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BREAST CANCER (B OVERMOYER, SECTION EDITOR)

Systemic Therapy of Central Nervous System Metastases of Breast Cancer

José Pablo Leone[1] · Nancy U. Lin[1]

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Abstract

Purpose of the Review Historically, systemic treatment options for patients with breast cancer brain metastases have been very limited. This review focuses on important considerations for systemic therapy as well as ongoing clinical trials evaluating novel agents.

Recent Findings For patients with hormone receptor-positive brain metastases, endocrine therapy or chemotherapy options can be considered. The role of CDK4/6 inhibitors is being explored in ongoing trials. Patients with HER2-positive disease have a number of treatment options, including ado-trastuzumab emtansine (TDM1) or lapatinib-capecitabine, and there is emerging evidence of the efficacy of neratinib- and tucatinib-based chemotherapy combinations in the CNS. Triple-negative tumors may respond to chemotherapy.

Summary Although much progress remains to be made, a number of effective systemic treatment options are emerging, particularly for patients with HER2-positive disease. Ongoing clinical trials will help define the role of novel agents.

Keywords Breast cancer · Brain metastases · Chemotherapy · Targeted therapies · Metastatic breast cancer

Introduction

Breast cancer is among the most common causes of brain metastases, and unfortunately a significant number of patients with advanced breast cancer will suffer this dreaded complication [1]. It is estimated that approximately 16% of all patients with metastatic breast cancer will develop brain metastases; however, the incidence varies considerably by subtype. In fact, it is around 25–45% in triple-negative breast cancer and up to 50% in human epidermal growth factor receptor 2 (HER2)-positive breast cancer when followed longitudinally [2–4].

In addition to the differences in incidence of brain metastases, breast cancer tumor subtypes are an important parameter for their timing. The time interval from initial breast cancer diagnosis to the development of brain metastases is shorter for triple-negative and HER2-positive breast cancers, and longer for estrogen receptor (ER)-positive disease [5].

Unfortunately, patients who develop brain metastases often have a poor prognosis, with median survival that ranges from 2 to 25.3 months [6–8]. During their disease, these patients can suffer from neurologic symptoms and complications, and significant morbidity which can lead to reduced quality of life [9]. We have a number of options with limited efficacy for the treatment of patients with brain metastases from breast cancer, including surgery, radiation therapy: in the form of stereotactic radiosurgery (SRS) or whole brain radiation therapy (WBRT), and systemic agents consisting of chemotherapy and targeted therapy [10, 11]. This review will focus on key issues of current systemic therapy options for each breast cancer subtype with brain metastases. We also describe ongoing clinical trials evaluating novel therapies.

Prognostic Factors

Although the prognosis of patients with breast cancer brain metastases is generally poor, there are a number of important factors that are taken into consideration when assessing individual patients. At the time of initial diagnosis of brain

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✉ José Pablo Leone
JoseP_Leone@dfci.harvard.edu

[1] Department of Medical Oncology, Division of Breast Oncology, Dana-Farber Cancer Institute, Harvard Medical School, 450 Brookline Ave., Boston, MA 02215, USA

metastases, patients who have Karnofsky Performance Status (KPS) scores ≥ 70 experience longer survival [7, 12, 13]. Another patient characteristic that has been negatively associated with survival is older age [14, 15].

Some tumor characteristics play an important prognostic role. In this regard, breast cancer tumor subtypes not only are associated with the incidence and timing of brain metastases but also demonstrate a strong correlation with overall survival. Patients with HER2-positive breast cancers have the best prognosis, with median overall survival around 22 months [8, 16, 17]. In contrast, patients with triple-negative breast cancer continue to have unfavorable outcomes and their median overall survival is in the range of only 3 to 6 months [8, 16, 18]. Lastly, increased intracranial or extracranial disease burden has been associated with worse survival in some studies [19–21].

Given the number and differential effects of the above mentioned prognostic factors, efforts have been made to create a tool to help clinicians assess prognosis of patients with brain metastases from breast cancer. One such tool is the graded prognostic assessment (GPA) [22]. This retrospectively validated index initially included patient age, KPS score, number of brain metastases, and the presence of extracranial metastases. The index was subsequently modified to create a breast cancer-specific GPA that incorporated tumor subtypes to the model [7]. More recently, with the addition of number of brain metastases, the breast cancer-specific GPA was further refined and validated [23].

Systemic Therapies

Despite recent advances in systemic therapies for metastatic breast cancer, there are currently no agents with regulatory approval for the treatment of brain metastases from breast cancer. However, using patient and tumor characteristics mentioned above, including tumor subtype, can help select the most appropriate systemic therapy options for individual patients.

Hormone Receptor-Positive Disease

Despite the higher propensity of HER2-positive and triple-negative breast cancers to develop brain metastases, population-based data shows that ER-positive brain metastases are the most frequent subtype, representing 46.6% of all de novo stage IV breast cancer brain metastases cases [8].

Patients presenting with stage IV ER-positive breast cancer should generally be treated with endocrine therapy as their first-line treatment, consistent with current guideline recommendations [24]. This can also include patients who present with brain metastases at the time of diagnosis of metastatic breast cancer. However, the data to support endocrine therapy for the treatment of brain metastases is weak, given that most randomized trials testing endocrine therapy have excluded patients with brain metastases. Nonetheless, there are reports of brain metastases responding to tamoxifen, megestrol acetate, and aromatase inhibitors [25–30]. Moreover, the concentration of tamoxifen and its metabolites can be up to 46-fold higher in brain metastatic tumor and brain tissue compared with serum [31]. Aromatase inhibitors, from a mechanistic standpoint, do not need to penetrate into the brain to exert their anti-tumor effect. Therefore, these endocrine therapy agents can be considered when treating brain metastases from ER-positive breast cancer.

More recently, cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors have been incorporated to the treatment of patients with metastatic ER-positive breast cancer. Among the three commercially available CDK4/6 inhibitors, abemaciclib demonstrates the best CNS penetration in preclinical models [32]. Therapeutic levels in the CNS have been demonstrated in patients exposed to abemaciclib prior to resection of brain metastasis [33]. In the phase 2 I3Y-MC-JPBO (JPBO) clinical trial, abemaciclib was associated with a clinical benefit rate of 17.4% for patients with ER-positive/HER2-negative brain metastases [34]. Final results of the study are pending. While promising, more data on the efficacy of these agents is warranted to further define their activity in the CNS in breast cancer patients.

Breast cancer brain metastases tend to be a late event in patients with ER-positive breast cancer. Because of this, treatment of brain metastases often occurs when the disease is already resistant to endocrine therapy. In such cases, chemotherapy will be the preferred treatment when systemic therapy is being considered. While no randomized trials have been done in this setting, observational data suggests a potential benefit of systemic therapy. For example, Niwinska et al. reported among patients with luminal (ER/PR-positive HER2-negative) breast cancer, an improvement in median survival from 3 to 14 months with the use of systemic therapy in the form of hormonal therapy or chemotherapy [35]. Similarly, another study reported an improvement in median overall survival of patients with luminal disease from 7.1 to 14.3 months with the use of chemotherapy [36]. Specific chemotherapy regimens are discussed in more detail in the section on triple-negative breast cancer.

HER2-Positive Disease

Despite significant improvements in overall survival of patients with metastatic HER2-positive breast cancer [37], these patients remain at risk for the development of brain metastases, which continue to be an important clinical challenge [4]. The longer control of systemic disease achieved with effective

anti-HER2 therapies have unveiled the ability of HER2-positive breast cancer cells to metastasize to the brain. This phenomenon could be explained in part by the fact that most anti-HER2 therapies either do not penetrate the intact blood-brain barrier (BBB), or when they do, they are effluxed out of the brain through P-glycoproteins present in the BBB. This results in insufficient therapeutic concentrations for the treatment of micro-metastases in the brain by most anti-HER2 therapies, and thus limited ability to prevent CNS spread.

Trastuzumab, for example, has a ratio in plasma to the cerebrospinal fluid of > 300:1 in a patient with meningeal carcinomatosis [38]. However, in patients with brain metastases, the BBB may be disrupted by a number of factors including surgery, radiation therapy, and tumor growth. In addition, the vasculature of brain metastases is frequently abnormal and leads to a heterogeneously permeable blood-tumor barrier. In fact, trastuzumab uptake in the brain parenchyma has been reported using labeled drug with the radioisotopes zirconium^{89} or copper^{64} [39, 40]. Despite difficulties with drug penetration, treatment with trastuzumab in combination with chemotherapy results in improved survival for patients with brain metastases [17, 41, 42]. However, the survival improvement may be due, at least in part, to better control of extracranial disease [43].

Pertuzumab has significantly improved outcomes for patients with metastatic HER2-positive breast cancer. When added to trastuzumab and docetaxel, the combination leads to an absolute increase of 15.7 months of median overall survival compared with placebo plus trastuzumab and docetaxel [37]. An interesting exploratory analysis of this trial showed that although the incidence of brain metastases as first site of disease progression was similar between treatment arms (around 13% for both), time to disease progression in the brain was longer in the pertuzumab-containing arm (15 months vs. 11.9, $P = 0.0049$) [44]. However, a limitation of this analysis was that neither baseline nor follow-up brain imaging was mandated per the protocol.

Trastuzumab-emtansine (T-DM1), an antibody-drug conjugate, has improved outcomes for patients with metastatic breast cancer after prior exposure to trastuzumab compared with lapatinib plus capecitabine [45]. Although patients with active brain metastases were excluded in this study, there was a group of 95 patients who had stable or treated brain metastases at baseline. These patients were analyzed retrospectively in an exploratory analysis that showed improved median overall survival with T-DM1 compared with lapatinib plus capecitabine (26.8 months vs. 12.9 months, respectively; $P = 0.008$), despite similar rates of disease progression in the brain between arms [46]. Taken together, the results observed with pertuzumab and with T-DM1 underscore the importance of extracranial disease control for improving overall survival, even in patients with brain metastases.

A number of retrospective studies have evaluated the activity of T-DM1 specifically for the treatment of brain metastases. A study from Austria that included 10 patients reported 3 patients achieving partial responses and 4 patients stable disease in the brain [47]. A study conducted in France evaluated 39 patients and described a median progression-free survival of 6.1 months with a clinical benefit rate of 59%, of which 44% had partial response and 15% had stable disease [48]. More recently, a study from Italy included 53 patients with brain metastases and reported 3.8% complete responses, 20.7% partial responses, and 30.1% stable disease [49].

Lapatinib is another agent to consider for the treatment of HER2-positive brain metastases. This is a tyrosine kinase inhibitor (TKI) of the epidermal growth factor receptor (EGFR) and HER2 that was hypothesized to cross the BBB given its small size. The first trials evaluated lapatinib monotherapy in heavily pre-treated patients and resulted in response rates in the brain of 2.6 to 6% [50, 51]. Subsequent trials tested lapatinib in combination with capecitabine and showed CNS response rates of 20 to 38% [51–54]. As expected, patients who derived most benefit were those previously untreated, who had an objective response rate of 65.9% with 1-year survival rate > 70% [55]. In an ad hoc analysis of the pivotal phase III trial, the addition of lapatinib to capecitabine was found to decrease the rate of brain metastases as the first site of disease progression from 6% with capecitabine alone to 2% with the combination ($P = 0.045$) [56]. This finding led to a clinical trial conducted to test the role of lapatinib for the prevention of brain metastases. In this study, patients who had HER2-positive metastatic breast cancer without brain metastases at study entry were randomized to receive either lapatinib or trastuzumab in combination with capecitabine [57]. The primary endpoint was the incidence of brain metastases, which was found to be similar between arms (3% for lapatinib vs. 5% for trastuzumab, $P = 0.36$). However, patients assigned to the trastuzumab arm had longer PFS and overall survival due to better control of extracranial disease [57].

Neratinib is an irreversible TKI of EGFR, HER2, and HER4, with clear activity against extracranial metastases as either monotherapy or in combination with chemotherapy [58–60]. Given its potency and small size, it was tested as monotherapy for the treatment of brain metastases from HER2-positive breast cancer and yielded an objective response rate of 8% [61]. However, when combined with capecitabine, neratinib resulted in an objective response rate of 49% [62•]. It is important to notice that neratinib's label in the USA is for the treatment of high-risk early breast cancer only, pending results of the phase III trial of neratinib plus capecitabine vs. lapatinib plus capecitabine (NALA) in the metastatic setting. However, given the results of the trial by Freedman et al., the NCCN guidelines in neuro-oncology now include neratinib with capecitabine as an option for the management of patients with brain metastases from HER2-

positive breast cancer. Further testing of other neratinib-based combinations in patients with brain metastases from breast cancer is ongoing.

In contrast with neratinib, tucatinib is a small TKI with more selective activity against HER2, rather than other EGFR family members, resulting in less diarrhea and less skin toxicity. A phase I study evaluating tucatinib in combination with trastuzumab reported an objective response rate in the brain of 12% with prolonged stable disease [63]. Moreover, in a phase Ib trial of tucatinib with trastuzumab and capecitabine, among 12 patients with measurable brain metastases at baseline, 42% achieved an objective response in the brain [64•]. This combination is being explored further in an ongoing randomized clinical trial (NCT02614794) that specifically includes patients with progressive brain metastases.

Triple-Negative Disease

Unlike HER2-positive breast cancer where treatment is designed around a backbone of anti-HER2 therapy, triple-negative tumors are treated primarily with chemotherapy.

Traditional combinations of chemotherapy resulted in CNS objective response rates of up to 54% [65–67]. A phase II study evaluated the combination of liposomal doxorubicin with temozolamide in patients with brain metastases from solid tumors and identified an objective response rate of 62% among eight patients with breast cancer [68].

Platinum salts, particularly cisplatin in combination with etoposide, were evaluated in a retrospective study that reported a CNS objective response rate of 55% [69]. Subsequently, a prospective study evaluating the same combination with the same dosing schedule showed a response rate of 38% in the brain [70]. Both topotecan as well as temozolomide, when used as single agents, appear to be ineffective for the primary treatment of brain metastasis from breast cancer [71, 72]. However, the combination of temozolomide with cisplatin induced an objective response rate in the CNS of 40% [73], and 18% objective response rate in the CNS when temozolomide is combined with capecitabine [74]. The experience with the use of capecitabine as a single agent is mostly limited to retrospective analyses [75]. In the studies above, it is not clear whether etoposide or temozolomide contributed materially to the response rates in the CNS, and thus, we tend to omit these agents when treating patients and simply use single-agent platinum salts or capecitabine.

Irinotecan has been studied in a single-arm, phase 2 trial enrolling only patients with triple-negative breast cancer brain metastases. A response rate of 12% was reported; notably, two of five patients with germline *BRCA1* or *BRCA2* alterations responded [76]. Etirinotecan pegol is an extended release formulation of irinotecan. In the large phase III trial that compared etirinotecan pegol vs. treatment of physician's choice, a pre-specified analysis was conducted among 67 patients who had previously treated and stable brain metastases. In these patients, overall survival was improved from 4.8 months in the control group to 10 months in the group treated with etirinotecan pegol ($P < 0.01$) [77•]. To confirm these findings, a clinical trial specifically enrolling only patients with stable or treated brain metastases is ongoing.

Table 1 Selected ongoing clinical trials of systemic therapy for the treatment of brain metastasis from breast cancer

Patient population/tumor subtype	Treatment/target	Study phase	Study intervention	Clinicaltrials.gov ID
HER2-positive	CDK4/6	Phase II	Palbociclib	NCT02774681
Any	PD-1	Phase I	Nivolumab with SRS	NCT03807765
Any	TKI	Phase I	Sorafenib with WBRT	NCT01724606
HER2-positive with treated/stable brain metastases	HER2 chemotherapy	Phase I/II	T-DM1 ± temozolamide	NCT03190967
Any with treated/stable brain metastases	Chemotherapy	Phase III	Etirinotecan pegol vs. treatment of physician's choice	NCT02915744
Any with at least two brain metastases	PD-1	Phase I/II	Pembrolizumab with SRS	NCT03449238
Triple-negative	PD-L1	Phase II	Atezolizumab with SRS	NCT03483012
HER2-positive	PD-L1	Phase II	Atezolizumab + trastuzumab + pertuzumab	NCT03417544
HER2-positive	HER2	Phase II	Neratinib with T-DM1	NCT01494662
HER2-positive	HER2	Phase II randomized	WBRT or SRS ± lapatinib	NCT01622868
HER2-positive	HER2	Phase II randomized	Capecitabine + trastuzumab with either tucatinib or placebo	NCT02614794
Triple-negative or *BRCA* mutation-associated	PARP	Phase II randomized	Cisplatin with either veliparib or placebo	NCT02595905

CDK cyclin-dependent kinase, HER2 human epidermal growth factor receptor 2, PARP poly ADP ribose polymerase, PD-1 programmed cell death-1, PD-L1 programmed death ligand 1, SRS stereotactic radiosurgery, T-DM1 trastuzumab emtansine, TKI tyrosine kinase inhibitor, WBRT whole-brain radiation therapy

The approval of poly ADP ribose polymerase (PARP) inhibitors in the USA for the treatment of *BRCA*-mutated HER2-negative advanced breast cancer marked the end of an era where the only systemic treatment option for triple-negative breast cancer was chemotherapy. Although patients with active brain metastases were excluded from the pivotal trial of the PARP inhibitor talazoparib, patients who had a history of brain metastases had a similar degree of extracranial disease control with talazoparib compared with those who did not have brain metastases [78•]. Whether PARP inhibitors will have activity in active/progressive metastases is unknown at this time. However, a cooperative group trial is evaluating this question as part of a randomized trial evaluating platinum ± the PARP inhibitor veliparib (NCT02595905).

Ongoing Clinical Trials

The clinical challenge posed by the diagnosis of brain metastases brings the opportunity for dedicated clinical trials that are currently ongoing, with the goal of improving outcomes in patients with metastatic breast cancer to the brain. A selected list of currently recruiting studies of systemic therapy is shown in Table 1.

Conclusions

For patients with metastatic breast cancer, the development of brain metastases represents a very challenging clinical scenario. Although systemic therapies are a critical component of the treatment plan, these patients should be evaluated in a multidisciplinary manner to discuss appropriateness of surgical resection as well as the timing and modality of radiation therapy for each case. Increasingly, as new data emerge, systemic therapy may be considered in lieu of local treatment options. Given that the prognosis remains poor, participation in clinical trials should be strongly considered. Fortunately, a growing number of important clinical trials are becoming available to patients, and this will hopefully help improve their outcomes.

Compliance with Ethical Standards

Conflict of Interest José Pablo Leone has received research funds paid to his institution (University of Iowa) from Merck and has also received research funds from Kazia Therapeutics and Eli Lilly.

Nancy U. Lin has received funding for clinical trials from Genentech, Seattle Genetics, Novartis, and Pfizer, and has received compensation from Puma and Daiichi for service as a consultant.

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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