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New Insights and Emerging Therapies for Breast Cancer Brain Metastases

Abstract: Breast cancer brain metastases (BCBMs) are the second most frequent secondary central nervous system metastases following those associated with non–small-cell lung cancer. It is increasingly evident that BCBM arises as a function of the biology of the primary tumor and the metastatic niche, which combine to create a unique microenvironment in the brain impacting both metastatic colonization and therapeutic response. Clinical outcomes are improving for BCBM patients as a result of modern combinatorial therapies, challenging the traditionally nihilistic approach to this patient subgroup. This review will focus on the breast cancer subtypes with the highest incidence of BCBM—human epidermal growth factor receptor 2 (HER2)-positive breast cancer, and triple-negative (estrogen receptor [ER]-negative, progesterone receptor [PR]-negative, and HER2-negative) breast cancer (TNBC)—and will characterize differences in the clinical behavior of brain metastases that arise from these different subtypes. We will also highlight some of the recent preclinical studies that may shed light on the biological mechanisms and mediators underlying brain metastases. Finally, we will review published and current prospective trials of systemic therapies specifically for BCBM, including novel pathway-specific therapies.

The Changing Landscape of Breast Cancer Brain Metastases

The diagnosis of central nervous system (CNS) recurrence is a much dreaded outcome among breast cancer patients, and its incidence varies with disease stage and cancer subtype. While less common than bony, lung, or liver metastases, breast cancer brain metastases (BCBMs) are associated with the shortest survival time once diagnosed.[1] BCBMs are also the second most frequent secondary CNS metastases following those associated with non–small-cell lung cancer. BCBMs are typically multifocal and intracerebral, and less commonly solitary and leptomeningeal.[2,3] It is increasingly evident that BCBM arises as a function of the biology of the primary tumor and the metastatic niche; the latter is comprised of the blood-brain barrier (BBB), pericytes, astrocytes, and glial cells, which combine to create a unique microenvironment in the brain that impacts both metastatic colonization and therapeutic response. Improvements in systemic therapy have altered the natural history of breast cancer, and BCBM occurs in a significant proportion of patients. However, patients with BCBM are excluded from many clinical trials, despite the urgent need to develop treatments for this critical challenge. In this article, we will compare the clinical behavior of BCBM associated with the various breast cancer subtypes, with a focus on the subtypes with the highest incidence of BCBM, human epidermal growth factor receptor 2 (HER2)-positive breast cancer and triple-negative (estrogen receptor [ER]-negative, progesterone receptor [PR]-negative, and HER2-negative) breast cancer (TNBC). We will also review therapies and research strategies currently in use and in development.

Differences between the molecular subtypes of breast cancer extend beyond prognosis and therapeutic response to include clinical behavior and patterns of metastatic spread (Table 1). In a study of 3726 patients with early-stage breast cancer diagnosed between 1986 and 1992, the 15-year cumulative incidence rates of brain metastasis were highest in the HER2-positive and TNBC subtypes and lowest in the luminal subtypes.[1] Similar subtype distributions have also been seen in the metastatic setting, where the incidence of BCBM in the HER2-positive and TNBC subtypes is 15% to 44% and 25% to 46%, respectively, with ER negativity and a higher disease burden predicting for a higher BCBM risk in HER2-positive breast cancer.[1,2,4-6] In a separate analysis of 213 patients with BCBM, the median brain metastasis–free survival (BMFS), defined as the time from the diagnosis of extracranial metastases to the time of BCBM, was 34, 18, and 12 months in the ER-positive, HER2-positive, and TNBC subtypes, respectively.[7] In the HER2-positive subgroup, ER co-expression resulted in a prolonged BMFS (26 vs 15 months without ER co-expression). In our series of patients with HER2-positive metastatic breast cancer diagnosed between 1999 and 2005, 8% of patients had BCBM at the time of first metastatic diagnosis, and

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Table 1 Clinical Characteristics of CNS Metastases According to Breast Cancer Subtype

Clinical Characteristics	HER2-Positive	TNBC	ER-Positive	Reference(s)
15-year incidence in early-stage breast cancer	14.3% (ER-negative), 7.9% (ER-positive)	10.9% (Basal)	2.2% (Lum A), 4.7% (Lum B)	[1]
Incidence in metastatic breast cancer	30%-44%	25%-46%		[2,4-6]
CNS metastases at time of 1st metastatic diagnosis	8%[a]	14%		[2], Olson et al[b]
Time from diagnosis of metastasis to CNS relapse	18 mos; 26 mos (ER-positive) 15 mos (ER-negative)	12 mos	36 mos	[7]
Control of extracranial metastases at time of CNS relapse	≈ 50%	< 20%		[2]
Median OS from time of CNS relapse	11-23 mos	3-5 mos		[2-6,8,9]
Impact of systemic therapy after WBRT	13 mos	4 mos		[8]
Cause of death	≈ 50% due to CNS PD	Rarely due to CNS PD alone		[5]

[a]Patients received trastuzumab (Herceptin) before or at the time of CNS metastases.

[b]Manuscript in preparation.

CNS = central nervous system; ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; lum = luminal; OS = overall survival; PD = progressive disease; TNBC = triple-negative breast cancer; WBRT = whole brain radiotherapy.

this increased to 55% with BCBM by the time of death or last follow-up. The BMFS and median survival from the time of BCBM diagnosis were 1.3 and 1.5 years, respectively (Olson EM et al, manuscript in preparation). The variability in the reported median time to CNS progression following diagnosis of HER2-positive metastatic disease may be explained in part by the variable use of HER2-directed therapy in the different studies. Control of extracranial disease at the time of diagnosis of HER2-positive BCBM is approximately 50%, in contrast to TNBC, in which such control is uncommon.[2] Consequently, the cause of death in patients with triple-negative BCBM is rarely due to progressive CNS disease alone, in contrast to HER2-positive BCBM, a setting in which up to 50% of patients die of progressive CNS disease.[2] Concordant with this observation is the longer median overall survival from time of BCBM diagnosis that is seen in the HER2-positive subtype compared with the TNBC subtype (1 to 2 years vs 3 to 5 months).[2-5,8,9] Finally, in a multi-institutional retrospective analysis of patients with newly diagnosed CNS metastases from various primary sites, including 400 patients with breast cancer, univariate and multivariate analyses of prognostic factors associated with outcomes revealed that performance status and tumor subtype were the primary determinants of outcome in BCBM.[10] In contrast, the number of CNS metastases and presence of extracranial metastases were not among the main determinants. Based on the results of their analysis, the authors put forth a disease-specific graded prognostic index for brain metastases, and subsequently refined it further for patients with BCBM; the median survival in the best-graded BCBM group in this index was approximately 25 months.[11]

The natural course of BCBM is thus strongly influenced by the biology of the primary tumor subtype. In HER2-positive disease, some patients experience extended survival relative to historical estimates due to effective targeted therapies in the extracranial setting; multiple lines of CNS-directed therapies are therefore needed, and there is an urgent need to develop therapies that are effective in the HER2-positive CNS. In contrast, patients with TNBC have relatively poorer outcomes, and both CNS and extracranial disease contribute to the shorter survival; thus, there is a need for better systemic treatments targeting all metastatic sites.

Biology of Breast Cancer Brain Metastases

The biological basis of BCBM is largely unknown. Distant metastases in breast cancer have been postulated as an early event, following which the disseminated tumor cells enter a state of

proliferative dormancy. The period of metastatic latency is defined by the temporal gap between metastatic infiltration and the acquisition of colonization competency in a distant organ—a competency that may result from progressive malignant evolution of the tumor and changes in the tumor microenvironment.[12]

The characterization of the molecular subtypes of breast cancer was a major advance in our understanding of the heterogeneity of breast cancer biology. These studies of breast cancer heterogeneity have so far yielded little insight into the different patterns of development of distant metastases across subtypes. One conceptual model classifies genes that underlie the metastatic process into "metastases initiation genes," which provide transformed cells with the ability to invade and enter the circulatory pathway, and "progression and virulence genes," which determine the ability to infiltrate and colonize distant organs.[12] Differences in the expression of these genes may underlie the different frequencies of and time to BCBM seen in the different breast cancer subtypes.

Recent breakthroughs in efforts to characterize organ-specific mediators of BCBM include results from gene-expression analyses of BCBM patient samples, which identified cyclooxygenase (COX)-2, epidermal growth factor receptor (EGFR) ligands, and ST6GALNAC5 (a sialyltransferase whose expression is normally restricted to the CNS), as mediators of cancer cell passage through the BBB.[13] In contrast to COX-2 and EGFR, which are also linked to other organ metastases, aberrant expression of ST6GALNAC5 specifically mediated BCBM, potentially by providing a means of enhancing its adhesion to the CNS endothelium and its passage through the BBB. In another study comparing 47 brain metastases and 165 primary breast cancer specimens, the authors found that KISS1 protein, a known metastasis suppressor, was downregulated in metastases compared with primary tumors, and was a prognostic marker for increased risk of breast cancer progression.[14] Finally, an understanding is also emerging of the role of the CNS stroma in the metastatic niche: it appears that reactive glial cells are recruited by highly proliferative CNS metastases, promoting metastatic cell colonization in vivo and supporting tumor cell growth in vitro.[15]

A major hurdle in preclinical brain metastasis research has been the development of suitable models that accurately reflect the biology of BCBM in patients. A unique feature of the CNS is the presence of the BBB, a tight layer of endothelial cells and adipocyte foot processes that acts as a selective barrier to both tumor cell infiltration and the diffusion of systemic therapies, in contrast to the more porous fenestrated endothelia found in bone marrow sinusoids and the liver, which are more readily traversed by circulating tumor cells.[12] The BBB is also characterized by drug efflux mechanisms; for example, preclinical studies in mice have identified a synergistic role between P-glycoprotein and breast cancer resistance protein in modulating the CNS penetration of lapatinib (Tykerb), a small molecule tyrosine kinase inhibitor, under steady-state conditions.[16] There are limited data comparing the concentration of antineoplastic agents in the CNS and in tumor tissue, and there is considerable heterogeneity in the methods by which these data were obtained. A recent overview found CNS-to-blood ratios that, in CNS tumors, were lowest for carboplatin and temozolomide (Temodar), intermediate for paclitaxel and lapatinib, and highest for mitoxantrone.[17] Despite these findings, temozolomide is one of the most effective agents for the treatment of primary CNS tumors; therefore, penetration of the BBB is apparently not always necessary for CNS activity, and the therapeutic effect is also dependent on other properties of the drug and the inherent sensitivity of the tumor. While intrathecal drug administration may represent a potential direct passage into the CNS, this has not routinely been done in the setting of solid malignancies due to the need for reformulation and testing, and the concern that only superficial lesions would be exposed to sufficient drug levels.

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Current Treatment Strategies for Breast Cancer Brain Metastases

The National Comprehensive Cancer Network (NCCN) has published guidelines that provide suggested treatment algorithms for patients with CNS metastases from solid tumors.[18] Recently, Kalkanis and colleagues have reformulated consensus guidelines for the management of metastatic brain tumors; standard approaches to symptom management include corticosteroids for the control of peritumoral edema and increased intracranial pressure, and seizure treatment and prevention.[19] While these guidelines represent a significant advance, they are general to all solid tumors, and there are currently none published specifically for the management of BCBM. Most of the cancer therapy recommendations are based on studies in which the majority of patients had non–small-cell lung cancer, and given what we know of the biology of different tumors, it is not clear that these results can be automatically extrapolated to patients with breast cancer.

Local therapies

The management of symptomatic CNS metastases is based on the number, size, and site of lesions, as well as on the status of systemic metastases and patient performance status. The NCCN guidelines for the management of three or fewer CNS lesions (not breast-specific)

include surgery and stereotactic radiosurgery (SRS); these approaches are thought to be particularly appropriate for patients with controlled systemic disease. Surgical resection is generally preferred for surgically accessible single CNS metastases, while SRS is an option for patients with lesions in surgically inaccessible locations and for those who are not surgical candidates. Whole brain radiotherapy (WBRT) is generally recommended when there are more than three lesions; WBRT should also be considered (although it is not mandatory) following surgery or SRS, since it has been shown to improve local control but not overall survival.[20] Recent recommendations of the American Society for Radiation Oncology (ASTRO) suggest that SRS may be considered in selected good-prognosis patients with more than three brain metastases. Most randomized controlled trials in patients with CNS metastases include various primary tumors, resulting in few data specific to breast cancer. Unlike with systemic therapies, there are few current published data on the effect of local therapies on BCBM according to breast cancer subtype.

The subject of SRS vs SRS and WBRT is controversial and is beyond the scope of this review. Multiple randomized trials have demonstrated improved intracranial control when WBRT is given following local therapy (ie, SRS and/or surgery).[21-23] At the same time, in a small study, this combination approach was associated with a greater risk of a significant decline in learning and memory function by 4 months compared with SRS alone.[24] However, patients with BCBM are underrepresented in studies of neurocognitive outcomes following local therapy, and there are few long-term outcome data available because of the associated high mortality rate. Potential neurocognitive toxicities resulting from WBRT are increasingly relevant as subgroups of patients with BCBM are experiencing increased median survivals with improved systemic therapies. Since WBRT has not demonstrated an overall survival benefit in this setting, a discussion of the risks and benefits is appropriate, and patients may choose to forgo routine WBRT.

Systemic chemotherapy

Conventional breast cancer chemotherapies are effective in the first-line setting for BCBM, but most of the studies of conventional chemotherapies are older, and the use of adjuvant chemotherapy was not as common then as it is today.[25] As with local therapies, there are few large BCBM-specific prospective systemic therapy trials; most of the relevant trial data are limited to small breast cancer patient cohorts. These trials involve agents such as cisplatin, temozolomide, epothilone B analogues, and combination therapies; CNS objective response rates of up to 40% have been reported in patients with breast cancer (Table 2). First-line therapies typically have better response rates than therapies in heavily pretreated disease, and there is a need to identify therapies that will work in CNS disease that progresses following local and systemic therapies.

Hormonal therapies have also been demonstrated to be effective in ER-positive BCBM. However ER-positive BCBM is relatively uncommon, and many patients have hormone-refractory disease by the time CNS metastases appear, thereby rendering this class of treatment of limited value.

Possible explanations for the failure of systemic treatment include de novo resistance, acquired resistance to prior systemic therapy and radiotherapy, and an inability to penetrate the BBB, resulting in low CNS drug levels. The in-

Table 2 Prospective Chemotherapy Trials in CNS Metastases

Agent	Breast Cancer Patient Subset (Total in Study)	CNS ORR in Breast Cancer	TTP/PFS	Prior Therapy	Reference
Temozolomide (Temodar)	21 (62) and 19 (19)	0-19%	< 2 mos	Heavily pretreated with systemic therapy	[47,48]
Cisplatin + etoposide	56 (107)	38%	4 mos	No prior CNS RT allowed; 36% chemotherapy-naive	[49]
Cisplatin + temozolomide	15 (32)	40%	2.9 mos		[50]
Capecitabine (Xeloda) + temozolomide	24 (24)	18%	3 mos	> 50% pts received prior CNS RT	[51]
Patupilone	36 (36)	19%	2.8 mos	All pts received prior CNS RT	[52]
Sagopilone	15 (15)	13%	1.4 mos	All pts received prior CNS RT	[53]

CNS = central nervous system; ORR = objective response rate; PFS = progression-free survival; pt = patient; RT = radiotherapy; TTP = time to progression.

trinsic sensitivity of tumor cells to the pharmacologic agent is likely the most important determinant of therapeutic success. Appropriate preclinical efforts are urgently required to address each of these challenges.

HER2-directed therapies

The pattern of disease recurrence in the HER2-positive breast cancer subtype has changed dramatically as a result of the routine use of adjuvant HER2-directed therapy. The use of adjuvant trastuzumab (Herceptin), a recombinant humanized monoclonal antibody directed against the extracellular domain of HER2, has not only been effective in reducing the recurrence rates of HER2-positive breast cancer, but it has also altered the pattern of relapse and survival following the diagnosis of BCBM.[26,27] Interestingly, about half of patients treated with trastuzumab will either be responding to therapy or have stable disease at the time of diagnosis of BCBM; the remainder will die of progressive CNS disease.[5] While trastuzumab is relatively effective in visceral and bony disease, the brain is increasingly recognized as a sanctuary site for tumor cells due to the relative difficulty larger monoclonal antibody therapies have in penetrating the BBB.[5,28] Evidence for this comes from the significantly lower cerebrospinal fluid levels of trastuzumab relative to plasma levels.[6,29] Interestingly, the CSF-to-serum trastuzumab concentration ratio has been shown to be improved in the setting of meningeal disease and WBRT.[6]

Lapatinib is a small molecule tyrosine kinase inhibitor that targets the cytoplasmic ATP-binding sites of the kinase domains of HER2 and EGFR. It is unclear whether lapatinib is able to cross the intact BBB. Unlike trastuzumab, for which the size of the molecule is a major impediment to penetrating the CNS, the mechanism that results in low CNS levels of lapatinib may be at least in part related to the agent's removal from the CNS by P-glycoprotein, a multidrug transporter.[30] The use of lapatinib is currently FDA-approved in combination with capecitabine (Xeloda), based on a pivotal phase III study of 324 patients with metastatic breast cancer who had received prior anthracycline, taxane, and trastuzumab therapy.[31] In this study, there were statistically fewer CNS progression events in patients treated with the combination than in patients who received capecitabine alone, although the number of events in either arm was small (4 vs 13 events).[32] We conducted two prospective phase II studies of single-agent lapatinib in patients with BCBM, the majority of whom had progressed on ≥ 2 lines of trastuzumab combination therapy and CNS radiotherapy, a common clinical scenario for which the optimal treatment strategy is not defined.[33,34] The objective CNS response rate was 2.6% to 6% and the progression-free survival was 2.6 to 3 months. We subsequently compared lapatinib in combination with capecitabine or topotecan in patients with CNS progression following standard CNS radiotherapy in a phase II trial. The study was closed early due to excess toxicity and lack of efficacy in the lapatinib plus topotecan arm. However, there were promising indications of CNS activity with lapatinib plus capecitabine, with an objective CNS response rate of 38%.[35] This combination has also been studied in a number of other trials (Table 3), none of which included a capecitabine-alone control arm in light of results from the pivotal metastatic breast cancer study.[31] The response criteria differed across trials, and included tumor volume reduction, improvement in neurologic symptoms and signs, reduced corticosteroid usage, and (in some) lack of non-CNS progression. CNS objective response rates with the lapatinib plus capecitabine combination were 18% to 38% in patients who had received prior trastuzumab combination therapies, and up to 67% in a trial in which the majority of patients received this combination as their first metastatic HER2-directed therapy and prior to WBRT.[34-39] In the latter trial, the median time to progression was 5.5 months, and the 1-year overall survival exceeded 70%, supporting the option of delaying WBRT and instead initiating a trial of systemic therapy.[36] Finally, novel HER2-directed therapies currently being studied in phase II trials in HER2-positive BCBM include neratinib and afatinib (ClinicalTrials.gov identifiers: NCT01494662 and NCT01441596, respectively).

Novel systemic and combination therapies

In designing therapies specific for BCBM, the ideal would be one that adequately penetrates the BBB, and targets markers that are specifically expressed by the CNS tumor cells. Novel therapies in development for brain metastases include GRN1005, a peptide (angiopep-2)-taxane conjugate that specifically targets lipoprotein receptor–related protein 1, which is upregulated on various tumor cells and highly expressed on the surface of the BBB, resulting in a CNS uptake that is significantly higher than that seen with other conventional systemic therapies. Phase I results of this compound in a heavily pretreated population with solid tumors and brain metastases revealed an overall partial response and a CNS objective response rate of 25% at the maximum tolerated dose (650 mg/m^2); also, 11% of patients who received treatment at 30 to 700 mg/m^2 experienced stable disease of ≥ 4 months.[40] A phase II trial with GRN1005 in BCBM is underway, in combination with trastuzumab (for patients with HER2-positive BCBM) or alone (for patients with HER2-negative BCBM) (ClinicalTrials.gov identifier: NCT01480583). Another drug designed to penetrate the BBB is 2B3-101, a glutathione-pegylated liposomal

Table 3 Studies of Lapatinib (Tykerb) and Capecitabine (Xeloda) for HER2-Positive BCBM

Study	N	Prior Chemo	Prior RT	Response Criteria	CNS ORR	TTP/PFS	OS
Lin et al, 2009[34]	50	81% with ≥ 2 T + chemo; PD on lapatinib monotherapy	100%	50% tumor vol reduction, NSS, steroid use, lack of non-CNS progression	20%	3.5 mos	NR
Boccardo et al, 2008[37]	138	Prior T required	NR	Investigator-assessed	18%	NR	NR
Sutherland et al, 2010[38]	34	82% with ≥ 2 chemo for MBC; prior T required	94%	RECIST criteria	21%	5.1 mos	NR
Metro et al, 2011[39]	22	Median of 2 prior T-based therapies for MBC	86%	WHO criteria	32%	5.1 mos	27.9 mos
Lin et al, 2011[35]	13	Prior T required	100%	50% tumor vol reduction, NSS, steroid use, lack of non-CNS progression	38%	NR	NR
Bachelot et al, 2011[22]	45	22% with ≥ 2 T + chemo (31% did not have prior T for MBC)	0%	50% tumor vol reduction, NSS, steroid use, lack of non-CNS progression	67%	5.5 mos	91% at 6 mos

BCBM = breast cancer brain metastases; CNS = central nervous system; MBC = metastatic breast cancer; NR = not reported; NSS = neurological symptoms and signs; ORR = objective response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; RECIST = response evaluation criteria in solid tumors; RT = radiotherapy; T = trastuzumab (Herceptin); TTP = time to progression; vol = volume; WHO = World Health Organization.

doxorubicin; a phase I study of 2B3-101 is currently enrolling patients with solid tumors with brain metastases and malignant gliomas (ClinicalTrials.gov identifier: NCT01386580). Lastly, TPI-287, a third-generation taxane designed to avoid the multidrug resistance (MDR)-1 protein drug efflux mechanism, has shown promising activity in taxane-resistant preclinical models[41]; TPI-287 is currently being evaluated in a phase II trial of patients with BCBM (ClinicalTrials.gov identifier: NCT01332630).

Bevacizumab (Avastin) is a monoclonal antibody that targets vascular endothelial growth factor (VEGF) and that is effective in treating glioblastoma multiforme (GBM). While there was initial concern about the risk of cerebral hemorrhage when treating GBM with bevacizumab, there are emerging data in the setting of CNS metastases from solid tumors that demonstrate the safety of this agent.[42] Also, while there is still controversy regarding the role of bevacizumab in metastatic breast cancer, clinical trials in BCBM are ongoing. We are currently conducting a phase II trial of carboplatin and bevacizumab with the primary end point of CNS objective response rates in patients with progressive BCBM (ClinicalTrials.gov identifier: NCT01004172).

Other therapies for BCBM are developing in parallel with therapies for breast cancer, and involve a number of novel pathways (Table 4). These include the oncogenic PI3K pathway; activating mutations of *PIK3CA* and/or *PTEN* loss are commonly found in breast cancer, and have been shown to be active in BCBM.[43] In particular, *PIK3CA* mutations are found in about one-third of HER2-positive breast cancers and *PTEN* loss in up to half of TNBC.[44] A phase II single-arm study of everolimus (Afinitor), trastuzumab, and vinorelbine is currently enrolling patients with HER2-positive BCBM, with CNS objective response rates as the primary end point (ClinicalTrials.gov identifier: NCT01305941). Preclinical studies of BKM120, a PI3K inhibitor, demonstrate BBB penetration and efficacy in the treatment of BCBM in mouse models (Zhao J, personal communication). With respect to TNBC, a number of poly (ADP ribose) polymerase (PARP) inhibitors are in various stages of clinical development, and patients carrying *BRCA* mutations have been shown to be particularly sensitive to treatment with agents in this class. It has been observed that there is a high incidence of BCBM in patients carrying *BRCA* mutations,[45] and PARP inhibitors currently being assessed in BCBM include ABT-888 (veliparib) in combination with WBRT (ClinicalTrials.gov identifier: NCT00649207). Iniparib, once thought to be a PARP in-

Table 4 Current Breast-Specific Trials of Novel Agents and Combinations in CNS Metastases

Agent	Class of Boldfaced Novel Agent	Subtype	Lead Site	ClinicalTrials.gov Identifier
2B3-101	Glutathione-pegylated liposomal doxorubicin	Solid tumors and malignant glioma	to-BBB	NCT01386580
GRN1005	Taxane-peptide conjugate	HER2-positive (plus trastuzumab [Herceptin]) and HER2-negative	Geron Corporation and Dana-Farber Cancer Institute	NCT01480583
TPI-287	Taxane	All subtypes	MD Anderson	NCT01332630
Neratinib	HER2-directed	HER2-positive	TBCRC and Dana-Farber Cancer Institute	NCT01494662
Afatinib	HER2-directed	HER2-positive	Boehringer Ingelheim	NCT01441596
Bevacizumab (Avastin) + carboplatin	VEGF inhibitor	HER2-positive (plus trastuzumab) and HER2-negative	Dana-Farber Cancer Institute	NCT01004172
Bevacizumab + cisplatin + etoposide	VEGF inhibitor	All subtypes	National Taiwan University	NCT01281696
Bevacizumab + WBRT	VEGF inhibitor	Solid tumors	Centre François Baclesse	NCT01332929
Everolimus (Afinitor) + trastuzumab + vinorelbine	mTOR inhibitor	HER2-positive	University of North Carolina	NCT01305941
ABT-888 (veliparib) + WBRT	PARP inhibitor	Solid tumors	Abbott	NCT00649207
Iniparib + irinotecan	Not defined	TNBC	Sanofi-Aventis and University of North Carolina	NCT01173497

CNS = central nervous system; HER2 = human epidermal growth factor receptor 2; mTOR = mammalian target of rapamycin; PARP = poly (ADP-ribose) polymerase; TBCRC = Translational Breast Cancer Research Consortium; TNBC = triple-negative breast cancer; VEGF = vascular endothelial growth factor; WBRT = whole brain radiotherapy.

hibitor, but whose exact mechanism of cytotoxicity is unclear, is being evaluated in a phase II trial in combination with irinotecan (Camptosar) in patients with triple-negative BCBM (ClinicalTrials.gov identifier: NCT01173497). Finally, systemic therapies have also been evaluated as radiosensitizers in combination with WBRT; however, the results of most of these trials have largely been negative. In addition to ABT-888, novel therapies currently being evaluated with WBRT include lapatinib and bevacizumab (ClinicalTrials.gov identifiers: NCT00470847 and NCT01332929, respectively).

Conclusions

CNS metastases are common in patients with the HER2-positive and TNBC breast cancer subtypes, and the natural course of BCBM is strongly influenced by the biology of the primary tumor subtype. The intrinsic sensitivity of tumor cells to various therapies is likely a key determinant of treatment outcomes. Although the biology of BCBM according to tumor subtypes is still poorly understood, recent breakthroughs have been achieved in the identification of specific mediators of CNS metastases and in the development of preclinical models for therapeutic studies. Clinical outcomes are improving for patients with BCBM as a result of modern combinatorial therapies, challenging the traditionally nihilistic approach to this subgroup of patients. Systemic therapies can be effective in BCBM; in particular, effective

HER2-directed combination therapies result in prolonged survival in HER2-positive BCBM. However, new treatments are required that effectively target BCBM and systemic metastases in general, particularly in the TNBC subtype. In light of this, reconsideration of the standard eligibility criteria for early-phase trials is needed, since patients with BCBM are routinely excluded on the basis of their historically poor and limited prognosis and the concern that CNS symptoms may complicate the assessment of toxicity.[46]

Because of the exclusion of BCBM patients from more general trials, there has been increasing interest in evaluating novel therapies, both alone and in combination, in BCBM-specific trials. After years of small studies of older chemotherapeutic agents applied unselectively across multiple primary tumor types, we have finally reached an era in which there is demonstrated proof-of-concept that novel targeted agents can produce deep and prolonged responses in some patients with BCBM. While these studies have yet to lead to registration or approval for a BCBM indication, the groundwork is finally being laid for potentially making this a reality in the near future. ❍

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THE LIM/LIN ARTICLE REVIEWED: SHAHEENAH DAWOOD, MASSIMO CRISTOFANILLI

Brain Metastasis in Breast Cancer: Last Barrier to the Cure?

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MASSIMO CRISTOFANILLI, MD[2]

The last two decades have seen the development of a variety of novel therapeutic agents that have improved prognoses for women with breast cancer. Certainly for women with human epidermal growth factor receptor 2 (HER2)-positive breast cancer, the introduction of trastuzumab (Herceptin) has altered the natural history of the disease, turning a once aggressive cancer into one with a favorable prognosis.[1] Moreover, our understanding of the biology of breast cancer has also grown; we have realized that it is not a homogeneous disease but rather a heterogeneous one composed of a number of subtypes, each with its own unique natural history and survival outcomes.[2] Despite such advances, however, a diagnosis of brain metastases in a woman with breast cancer still connotes a debilitating and incurable condition. This review by Elgene Lim and Nancy U. Lin is timely and takes us on a biological tour of brain metastases in women with breast cancer; against this backdrop, it comprehensively summarizes all the data currently available on the development of—and survival following—some of the newer management approaches evaluated in patients with brain metastases. Several important questions are alluded to in the review that deserve more attention, however.

Current management strategies for brain metastases do not drastically alter associated outcomes. The question, then, is whether there is a role for the prevention of brain metastases. Lim and Lin correctly point out that the subtype of the primary breast tumor influences the natural development of brain metastases. Data indicate that the highest incidences of brain metastases occur in women with HER2-positive and triple receptor-negative breast cancer (TNBC). In a recent publication, Dawood et al[3] noted an 8% 2-year cumulative incidence of brain metastases in women with stage III TNBC. However, most women with TNBC who have brain metastases succumb as a result of progression of disease in both the CNS and concomitant distant sites, which is in contrast to women with HER2-positive disease who have brain metastases, more than half of whom die as a result of progression of disease in the CNS.[4]

From the epidemiologic data that have been published and from what is known of the course of each breast cancer subtype, it appears that prevention of brain metastases would be an option to explore among women with HER2-positive breast cancer. The next logical question would be whether all women with HER2-positive breast cancer would benefit from brain metastases–prevention strategies. Not all women with HER2-positive breast cancer develop brain metastases, and it would be necessary to accurately identify the women who are at high risk of developing this complication. At ASCO 2012, Duchnowska et al[5] presented interesting results of a study that attempted to address these issues. The investigators developed a 13-gene signature that strongly predicted for the rapid development of brain metastases among women with advanced HER2-positive breast cancer. They reported a median brain metastases–free survival of 54 months vs 86 months ($P = .032$) among tumors that had high and low expressions of the 13-gene signature, respectively. If we were to accurately identify groups of women with HER2-positive disease who would eventually develop brain metastases, what strategy for prevention would be ideal? The long-term neurocognitive side effects typically associated with whole brain radiation therapy (WBRT) have resulted in this treatment modality being reserved for established brain metastases. A tyrosine kinase inhibitor such as lapatinib (Tykerb), which is able to cross the blood-brain barrier, would be an interesting preventive agent, but lapatinib is also associated with side effects, and the length of time required for preventive treatment might be an issue. Indeed, in a recent study, Bachelot et al[6] demonstrated activity of the lapatinib and capecitabine combination in women with HER2-positive breast cancer and brain metastases before treatment with WBRT. The authors were able to demonstrate an overall CNS response rate of 67%. Results of prospective clinical trials incorporating lapatinib—such as the ALTTO (Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation) study, which includes the incidence of CNS metastases as a secondary end point—should be able to better define the role of this agent in the prevention setting.

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Lim and Lin discuss at length management strategies for women with brain metastases and the advances seen over time in this area. However, the fact remains that the options available to oncologists treating women with brain metastases are limited; these limited options are further complicated by issues of how to incorporate CNS-targeted treatments and management of other systemic metastases while at the same time maintaining an adequate quality of life. In women with TNBC, radiation therapy and surgery remain standard of care. Several agents are being explored in prospective studies for women with HER2-negative breast cancer, including poly (ADP-ribose) polymerase (PARP) inhibitors and, interestingly, bevacizumab (Avastin). Bevacizumab, a monoclonal antibody targeting vascular endothelial growth factor, has been shown to have modest activity in metastatic breast cancer; nonetheless, the US Food and Drug Administration (FDA) recently withdrew its approval of bevacizumab in this setting due to lack of demonstration of an overall survival benefit. However, given the agent's known activity in gliobastoma multiforme, it will be interesting to prospectively evaluate its activity in brain metastases from breast cancer.

In conclusion, we certainly have witnessed significant improvements in the management of breast cancer. We have moved from an era in which the development of brain metastases signified the end of the natural course of an aggressive disease and moved into one in which the development of brain metastases signifies that women are living long enough for these to develop. The incidence of brain metastases is actually rising, signifying a need for better screening, prevention, and therapeutic strategies. If we truly believe that the subtype of the primary breast tumor drives the incidence and the natural history of brain metastases, then our knowledge of the biology of the various tumor subtypes should guide research aimed at identifying therapeutic targets for each subtype of disease in both the prevention and therapeutic settings.

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THE LIM/LIN ARTICLE REVIEWED: MARK D. PEGRAM

Tumor Biology Trumps Anatomy in Breast Cancer Brain Metastases

MARK D. PEGRAM, MD[1,2]

In this issue of ONCOLOGY, Drs. Lim and Lin present a comprehensive and up-to-date review of the basic biology of breast cancer brain metastasis (BCBM) and of emerging strategies for treating this increasingly common complication of advanced breast cancer (BC) (BC is second only to non–small-cell lung cancer in the frequency of central nervous system [CNS] metastasis.) It is clear that as the efficacy of treatments for extracranial metastatic BC have improved over time, CNS metastases have increasingly been exposed as a vulnerability, with the CNS indeed a sanctuary site; they necessitate directed (often multidisciplinary) therapeutic approaches requiring special expertise (ideally via an experienced interdisciplinary team).

The authors rightly argue that there is compelling evidence that a strong biological basis drives risk for BCBM. This hypothesis is supported by the clinical ob-

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servation that BCBM risk is highest in patients with human epidermal growth factor receptor 2 (HER2)-positive disease and those who lack expression of steroid receptors and HER2 (ie, triple-negative breast cancer [TNBC]). Remarkably, in their own series dating to the beginning of the trastuzumab (Herceptin) era, the authors report that over half of their HER2-positive patients with advanced BC have developed BCBM. That there is a biological basis for risk of BCBM is underscored by the fact that even within the intrinsic subtype of HER2-positive disease, the latency for onset of CNS metastasis is significantly prolonged in patients with estrogen receptor (ER) coexpression. And since TNBC is an impure classification consisting of more than one intrinsic BC subtype (although dominated by the basal subtype), as well as *BRCA*-mutant genotypes, it may theoretically be possible, as more precise and standardized methods become available for routine assessment of intrinsic BC phenotypes, to discriminate levels of risk for BCBM even among patients with TNBC.[1] Moreover, it will be critical to validate particular gene expression signatures that have been linked to BCBM in pilot studies (largely preclinical) in order to identify potential markers for risk that could be clinically useful, and to identify potential targets for new molecularly targeted therapeutics aimed at BCBM.[2]

Importantly, the authors point out the significance of the CNS microenvironment, which consists of a unique vascular endothelium (the so-called blood-brain barrier), pericytes, astrocytes, and glial cells, all of which may contribute in concert to pathogenesis of the CNS metastatic niche. If pathogenic factors within this niche can be identified (such as chemotactic factors, adhesion and transendothelial tumor cell extravasation factors, and peptide growth factors), these might offer unique opportunities for exploiting novel treatment approaches, or perhaps more importantly, opportunities for prophylaxis against BCBM altogether.

It is interesting to note that, despite advances in our understanding of the biological factors associated with risk for BCBM, the authors stop short of recommending routine screening for occult BCBM in asymptomatic patients. This will remain a contentious issue until more data are available to determine whether early intervention with available treatment modalities (largely centered on neurosurgical resection and/or radiotherapy) ultimately has an impact on overall survival, and perhaps more importantly, on quality-of-life–adjusted survival. Screening recommendations for detection of occult CNS metastasis could also change as more effective targeted therapeutic approaches emerge. Support for this notion is suggested by the authors based on their own work in the area of HER2-targeted therapy with lapatinib (Tykerb) for BCBM. However, despite the theoretical advantages of a small molecule tyrosine kinase inhibitor (TKI) in achieving greater CNS penetration (compared with macromolecular therapeutics such as monoclonal antibodies), the results of treatment of relapsed CNS metastasis with single-agent lapatinib are frankly very modest. And even lapatinib in combination with capecitabine (Xeloda) yields objective responses in well less than half of treated subjects. Still, updated results from the pivotal randomized registrational trial of lapatinib suggest that lapatinib may prevent (or at least delay) onset of BCBM in patients with HER2-positive metastatic disease,[3] such that perhaps an "adjuvant" HER2-TKI immediately following primary neurosurgery and/or radiotherapy for newly diagnosed BCBM might be a more compelling treatment strategy than waiting for measurable relapse to occur following primary local therapy for HER2-positive CNS metastasis. An important trial that will investigate the potential of lapatinib to help prevent CNS relapse in early-stage HER2-positive BC is the ongoing ALTTO (Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation) trial, which is comparing adjuvant trastuzumab to trastuzumab plus lapatinib (in combination or in sequence), and which will attempt to capture CNS relapse event data as a secondary endpoint. The non-trastuzumab arm of this trial was recently terminated due to futility in demonstrating noninferiority of an adjuvant lapatinib HER2-targeting strategy as a substitute for standard trastuzumab-based adjuvant therapy. As highlighted by the authors, for HER2-positive patients who are unfortunate enough to experience BCBM, participation in ongoing clinical trials of HER2-targeting agents aimed at BCBM is strongly encouraged.

In terms of novel systemic and combination therapies for BCBM, the authors are to be commended for their thorough and up-to-date presentation of the current inventory of ongoing clinical trials in this area. There is a new sense of optimism in this field as a result of the new agents under active investigation; these include agents such as GRN1005, designed to exploit a fundamental understanding of basic biological mechanisms of active transport into the CNS, and new agents

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like TPI-287, designed deliberately to avoid drug efflux via MDR (multi-drug resistance) transporter(s). Moreover, the novel targeted agents listed in Table 4, including PIK3CA inhibitors, mammalian target of rapamycin (mTOR) inhibitors, poly (ADP ribose) polymerase (PARP) inhibitors, and vascular endothelial growth factor (VEGF)-targeting agents, hold great promise, especially in cases where some of these dysregulated signaling pathways are thought to be playing a role in pathogenesis of BCBM.

Finally, with the proposition advanced in this review that tumor biology trumps anatomy, and that the era of therapeutic nihilism in management of BCBM has now ended. This notion is supported by the fact that a surprisingly high percentage of patients with BCBM actually succumb to extracranial metastatic disease, indicating that clinicians must not ignore systemic disease control in patients with treated BCBM. In particular, for BC patients with a long natural history and demonstration of controlled CNS metastasis, there is no reason that, in the absence of other comorbidities or decline in performance status, they should be excluded from participation in phase I clinical trials. A corollary to this theorem is that current published treatment guidelines for CNS metastasis are not BC-specific—and they certainly do not capture, much less embrace, the nuance of intrinsic biological BC subtypes. Therefore, these guidelines are of limited value to, and no substitute for, a thoughtful and experienced clinician supported by appropriate multidisciplinary expertise. The authors conclude that only through BCBM-specific and dedicated clinical/translational research will important advances be made that exploit new insights into tumor biology of BCBM.

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gen receptor–positive breast cancer in the upper outer quadrant of the patient's left breast without evidence of metastases and that it has been completely excised will be getting coding queries up to ying yang. Where physician financial productivity is tied to high volume and poor documentation, through-put will have to take second seat.

And when all is said and done, it is not a given that ICD-10 will make good on its promises. ICD-10 is heavy into anatomy and light on histology. It is much more interested in knowing what lobe a metastatic lung cancer began in than in descriptors such as cancer cell type, stage, and histologic grade, which are far more important in determining what drug to use. The improvements in ICD-10 do more for primary care, ambulatory care, mental health, and preventive medicine encounters than they do for specific disease states such as cancer. Time will tell, but ICD-10 may prove to be little more than a very expensive stop gap to an ICD-11.

Taking Ownership and Getting Prepared

Short of burning tires in the streets (and maybe even then), ICD-10 seems bound to happen, and whether you herald it as a dramatic improvement or the lesser of two evils, putting off preparation would be a mistake; better to take ownership of the problem and command of the situation.

The first step in preparation is to take an appraisal of where you are at now, and that means not only your practice but outside entities such as your EHR and other software vendors, claims clearinghouses, outsourced billing services, and payers. If they aren't ready, you aren't either.

In the process of this stock-taking, you will identify diagnosis coding tools, superbills, public health reporting tools, compliance plans, and documentation templates, to name a few, that will need to be updated and translated from ICD-9 to the new Greek of ICD-10. It is important to recognize that this project is much more than a billing issue—you must be sure to identify *all* those who will need training in ICD-10 and what that training will entail. Once the size of the task is understood, a budget and timeline can be established and oversight assigned to practice management. A physician champion, if you can roust one, will prove invaluable.

Staff training will be an arduous task, but the rewards of a job well done will be self-evident. When Canada converted to ICD-10, it reported a 55% reduction in productivity that took 6 months of on-the-job training to reverse. [6] It may well be that the most critical and resistant group to train will be physicians who are reluctant to tighten up their notes. The goal is not to turn doctors into coders, as they should focus on being good clinicians; however, good documentation is good clinical practice.

These steps should all be accomplished well before the deadline for compliance to allow time to conduct in-depth

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