Multidisciplinary Management of Brain Metastasis from Breast Cancer

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KEYWORDS

• Breast cancer • Brain metastases • Multidisciplinary care • Multimodal treatments

KEY POINTS

- The treatment approach to brain metastases (BM) in breast cancer is multidisciplinary.
- In patients with a single to limited BM, surgery and/or SRS are preferred; whereas, for patients with more extensive intracranial involvement, WBRT, with hippocampal-sparing approaches and use of memantine can be more strongly considered.
- In clinical practice, the threshold to consider WBRT varies according to clinical factors.
- The role of systemic therapy is rapidly evolving, particularly in patients with HER2-positive breast cancer.

INTRODUCTION

Breast cancer (BC) is the most commonly diagnosed malignancy and represents a major cause of death in women worldwide.[1] The metastatic pattern of spread is a major determinant of outcome,[2] and the presence of central nervous system (CNS) metastasis has historically been associated with worse outcomes.[3] Patterns of spread to the CNS can be recapitulated by three clinically relevant types: parenchymal brain recurrence, leptomeningeal disease (LMD), and epidural spinal cord compression.[4]

Central nervous system recurrence risk across subtypes. Higher incidence of brain metastases (BMs) is reported with human epidermal growth factor receptor 2 (HER2)-positive and triple-negative BC (TNBC), with rates of brain-first recurrence of 3.3% to 7%.[5] Inflammatory BC has a particularly elevated risk of BMs.[6] Patients with germline *BRCA1* pathogenetic mutations have a higher risk of brain-first recurrence.[7] Once patients develop metastatic disease, up to 25% of patients can experience BMs, with widely varying risks depending on tumor subtype (~50% in

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Hematol Oncol Clin N Am 37 (2023) 183–202
https://doi.org/10.1016/j.hoc.2022.08.017
hemonc.theclinics.com

HER2-positive, 25%–45% in TNBC, 10%–15% in hormone receptor-positive)[1,3] (Fig. 1). Differences in overall survival (OS) are heavily driven by performance status (PS) and tumor subtype.[8,9] In the modern era, and with access to multimodality therapy, younger patients with good PS and HER2-positive subtype may experience

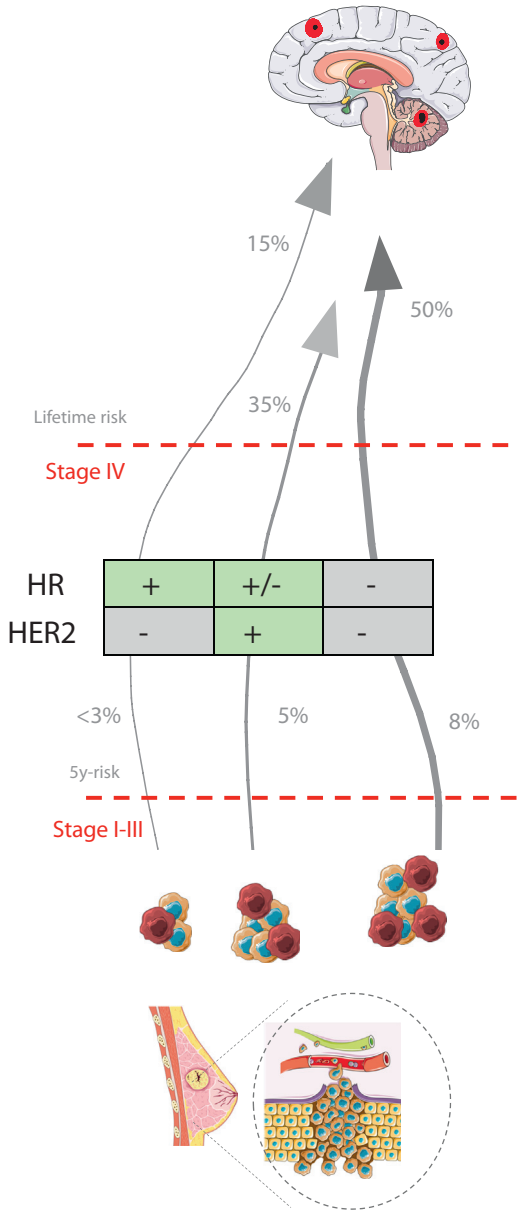

Fig. 1. Incidence of brain metastatic recurrence or progression in patients with localized or metastatic breast cancer across clinical subtypes. HER2, human epidermal growth factor receptor 2; HR, hormone receptor. (Ref: Brosnan EM, Ann Transl Med 2018 Ref: Arvold ND, Breast Cancer Res Treat 2012.)

median survival ~3 years after a BM diagnosis, whereas patients with poor PS and triple-negative subtype experience median survival of 6 months or less.

Non-parenchymal patterns of central nervous system spread. LMD is a prognostically adverse clinical event, occurring in no more than 5% of all patients with advanced BC.[10] LMD is associated with treatment resistance and rapid fatal progression; lobular histology and TNBC have the highest risk of LMD. Median OS after a diagnosis can be as poor as 6 months or less. Meningeal involvement can also occur by cancer growth in the epidural space (10% of the cases); spine compression is a catastrophic clinical event, with a substantial risk of permanent neurologic impairments.[11,12]

BLOOD–BRAIN BARRIER, BRAIN MICROENVIRONMENT, AND BLOOD TUMOR BARRIER

CNS seeding can only occur when BC cells overcome the blood–brain barrier (BBB), designed to protect the brain parenchyma from exogenous noxa.[13] Studies of primary versus BMs suggest that subtype-specific alterations can affect CNS-tropism.[14–16]

The interplay between BC and immune-competent cells results in key changes in the BBB, making it a more permissive microenvironment for secondary cancer cell growth. The milieu of BMs is immune-suppressive.[14,17] The BBB functions as a primary protective structure against external agents, but can wrap BMs in a "sanctuary" environment, by excluding many systemic cytotoxic agents.[18] The BBB appears greatly deranged in BMs, leading to the concept of blood-tumor barrier, to better capture its heterogeneous nature.[19,20] Indeed, many agents unable to cross the intact BBB (eg, antibody-drug conjugates) have clear intracranial efficacy.

DIAGNOSIS

In clinical practice, current guidelines do not recommend screening asymptomatic patients with imaging for BMs. Imaging is prompted by neurologic symptoms.[21] It is unclear if earlier identification of BMs with surveillance imaging results in better health outcomes, and retrospective studies have not shown the improvement of OS.[22] However, retrospective comparisons of the presentation and treatment patterns of patients with BC (generally not screened with brain MRI) versus lung cancer (screened routinely with brain MRI) have suggested higher intracranial burden at presentation and more frequent use of whole-brain radiation therapy (WBRT) in patients with BC.[22] Ongoing prospective studies are testing the value of surveillance brain MRI screening on patient-centric endpoints such as neurocognitive functioning, neurologic symptoms, avoidance of WBRT, and quality of life.

THERAPEUTIC OPTIONS

The treatment of BMs is complex. Local treatments are commonly associated with high efficacy with respect to immediate disease control, whereas systemic treatments aim to provide continuous disease control of the overall burden of disease. The number, size, and location of BMs, prior treatment history, BM velocity,[23] tumor subtype, predicted efficacy and adverse effects, possible treatment options, PS and comorbidities, extracranial disease status, and patient preference must be considered at each CNS progression event (**Fig. 2**). Integration of local and systemic therapies is critical in this setting, having been demonstrated to improve health outcomes[24]: multidisciplinary clinics (MDC) pursue more personalized, consistent and up-to-date decisions.[24,25] An essential component of MDC is supportive and palliative care, including social and psychological care, to maximize patient-centered outcomes.

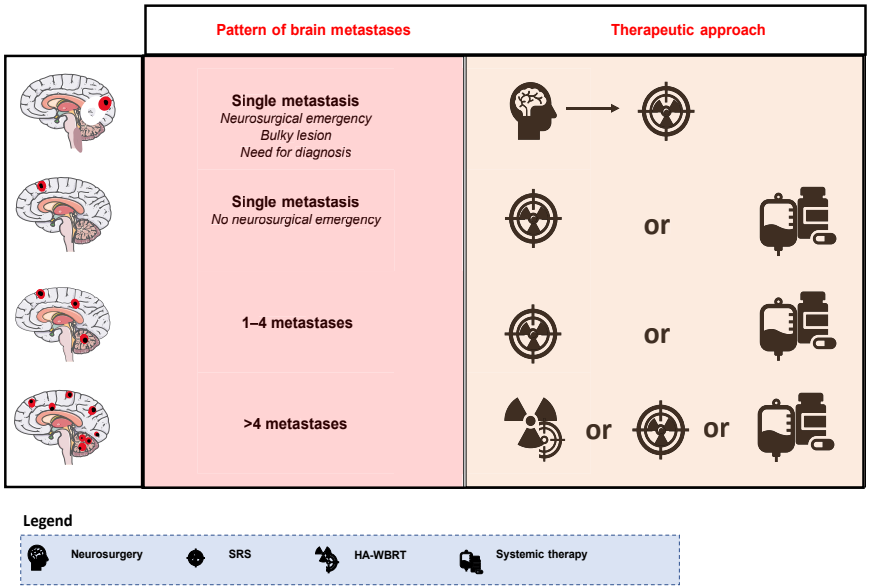

Fig. 2. Treatment approaches for patients with breast cancer and brain metastases. The standard approach for patients with one to four brain metastases is based on SRS, in the absence of neurosurgical emergency. Patients with more than four metastases are commonly managed with HA-WBRT, but SRS can be considered in specific clinical scenarios, for example, in the context of longer life expectancy. In some patients, systemic treatment can be an option in lieu of radiotherapy, such as in the case of CNS disease progression with availability of CNS-active drugs. For an expanded discussion of the potential clinical scenarios, refer to the text. CNS, central nervous system; HA-WBRT, hippocampal-avoiding whole-brain radiation therapy; SRS, stereotactic radiation therapy.

Local Treatments

Patients with a single brain metastasis

Surgery. The benefit of surgical resection to establish a pathologic diagnosis and extend OS in patients with a single BM has been established in randomized clinical trials, in combination with radiation therapy (RT). A clinical trial randomizing patients with a single BM to surgery plus WBRT or WBRT alone (36 Gy; years: 1985–1988; 6% of patients had BC) showed a reduced risk of recurrence in the original metastatic site (20% vs 52%), longer survival (9.2 vs 3.5 months), and longer time to PS detriment (8.7 vs 1.8 months).[26] A European trial compared WBRT (40 Gy) plus surgery versus WBRT,[27] showing a gain of 3.7 months in the median OS, albeit restricted to patients with no extra-CNS active disease. Subset analysis of surgery versus no surgery trials in patients with a single BM suggests that the benefit of surgery may be most significant in patients with controlled extracranial disease and a good PS.[26–28]

Surgery and stereotactic radiotherapy. The NCCTG-N107 C trial randomized patients with a single resected BM (cavity up to 5 cm) to receive WBRT (30–37.5 Gy in 10–15 fractions) or stereotactic radiosurgery (SRS) (12–20 Gy single fraction) in 2011 to 2015.[29] The trial reported no significant difference in OS (median: 12.2 and 11.6 months) and better preservation of the cognitive function at 6 months (52% and 85%) with SRS. Of note, the 1-year cavity recurrence rate was approximately

40% versus 20% in patients managed with SRS versus WBRT, respectively, which underscores the need for optimization of stereotactic technique and approach.

Extent of the surgical resection. Complete resection of BMs is largely seen as a gold standard, portending survival benefits.[30,31] With the consolidation of the adjuvant radiotherapy practice, it has been questioned whether complete surgical resection is still prognostic for BMs.[32–34] A retrospective series from South Korea reported that data on 157 patients with BMs eligible for surgical resection[35] showed a survival benefit for patients receiving gross total versus subtotal resection (+5.3 months of OS).[35] A gross resection is commonly achievable in up to 80% of the cases.[34] However, the addition of RT seems to equalize such a risk in case of subtotal resections, as suggested by a recent study showing a rate of progression at the surgical site of 23.4%, unaffected by the extent of the surgical resection.[34] Still, complete resection may facilitate lower adjuvant radiation doses to be used. The debate is relevant for treatment decision in patients with BMs in eloquent brain areas.

Clinical recommendation. Based on the more favorable survival and functional outcomes, surgery plus SRS to the surgical bed is considered the current standard of care for patients with a single, resectable BM.

Options for Patients with Multiple Brain Metastases at Initial Presentation and Beyond

Surgery

The role of surgery in patients with multiple BMs is limited to the relief of symptoms and management of life-threatening complications. Most nonsurgical approaches cannot reliably and quickly achieve symptom relief in such patients. Surgery may also have a role for bulky tumors (eg, >3–4 cm), even in asymptomatic patients, given the lower success and increased toxicity of stereotactic radiation in such scenarios. The priority in multisite brain disseminated disease is to provide broad disease control, not commonly achievable with surgery. Surgery may also be considered in symptomatic radiation necrosis despite maximizing conservative treatments. Last, in cases of diagnostic uncertainty in which observation is not a viable strategy, the value of surgery for diagnostic purposes can be significant.

Whole-brain radiation therapy and hippocampal-sparing whole-brain radiation therapy

Since the 1970s, the gold standard for patients with multiple BMs has been WBRT.[36] Clinical studies showed the relief of CNS symptoms in up to 80% of patients.[37,38] WBRT for multiple BMs should be carefully considered in patients with very limited estimated life expectancy driven by extracranial disease, as a clear benefit has not been demonstrated, and best supportive care may be more appropriate, as supported by the QUARTZ study in patients with lung cancer.[39] Also, WBRT can affect brain areas delegated to higher cortical functions, resulting in accelerated cognitive detriment. More modern WBRT approaches such as hippocampal-sparing (HS), and the addition of nootropic drugs such as memantine, have been shown to improve neurocognitive outcomes. The NRG-CC001 study of WBRT and memantine, with or without HS, demonstrated improved cognitive function posttreatment, with less deterioration in executive function, learning, and memory.[40] Of note, NRG-CC001 excluded patients with metastases in or near (within 5 mm) the hippocampi as well as LMD. Memantine per se reduces the risk of cognitive function decline at 6 months (53.8% vs 64.9%) based on a randomized study showing a strong trend to improvement ($P = .06$) relative to placebo.[41]

Stereotactic radiosurgery

SRS can be an option in the context of multiple BMs. A Japanese multicenter prospective randomized trial tested WBRT plus SRS versus SRS in patients with ≤4 BMs (diameter < 3 cm) in 1999 to 2003.[42] The study reported a comparable OS of 7.5 to 8 months, but a higher risk of brain recurrence within 12 months with SRS (46.8% vs 76.4%). Of note, at 3 years, 85.3% of patients treated with WBRT experienced neurocognitive deficits (vs 48.1%).[43] The improved neurocognitive safety of SRS was confirmed in the phase III N0574 trial,[44] conducted in 34 institutions in North America in 2002 to 2013 for patients with 1 to 3 BMs. The study reported significantly less neurocognitive deterioration at 3 months with SRS (63.5%) versus SRS plus WBRT (91.7%) ($P < .001$). Disease control outcomes favored WBRT, having fewer intracranial recurrences (hazard ratio [HR] = 3.6; 2.2–5.9), but without OS difference (HR = 1.02, $P = .92$). For patients with greater than 4 BMs, there is no high-quality published evidence of non-inferiority of SRS versus WBRT, although randomized trials are ongoing, and the assumptions are mostly based on small studies.[45–47]

Systemic Treatments

For patients with active (ie, new and/or progressive) BMs, systemic treatments may be weighed in the context of local therapy options, and in some cases, selected in lieu of local therapies for CNS disease control. Systemic treatments such as tucatinib and neratinib can reasonably be expected to exert activity on progressing BMs. Treatment choice in patients with stable BMs is dictated by the need to control extra-CNS disease, although some new drugs seem to stabilize and reduce the risk of further BM progression (**Table 1**).

Chemotherapy

Traditional chemotherapy regimens with cyclophosphamide, methotrexate, fluoropyrimidines, camptothecins, platinum, and anthracyclines have demonstrated some CNS activity, with variable objective response rates (ORR: 10%–60%) across BC subtypes.[48,49] Temozolomide has ability to penetrate the BBB but has limited CNS activity (CNS ORR ∼5%), including when used as a radiosensitizer in BC.[50,51]

High-dose intravenous chemotherapy and intrathecal administration (lumbar puncture or ventricular Ommaya reservoir) aim at increasing CNS bioavailability of antineoplastic compounds at clinically active doses. These approaches have a limited role in patients with parenchymal-only BMs, but can be considered in the presence of LMD, with or without BMs. In small studies, high-dose chemotherapy (eg, methotrexate) has been reported to achieve CNS-ORR up to ≈30%; however, the toxicity profile must be carefully considered in the context of a patient's PS and comorbidities.[52,53] Drugs tested for intrathecal administrations are methotrexate, liposomal cytarabine, and thioTEPA (ORR: up to 55%), showing median OS of 4 to 5 months.[54,55] We generally do not recommend concomitant radiation with intrathecal chemotherapy, as high rates of neurotoxicity have been reported, with 2% to 27% of patients having severe CNS toxicities.[56] Data on combined high-dose intravenous plus intrathecal chemotherapy are limited.[57]

Human epidermal growth factor receptor 2-directed targeted agents

Tyrosine kinase inhibitors. Lapatinib was the first tyrosine kinase inhibitor (TKI) successfully developed for HER2-positive BC, and the first in this setting to be used with an intent to treat BMs. Clinical trials reported modest intracranial activity (ORR <10% as a single agent and up to 20% with capecitabine, etoposide, or temozolomide) in pretreated patients.[58–60] A large phase II clinical trial evaluated lapatinib and capecitabine in patients with active BMs previously treated with RT/

Table 1
Systemic treatments recommended in clinical guidelines for the management of patients with breast cancer and brain metastases

Breast Cancer Subtype	Treatment Regimen	Reference Clinical Study	Intracranial Response[a]	PFS
HER2-positive	T-DM1	KAMILLA	42.9%	5.5 mo
	Capecitabine and lapatinib	LANDSCAPE	65%	5.5 mo
	Capecitabine and neratinib	TBCRC 022	33%–49%	3.1–5.5 mo
	Paclitaxel and neratinib	NEfERT-T	Incidence of symptomatic or progressive CNS lesions: • 10.1% with neratinib • 20.2% with trastuzumab	NA
	Tucatinib, trastuzumab, and capecitabine	HER2CLIMB	47.3%	All patients with BMs: • 1-y PFS: 24.9% • Median: 7.6 mo • CNS-PFS: 9.9 mo Active BMs: • PFS: 7.6 mo • ORR: 47.3% • CNS-PFS: 9.6 mo
	T-DXd	Destiny-Breast 03, DEBBRAH, TUXEDO-1	63.9%–73%	15 mo
	Pertuzumab and high-dose trastuzumab	PATRICIA	11% *6-mo BM control:51%*	-
All-type	Capecitabine	Rivera et al, Cancer 2006 [b]	18%	*Time to CNS progression*: 3 mo
	Cisplatin and etoposide	Franciosi, Cancer 1999; Viñolas, J Neurooncol 1997	14%–37.5%	—

Indications are based on the National Comprehensive Cancer Network Breast Cancer guidelines (2022).

Abbreviations: BM, brain metastasis; CNS, central nervous system; DM1, trastuzumab emtansine; Mo, months; ORR, objective response rate; PFS, progression-free survival; T-T-DXd, trastuzumab deruxtecan.

[a] Criteria to assess tumor responses can vary across clinical trials. For the references, see the text.

[b] Capecitabine was combined with temozolomide in this study. However, temozolomide as a single agent yields poor intra-brain activity in breast cancer, and no synergism is anticipated, so most of the activity is likely due to capecitabine alone.

trastuzumab.[59] The study showed a CNS response (volumetric reduction of BMs of 50% and higher) in 6% of the patients, with a shrinkage of 20% or higher in 21% with single agent lapatinib, and CNS response rate of 20% with the doublet of lapatinib and capecitabine.[59] The combination of lapatinib and capecitabine was then tested in patients with newly diagnosed RT-naive BMs. The LANDSCAPE study[61] showed a rate of volumetric response of 65.9%, with a median time to progression of 5.5 months. Comparable ORRs were reported for the concomitant use of lapatinib and WBRT; however, a randomized phase II study of WBRT with or without concurrent lapatinib did not meet its primary endpoint.[58,62,63]

Neratinib is an irreversible HER2-blocker. A small substudy within the TBCRC022 clinical trial demonstrated uneven distribution of neratinib in resected BMs, with some areas reaching therapeutic concentrations.[64] Despite this, TBCRC022 reported an ORR of 49% in patients TKI- naive and 33% in the post-lapatinib setting in patients with active BMs (median progression-free survival [PFS]: 5.5 and 3.1 months, respectively).[65] In addition, neratinib in patients with stable BMs seems to reduce subsequent CNS progression, as reported in the pivotal clinical trial NALA.[66] Patients with baseline stable BMs trended to longer PFS compared with lapatinib (7.8 vs 5.5 months, HR 0.66; 95% CI 0.41–1.05) with lower cumulative incidence of new CNS progression (26.2% vs 41.6% [$P = .36$]).[66]

The opportunity to optimize CNS disease control through a systemic treatment approach has yielded the development of the HER2-selective TKI tucatinib, which in preclinical models demonstrated high CNS penetration and efficacy in BMs.[67,68] The pivotal HER2CLIMB study enrolled patients with and without BMs, including a subset with active BMs. Overall, the triplet of tucatinib, trastuzumab, and capecitabine outperformed trastuzumab and capecitabine alone, with a median PFS of 7.6 versus 4.9 months, and OS of 24.7 versus 19.2 months.[69] A secondary analysis on patients with BMs confirmed the overall benefit, with an improvement of overall PFS (7.6 vs 5.4 months), CNS-PFS (HR 0.39; medians 9.9 vs 4.2 Months) and OS (HR 0.60; medians 21.6 vs 12.5 months).[70–72] Results were similar in patients with active BMs at baseline (CNS ORR 47.3% vs 20%, restricted to patients with active, measurable BMs at baseline; OS HR 0.52, medians 21.4 months vs 11.8 months).

Monoclonal antibodies. The positioning of monoclonal antibodies for BMs has been controversial. Initial evidence suggested that patients treated with adjuvant trastuzumab experienced more BMs as first relapse.[73,74] However, more recent trials with pertuzumab and trastuzumab or trastuzumab emtansine (T-DM1) showed no differences.[75,76] The bioavailability of monoclonal antibodies in BMs has been classically judged as insufficient to anticipate clinical benefit. However, disruption of the BBB induced by BMs, which also can occur following RT, can enhance permeability.[77] Murine models of brain metastatic HER2-positive BC showed limited activity of standard dosing trastuzumab; however, there was an intriguing observation of a dose-response curve of BMs to increased trastuzumab doses.[78] Furthermore, BM models resistant to trastuzumab were sensitive to the antibody drug-conjugate (ADC) T-DM1.[78] The proof-of-concept PATRICIA study[79] assessed safety and efficacy of a high-dose schedule of trastuzumab at 6 mg/kg weekly plus pertuzumab in patients who had brain-only progressing BC and who had progressed despite prior RT. The investigators reported a CNS ORR of 11%, with clinical benefit rate (in both CNS and extracranial sites) of 51% at 6 months.[79] Several case series and at least two phase I/II prospective clinical trials have been reported with intrathecal trastuzumab, in patients with HER2-positive LMD.[80–83] The use of intrathecal trastuzumab seems safe. In one study, OS was ~10 months, which exceeds historical control expectations for patients with LMD. The first prospective

demonstration of intracranial activity of an ADC was in the phase IIIb KAMILLA trial, with T-DM1, including patients with RT-treated stable or asymptomatic untreated BMs.[84] T-DM1 yielded a CNS response in 42.9% of patients, with a median PFS of 5.5 months and OS 18.9 months; in RT-naive patients, the ORR was 49.3%. More recently, the ADC trastuzumab deruxtecan (T-DXd) in patients with stable BMs showed better overall disease control as compared with T-DM1, with a median PFS of 15 and 3 months, respectively, in the phase III trial Destiny-Breast 03.[85] Overall ORR favored T-DXd (63.9% vs 33.4%).[86] Activity was also reported for progressing BMs in the single-arm study DEBBRAH[87] (CNS ORR 44% in patients with active BMs) and TUXEDO-1[88] (CNS ORR 73% in active BMs) and a multi-institution case series (CNS ORR 73% in all BM patients; CNS ORR 70% in subset with active BMs).[89]

Antiangiogenic agents. High vascular density and abnormal neoangiogenesis are landmark alterations in BMs, partly driven by the vascular endothelial growth factor (VEGF).[90] The anti-VEGF monoclonal antibody bevacizumab has demonstrated to potentially abrogate neovasculature.[91] Data of bevacizumab in patients with BMs have traditionally been limited, as patients with BMs were excluded from all but a handful of phase I, II, and III BC clinical trials. A single-arm, phase II trial reported by Leone and colleagues demonstrated a potential role for bevacizumab with carboplatin (and trastuzumab for HER2-positive BC) in patients with BMs, showing a favorable safety profile, CNS-ORR of 63%, and a median PFS of 5.6 months.[92] The findings mirrored a trial conducted in Taiwan with bevacizumab, etoposide, and cisplatin, which reported CNS ORR of 77.1% and median CNS-PFS of 7.3 months.[93] Bevacizumab can also improve CNS symptoms and serve as a steroid-sparing agent, as shown in a mixed cohort (40.9% with BC) of patients with symptomatic brain recurrence and has an established role for the treatment of symptomatic radiation necrosis.[94,95]

Other targets. In the context of luminal-like BC, abemaciclib, a selective CDK 4/6 inhibitor, has demonstrated to achieve an intra-brain concentration above the level of clinical efficacy, albeit exerting limited activity in pretreated patients (CNS ORR 5.2%).[96] Efficacy of the mammalian target of rapamycin (mTOR) inhibitor everolimus with trastuzumab/vinorelbine in HER2-positive BC and BMs was not dissimilar (4% ORR).[97] In the setting of HER2-negative BC, the anti-trop2 ADC sacituzumab govitecan is being studied in patients with BMs. In a presurgical window study, supratherapeutic levels of the payload, SN-38, were present in patients who were treated with sacituzumab before resection of BMs.[98] S2007 is an ongoing phase II trial to test the utility of sacituzumab in the treatment of patients with active BMs. Potential CNS efficacy of other targeted agents (eg, olaparib, alpelisib) has been published only as case reports and series.[99,100]

Clinical recommendation: initial presentation. For patients presenting with a limited number of BMs, SRS is preferred. SRS and WBRT lead to similar OS, with an advantage of SRS on neurocognitive outcomes, but better overall intracranial control with WBRT. WBRT is considered standard for patients presenting with a more extensive number of BMs. However, for selected patients with longer expected survival (eg, those with HER2-positive subtype, well-controlled systemic disease, effective systemic options) and more extensive intracranial involvement, we favor individualized discussions regarding avoidance of radiation in lieu of systemic therapy for asymptomatic/minimally symptomatic patients with room to tolerate growth before decline and consideration of radiotherapeutic approaches or studies for patients who are symptomatic or approaching the point of symptom development. If radiation is deferred in favor of systemic therapy, patients should be informed about the uncertainties of the approach and need for close interval follow-up.

Table 2
Clinical trials ongoing assessing new treatments for the treatment of brain metastatic breast cancer

Experimental Treatment	Experimental Molecule Type	Breast Cancer Type	Phase of Development	Sample Size	Clinicaltrials.gov ID
Systemic					
Trastuzumab deruxtecan	ADC	HER2+	3	500 [a]	NCT04739761 (Destiny-Breast 12)
Pyrotinib, capecitabine	TKI	CELsignia HER2-active [b]	2	22	NCT04965064
Pyrotinib, vinorelbine	TKI	HER2+	2	30	NCT03933982
SRS and nivolumab	IO		1b	14	NCT03807765
GDC-0084 (Paxalisib) trastuzumab	TKI	HER2+	2	47	NCT03765983
SRS and abemaciclib/ET	TKI	Luminal	2	31	NCT04923542
THP vs TH-pyrotinib	TKI	HER2+	2	120	NCT04760431
QBS72S[c]	Chemo	TNBC	2	35	NCT05305365
SRS and pembrolizumab	IO	All type	1/2	41	NCT03449238
ARX788	ADC	HER2+	32	32	NCT05018702
SRS, olaparib, and durvalumab	PARPi, IO	All type	1/2	41	NCT04711824
SRS or WBRT and pyrotinib plus capecitabine	TKI	HER2+	1/2	47	NCT04582968
Elacestrant (SERD), abemaciclib	ET, TKI	Luminal	1/2	44	NCT04791384
Afatinib, T-DM1	TKI, ADC	HER2+	2	130	NCT04158947
Nal-IRI, pembrolizumab	Chemo, IO	TNBC	2	42	NCT05255666
Tucatinib (added to HP or T-DM1)	TKI	HER2+	2	48	NCT05323955 *(Prevention of secondary PD after isolated brain recurrence)*
Sacituzumab govitecan	ADC	HER2-negative	2	44	NCT04647916
SCR-6852[d], palbociclib	ET, TKI	Luminal	1	146	NCT05293964
Bintrafusp Alfa and pimasertib	IO, TKI	HER2-negative	1/2	36	NCT04789668
NUV-422 [e]	TKI	Luminal	1/2	269	NCT04541225

HER2- CAR-T Chimeric Antigen Receptor T-Cell Therapy	IO	HER2+	1	39	NCT03696030
DZD1516[f] with capecitabine or T-DM1	TKI	HER2+	1	94	NCT04509596
T-DXd, tucatinib	ADC, TKI	HER2+	2	70	NCT04539938
Locoregional					
ExAblate 4000-system Type 2[g]		HER2+	NA	10	NCT03714243
SRS and Aguix Gadolinium-Based Nanoparticles	Radiosensitizer	All type	2	134	NCT04899908
HS-WBRT vs SRS	RT	All type (5–20 BMs)	3	196	NCT03075072

Clinicaltrial.gov (April 2022). The trials listed in the table enroll patients with active brain metastasis.

Abbreviations: ADC, antibody-drug conjugate; BBB, blood–brain barrier; BMs, brain metastases; Chemo, chemotherapy; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HS-WBRT, hippocampal-sparing whole-brain radiation therapy; IO, immunotherapy; PARPi, poly (ADP-ribose) polymerase inhibitor; PD, progression of disease; RT, radiation therapy; SRS, stereotactic radiotherapy; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TH, trastuzumab and pertuzumab; THP, trastuzumab, pertuzumab, and docetaxel; TKI, tyrosine kinase inhibitor; TNBC, triple-negative breast cancer; WBRT, whole-brain radiation therapy.

[a] The study has two cohorts, with or without baseline brain metastases. The cohort of patients with brain metastasis will enroll 250 patients.

[b] CELsignia is used in this trial to evaluate HER2 pathway hyperactivation in HER2-negative breast cancer.

[c] QBS72S is a selective substrate of LAT1 (blood–brain barrier transporter), with brain permeable and cytotoxic properties.

[d] Brain–blood barrier permeable endocrine agent.

[e] Brain–blood barrier permeable inhibitor of CDK4/6.

[f] Brain–blood barrier permeable anti-HER2.

[g] ExAblate 4000-system Type 2 is a magnetic resonance image-guided focused ultrasound device intended to disrupt the brain–blood barrier.

Clinical recommendation: subsequent central nervous system progression. We base our approach on multiple factors, including the number, size, and location of lesions, BM velocity, prior therapies, extracranial disease status, PS, and the estimated likelihood of clinical benefit to each of the available treatment options. As always, patient preferences and values remain paramount in treatment recommendations. For example, for a patient who develops two small new lesions 14 months after initial SRS (ie, low BM velocity), and whose extracranial disease is controlled on their current systemic therapy, we will frequently offer SRS to the new CNS lesions and continue the same systemic therapy. In contrast, for an asymptomatic or minimally symptomatic patient with HER2-positive BC with rapid intracranial progression in multiple sites after initial RT, we are more likely to defer radiation and offer a CNS-active, HER2-targeted, systemic regimen. In patients in whom local therapy is not expected to be effective, or is deemed overly toxic (eg, in previously irradiated lesions), we also strongly consider systemic therapy if patients desire continued antineoplastic therapy and there is an available option.

ONGOING STUDIES

The landscape for the treatment of brain metastatic patients is in continuous evolution. The future for the treatment of BMs is an integrated approach, with careful use of the treatments and a successful interplay of local and systemic therapies. Ongoing clinical trials (**Table 2**) are evaluating several locoregional techniques, such as WBRT-sparing approaches in patients with greater than 4 BMs (NCT03075072). Compounds with radio-sensitizing properties are being tested to enhance the disease control, either with gadolinium-based tracers (NCT04899908) or other antineoplastic agents (olaparib: NCT04711824). Systemic therapy trials testing pyrotinib (NCT03933982, NCT04760431, NCT04582968), neratinib (NCT02236000), tucatinib, and ADCs (T-DXd: NCT04539938; ARX-788: NCT05018702) are ongoing. Specific BMs vulnerabilities or mechanisms of resistance are also being tackled, by targeting key pathways such as PIK3CA/mTOR signaling[15] (paxalisib: NCT03765983) and MAPK (pimasertib: NCT04789668).[101] Of interest, some new compounds are under development as primarily BBB permeable such as QBS72S (a cytotoxic agent that is also a substrate of the LAT-1 BBB transporter), DZD1516 (anti-HER2; NCT04509596), estrogen receptor down-regulators (elacestrant: NCT04791384; SCR-6852: NCT05293964; NUV-422: NCT04541225), and liposomal formulations (Nal-Iri: NCT05255666).

SUMMARY

The bedrock for a quality management of patients with BM is a multidisciplinary approach, patient-centered and aimed at integrating the patient experience in the clinical decision-making process. As generally in breast oncology, in the setting of brain metastatic BC, patients' needs and values are the drivers of the care.

Systemic treatments can help stabilize and reduce further progression of stable and asymptomatic BMs and, in limited cases, can help control progressing BMs (eg, tucatinib and neratinib). New treatments are emerging that could yield paradigm shifts in the multidisciplinary treatment approach.

CLINICS CARE POINTS

- Routine screening with imaging to identify clinically silent brain metastases (BMs) is currently not recommended in patients with metastatic breast cancer (BC) without a history of BM;

however, prospective studies are ongoing to determine whether surveillance screening may provide clinical benefit to patients.

- Patients presenting with significant symptoms (eg, mass effect from a large lesion) due to BMs or bulky BM (>3–4 cm) should be offered neurosurgical consultation, similarly when there is diagnostic uncertainty, neurosurgery should be considered.
- For patients with a limited number of BMs, stereotactic radiosurgery (SRS) is the preferred approach.
- For patients with more extensive intracranial involvement, whole-brain radiation therapy (WBRT) with hippocampal sparing, if viable, and memantine is the current standard of care. In select patients (eg, with longer life expectancy), we discuss clinical trials evaluating SRS to multiple lesions versus a systemic therapy approach versus WBRT.
- Patients with poor performance status and limited life expectancy with multiple BMs can be managed with best supportive care, where goals of care discussion are appropriate, as the benefits of local or systemic therapies can be very limited.
- The role of systemic therapy to control new/progressing BMs is evolving. We are most likely to consider systemic therapy in lieu of local approaches in select patients with human epidermal growth factor receptor 2 (HER2)-positive BC. The strongest data exist for HER2-targeted tyrosine kinase inhibitors, of which tucatinib-capecitabine-trastuzumab is our preferred regimen. Other options (with varying levels of evidence) include neratinib-capecitabine, trastuzumab emtansine, high-dose trastuzumab with pertuzumab, lapatinib-capecitabine, and trastuzumab deruxtecan. For patients with HER2-negative BC, we tend to prioritize local approaches when feasible, as the data for systemic options are more limited and generally less favorable. However, we do consider systemic therapy in HER2-negative patients with more limited or less favorable local therapy options.
- More conservative, focused and less toxic local treatments, and novel systemic drugs are under investigation for patients with BC and BMs. A discussion of clinical trials with patients provides a full spectrum of treatment options and may yield new advances in management for patients with BMs.

DISCLOSURE

D. Trapani has no potential conflict to report. A.A. Aizer reports research funding from Varian Medical Systems and NH TherAguix and consulting/advisory board fees from Novartis and Seagen. N.U. Lin reports research funding from Genentech, Merck, Pfizer, Seattle Genetics, AstraZeneca, Zion Pharmaceuticals, and Olema Pharmaceuticals; honoraria for consulting/ad boards from Pfizer, Puma, Seattle Genetics, Daiichi Sankyo, AstraZeneca, Prelude Therapeutics, Denali Therapeutics, Olema Pharmaceuticals, Aleta BioPharma, Affinia Therapeutics, Voyager Therapeutics, and Artera Inc; and royalties from UpToDate.

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