% at 12 months
Freedman et al. [76]	Neratinib + capecitabine	Phase II trial	93	49%	38% at 6 months	13.5

PTEN deletion and PIK3CA mutation. PIK3CA mutations are seen in 28–47% of hormone receptor-positive tumors and 23–33% of HER2-positive tumors [80]. The PTEN deletion is seen in 29–44% of hormone receptor-positive tumors and 22% of HER2-positive tumors [80]. In the Breast Cancer Trials of OraL EveROlimus-2 (BOLERO-2) trial, everolimus was approved for use with an aromatase inhibitor in post-menopausal hormone receptor-positive metastatic breast cancer that has progressed on or after a non-steroidal aromatase inhibitor [81]. The BOLERO-3 trial was done in patients with trastuzumab-resistant advanced HER2-positive breast cancer [82]. It showed that vinorelbine, trastuzumab, and everolimus in combination were superior to vinorelbine, trastuzumab, and placebo although both these trials excluded patients with BCBM. Two new trials are underway. One is a phase Ib trial in which patients with BCBM progressing on trastuzumab will be treated with lapatinib, everolimus, and capecitabine. The second trial is a phase II trial to evaluate the safety and efficacy of trastuzumab, everolimus, and vinorelbine [83].

Targeting the vascular endothelial growth factor pathway in BCBM

Several phase III trials and meta-analyses have not shown any survival benefit of adding VEGF inhibitors like bevacizumab to metastatic breast cancer treatment and most of these did not involve BCBM patients due to the potential of intracranial hemorrhage [84, 85]. It should be noted that bevacizumab causes changes in the peritumoral vascular system, which can lead to errors in detecting responses with follow-up imaging. Bevacizumab was used as a conditioning agent followed by cisplatin and etoposide for BCBM who had CNS progression after WBRT. This study showed an intracranial response rate of 77% with the possibility of error due to the abovementioned phenomenon [86].

Targeting CDK inhibitors in BCBM

The G1 to S phase of cell division is regulated by the cyclin D-CDK4/6-INK4-Rb pathway. During this transition, an intact pRb gene undergoes hyperphosphorylation which leads to the release of various transcription factors. Several cancers are triggered by the dysregulation of this critical pathway [87, 88]. Currently available drugs in this class include abemaciclib, ribociclib, and palbociclib. These have been used in the management of patients with ER-positive metastatic breast cancer with favorable results [89]. A caveat for this class of drugs is that they need an intact pRb pathway as their target and may be ineffective in advanced breast cancer. Abemaciclib is being evaluated in hormone receptor-positive BCBM and BM from lung cancer and melanoma in a phase II trial [90]. In another phase II clinical trial, palbociclib is being used in hormone receptor-positive or triple-negative BCBM [48].

Targeting EGFR pathway in BCBM

A phase II study that compared afatinib to afatinib with vinorelbine and treatment of the investigator's choice led to disappointing results [91]. As mentioned above, lapatinib which targets both the HER2 and EGFR receptors can cross the BBB more effectively with BM. The LANDSCAPE trial showed a response rate of 66% and a median time to intracranial progression of 5.5 months when capecitabine was used in conjunction with lapatinib in a single-arm phase II, open-label, multicenter study with HER2 BCBM without

prior WBRT [69, 70, 92]. Another phase II trial showed lapatinib plus capecitabine ($N = 13$) to have a CNS ORR of 38% (95% CI 13.9–68.4) as compared to lapatinib plus topotecan ($N = 9$) [71•]. There is a need for additional trials in BCBM for this class of drugs.

Checkpoint inhibitors in BCBM

It is still early in the field to have established efficacy and safety of the various clinically available immune checkpoint inhibitors in BCBM. To date, several such agents have been approved in solid tumors [93] including ipilimumab (which targets the inhibitory cytotoxic T lymphocyte-associated protein 4 (CTLA4) protein expressed on T cells [94] and five other agents that disrupt the programmed cell death protein 1 (PD-1)/programmed cell death ligand 1 (PD-L1) axis (i.e., atezolizumab, avelumab, durvalumab, nivolumab, and pembrolizumab). Currently, there are several ongoing trials assessing the activity of checkpoint inhibitors in CNS metastases (NCT02886585) and in combination with SRS in BCBM (NCT03449238, NCT03483012). NCT02886585 is a phase II open-label, parallel assignment trial that is testing pembrolizumab monotherapy in four cohorts: previously untreated BM, progressive BM, neoplastic meningitis, and 1–4 BM secondary to melanoma. NCT03449238 was recently opened (February 2018) and is a phase I/II single-cohort trial that will recruit breast cancer patients ($N = 41$) with at least 2 BM and eligible to receive SRS. All patients will receive the standard dose of pembrolizumab (200 mg IV administered over 30 min) 1 day before SRS and then repeated every 3 weeks until the patient has progressed or experienced intolerable toxicity. NCT03483012 is a phase II open-label, single-group trial that will administer the combination of atezolizumab (once every 3 weeks) and SRS in patients with triple-negative breast cancer and ≤ 5 brain metastases ($N = 45$).

Conclusion

The management of BCBM has evolved significantly in the last decade. Surgical resection can be considered for limited number of intracranial lesions as detailed above. WBRT is no longer recommended after surgery or SRS as it does not improve OS in patients with limited number of brain metastases. The role of systemic therapy is being re-evaluated given the emergence of novel monoclonal antibodies, antibody-drug conjugates, and small molecule TKIs. Number of TKIs that have shown promise include combination of capecitabine with lapatinib, with higher response rates seen with neratinib. Preliminary data with tucatinib is promising. There is role of TDM1 as retrospective reports have shown efficacy. Other key targets that should be further studied in BCBM include VEGF, CDK, and EGFR receptors. An emerging area of research is the integration of radiation therapy (both SRS and WBRT) with targeted therapy and immunotherapy. The abscopal effect serves as rationale for combining radiation with immunotherapy and will need further evaluation in prospective studies. It is still early in the field to determine whether checkpoint inhibitors will show efficacy in BCBM with several agents currently in trials.

Compliance with Ethical Standards

Conflict of Interest

Arrvind Raghunath declares that he has no conflict of interest. Kunal Desai declares that he has no conflict of interest. Manmeet S. Ahluwalia has received research funding from Incyte, Bristol-Myers Squibb, AstraZeneca, TRACON, Novartis, Novocure, AbbVie, Pharmacyclics, Merck, and Bayer; has received compensation from Incyte, Bristol-Myers Squibb, AstraZeneca, Novocure, Monteris Medical, Caris Life Sciences, MR Solutions, AbbVie, CBT Pharmaceuticals, Flatiron Health, Varian Medical Systems, and MimiVax for service as a consultant; has received compensation from VBI Vaccines for participating on a data and safety monitoring board; and has stock options in MimiVax and Doctible.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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