Therapy of breast cancer brain metastases: challenges, emerging treatments and perspectives

Ther Adv Med Oncol

2018, Vol. 10: 1–10

DOI: 10.1177/1758835918780312

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Abstract: Brain metastases are the most common central nervous system tumors in adults, and incidence of brain metastases is increasing due to both improved diagnostic techniques (e.g. magnetic resonance imaging) and increased cancer patient survival through advanced systemic treatments. Outcomes of patients remain disappointing and treatment options are limited, usually involving multimodality approaches. Brain metastases represent an unmet medical need in solid tumor care, especially in breast cancer, where brain metastases are frequent and result in impaired quality of life and death. Challenges in the management of brain metastases have been highlighted in this review. Innovative research and treatment strategies, including prevention approaches and emerging systemic treatment options for brain metastases of breast cancer, are further discussed.

Keywords: brain metastases, breast cancer, challenges, innovation, therapy

Received: 25 February 2018; revised manuscript accepted: 25 April 2018.

Introduction

Brain metastases (BMs) are the most common central nervous system (CNS) tumors in adults. The incidence of BMs is increasing due to both improved diagnostic techniques (e.g. magnetic resonance imaging: (MRI)) and increased cancer patient survival through advanced systemic treatment approaches (e.g. anti-*HER2* in metastatic *HER2* breast cancer, epidermal growth factor receptor (EGFR) tyrosine-kinase inhibitors in EGFR-mutated non-small cell lung cancer (NSCLC)).[1–3] The incidence of BMs depends on the type of primary cancer, varying from approximately 5–50%.[4] CNS involvement occur more commonly in lung cancer, breast cancer, melanoma, and renal cell carcinoma patients.[4] BMs are associated with a poor prognosis. Overall survival varies according to the tumor types and tumor subtypes from 3 to 25 months.[4] In breast cancer, differences in survival of patients with BMs by tumor subtype (luminal, *HER2* and triple-negative metastatic breast cancer) have been observed and highlight the need for a tailored approach in this patient population.[5] Several predicting factors for BMs have been identified to date and include age, histological grade, negative status of estrogen receptor, *HER2* and number of non-CNS metastatic sites (1 *versus* >1).[6]

Treatment options are limited and usually involve multimodality approaches that include surgery, radiotherapy, radiosurgery and rarely systemic therapy, depending on the number of CNS lesions, location, and primary tumor type, as well as patient performance status, considering validated prognostic indexes.[7,8] Moreover, quality of life (QoL) and neurocognitive function are often impaired in patients with BMs compared with patients with extracranial metastases due to both the CNS disease and its treatments.[9,10] In particular, the role of whole brain radiotherapy (WBRT) is subject to discussion especially since a recent phase III trial showed that WBRT provides little additional clinically significant benefit on either overall survival and QoL in NSCLC patients with BMs.[11] Treatments and outcomes of patients with BMs remain disappointing and represent an unmet medical need in current care of cancer patients, especially in breast cancer, where BMs are frequent and result in impaired QoL and

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death.[12] Challenges in the management of BMs will be highlighted in this review. Emerging research and treatment strategies in BMs from breast cancer will be discussed.

Challenges in the management of BMs

Understanding BM biology

BM pathogenesis. The pathogenesis of BMs has not been thoroughly characterized to date. Tumor cells spread from the primary tumor or from the metastatic lesion and colonize the brain parenchyma, involving several biological processes: local invasion, intravasation into the bloodstream, extravasation into the brain parenchyma through the blood–brain barrier (BBB) and interaction with the CNS microenvironment.[13] The importance of genetic and epigenetic changes, in brain metastasization of breast cancer, has also been recently promoted.[14] The BBB is a selective barrier formed by endothelial cells interconnected by tight junctions, pericytes, astrocytes, neuronal end-foots and other cells from the microglia forming the neurovascular unit and that separates the bloodstream circulation from the brain and the cerebrospinal fluid (CSF). Transport across the BBB is highly regulated and includes paracellular transport, passive and active transport and cell-mediated transcytosis. Consequently, pathogenesis of BMs results in a multitude of biological pathway activations in both tumor and the brain microenvironment.[15] The existence of brain metastases initiating cells (BMICs) is being increasingly discussed. BMICs have the ability to escape the primary tumor and invade the neural niche to initiate tumor growth. These cells might also exploit a period of dormancy to transform the local brain milieu into a favorable environment and reactivate years later.[16] In addition, although the BBB is frequently compromised by BMs, the residual BBB permeability also limits drug delivery (e.g. efflux pumps).[17]

Further biological findings may help to identify promising therapeutic targets and the development of new compounds. This research could be undertaken with the help of more accurate preclinical models to recapitulate BM pathogenesis. By combining both *in vitro* models (e.g. Transwell, cell exclusion, scratch wound, microfluidics) and *in vivo* models (e.g. genetically engineered mouse models, patient-derived xenograft (PDX) models), it might be possible to identify crosstalk between signaling pathways, search for specific BM homing signatures, use *in vivo* imaging techniques and identify targets associated with the BMs, the BBB or the microenvironment.[18] As an example, Singh and colleagues used an *in vitro* model to identify a subset of stem-like cells from primary human patient BMs, known as BMICs, and managed to establish a BMIC PDX transplantation model that enabled them to identify essential regulators of BMICs potentially targetable.[19] Also, several preclinical data suggest that the PI3K-AKT-mTOR pathway activation is a frequent brain-specific mechanism of drug resistance to *HER2*-targeted therapies suggesting that preclinical knowledge will help to identify new drug targets that could be tested in clinical trials.[20–22] For example, *HER3* blockade has been shown to overcame the resistance of *HER2*-amplified or *PIK3CA*-mutant breast cancer BMs to PI3K inhibitors *in vivo*[21] and combined inhibition of PI3K and mTOR resulted in durable tumor regressions in breast cancer BMs from PDX models.[22]

Heterogeneity between the primary tumor and the BMs. BMs share alterations that are not necessarily detected in primary tumors, regional lymph nodes, or extracranial metastases as demonstrated by whole-exome sequencing of 86 matched BMs, primary tumors, extracranial metastases and normal tissue.[23] Consequently, primary tumor or extracranial metastatic site genotyping could potentially overlook actionable oncogenic driver mutations present on the BMs. Moreover, BMs can harbor mutations conferring specific drug resistance or activation of an alternative signaling pathway interfering with drug activity.[23] Brain biopsies are considered invasive. Liquid biopsy is being investigated as potential screening tool by using for example ctDNA or circulating tumor cells (CTCs) in the CSF or ctDNA, miRNA and exosomes in the circulation.[24–30] Pentsova and colleagues sequenced cancer-associated genes in cell-free DNA from CSF in 53 patients with suspected or known CNS cancer involvement and detected somatic alterations in 63% (n = 20/32) of patients with CNS metastases of solid tumors and, interestingly, in none of the patients without BMs.[25] Similar results have also been shown recently in BMs from NSCLC.[31] Furthermore, Boral and colleagues showed a difference in CTC transcriptomic signatures in patients with breast cancer BMs that is different from primary tumors that may be used either as a screening, monitoring and therapeutic tools.[26]

Challenges and opportunities in clinical research of BMs

Patients with progressive BMs are often excluded from clinical trials, usually because they are known to have a poor prognosis and because most of systemic treatments fail to penetrate the BBB, but also due to the high risk of CNS hemorrhage or toxicity.[32] Patients with BMs are often heavily pretreated, randomized trials in patients with BMs are difficult to perform and anticancer response is difficult to observe. In existing clinical trials, definitions of clinical endpoints are also variable. Moreover, most of the studies do not take into consideration the number of BMs, the extracranial disease status, prior therapies received or sensitivity to these therapeutic approaches.[33] However, due to the improvement in systemic therapies and better systemic control, a number of patients remain in good clinical condition for an extended period of time. Therefore, prospective clinical trials in a selected patient population could be feasible. Recommendations for clinical trial eligibility criteria have been recently published by the American Society of Clinical Oncology (ASCO) BMs working group as described hereunder. First, they proposed to include patients with treated and stable BMs for at least 4 weeks or patients with active BMs in early phase trials when there is a strong scientific rationale for probability of benefit.[34] Similarly the RANO-BM (Response Assessment in Neuro-Oncology Brain Metastases) group suggested to consider the likelihood of CNS activity of the agent to establish inclusion/exclusion criteria in clinical trials.[35] The ASCO BMs working group also proposed to consider a parallel cohort in later phase trials and include brain imaging monitoring in tumors with high risk of developing BMs, that statistical approaches should also be adapted allowing these patients into the intent to treat population and to differentiate intracranial and extracranial progression in these patients.[34] Likewise, use of alternative study designs and methodology could also be proposed (e.g. window of opportunity trials), N-of-1 trials using the patient as their own control, as well as specific surrogate endpoints [time to next event in the CNS, intracranial progression-free-survival, intracranial objective response rate (ORR)].[12] Neurological, neurocognitive, and QoL reporting should be part of the trial design. Considering the current failure rates of existing treatments and the impaired QoL, an interesting approach would be to focus on primary prevention, and secondary prevention, avoiding or delaying the next CNS event and associated symptoms after a first CNS metastatic event.[36,37]

In this context, potential predictive biomarkers for BMs should be investigated. Circulating biomarkers, including in the CSF, as well as functional imaging are under evaluation and might in the future be of help for treatment guidance.[25–30,38–42]

Uniformity in the assessment of CNS metastases using novel imaging techniques and common criteria for evaluation, should be put forward (e.g. RANO-BM criteria).[43] Recently, The RANO group proposed also the iRANO guidelines integrating the concept of pseudoprogression of disease that will evolve successively with further experience from immunotherapy trials in neuro-oncology[44] and the NANO (Neurological Assessment in Neuro-Oncology) scale, which is a tool to assess neurological function for integration into the RANO criteria to provide an overall assessment of outcome for neuro-oncology patients.[45]

Emerging treatments in BMs from breast cancer

To date, general indications to use systemic treatments for BMs is limited to highly chemotherapy-sensitive primary tumors, BMs from primary tumors with identified molecular alterations amenable to targeted therapy crossing the BBB, asymptomatic BMs found on screening MRI with planned systemic treatment, or in cases in which other therapeutic options have been exhausted and there is a drug available.[7] This is due to the lack of efficacy of systemic treatment including in breast cancer patients with BMs. Consequently, until recently, treatment of BMs from breast cancer was focused on local therapy (surgery or radiotherapy).[46]

General considerations to improve treatments efficacy

The ability to manipulate the BBB offers hope to increase the efficacy of systemic treatments. Several strategies enable to manipulate the BBB and some of them are currently investigated for the treatment of BMs and primary brain tumors: (1) enhancement of drug permeability through the BBB using osmotic/chemical disruption of the BBB (e.g. mannitol, intra-arterial vasoactive agents), colloidal-based drug delivery or by targeting BBB transport systems[47–49]; (2) interstitial delivery by using, for example, intranasal administration, intrathecal or intracranial catheters[47,50–52]; (3) the use of polymers and microchips for local drug delivery[47]; or finally, (4) temporary

disruption of the BBB (e.g. radiotherapy techniques, pulsed ultrasound).[47,53,54]

Indeed, adding active systemic therapy to local (radiation, surgery) therapy could be one effective way to improve the outcome of patients with BMs. The concept aims to use and to enhance both local and systemic effects of the treatment. The immune stimulatory effects of radiation therapy in combination with immunotherapy [e.g. checkpoint inhibitors, CAR (chimeric antigen receptor)-T cells][55] is an example of this innovative approach. Another major advantage of this approach will be to control both intracranial and extracranial disease.

Emerging systemic therapies in BMs from breast cancer

Currently there are several systemic treatments being developed with promising CNS activity, especially for breast cancer (Table 1).

Chemotherapy

Potential role of etirinotecan pegol. Etirinotecan pegol is a next-generation long-acting topoisomerase-I inhibitor-polymer conjugate, enabling penetration through the tumor endothelia, thereby enhancing irinotecan and its active metabolite (SN38) exposure in BMs.[62] In addition, compared with irinotecan, etirinotecan pegol has a longer half-life than SN38, the active compound.[63,64] Etirinotecan showed sustained tumor exposure in multiple cancer cell lines and preclinical models, which may increase the therapeutic window.[62] Preclinical data showed higher concentrations of irinotecan and SN38 in brain tumor tissue *versus* plasma on day 7 after etirinotecan pegol administration in mice with intracranial implanted triple-negative breast cancer tumors.[65] Moreover, etirinotecan pegol leads to regression of established BMs and prolongs survival of animals with triple-negative breast cancer BMs.[65]

In a phase III study, BEACON trial, patients with metastatic breast cancer who had failed multiple prior therapies were randomized to etirinotecan pegol or treatment of the physician's choice. Etirinotecan pegol was associated with a nonstatistically significant 2.1 months improvement in overall survival. However, in patients with a history of treated, stable BMs (planned subgroup analyses), etirinotecan pegol reduced the risk of death by nearly half for the treated subset of women (hazard ratio (HR) 0.51) and demonstrated a doubling of 12-month survival rate (44% *versus* 20%)[60,66] with less toxicity and better QoL compared with treatment of the physician's choice.[60,61] In patients with radiologically detectable but stable brain lesions, treatment with etirinotecan pegol allowed a 7.4-month survival advantage compared with treatment of physician's choice[66] (Table 1).

Based on these findings, an open-label, randomized multicenter phase III trial in patients with stable BMs from advanced breast cancer is currently recruiting [ClinicalTrials.gov identifier: NCT02915744].[67] A total of 350 patients with metastatic breast cancer who have stable BMs and have been previously treated with an anthracycline, a taxane, and capecitabine will be randomized 1:1 to etirinotecan pegol or treatment of the physician's choice, limited to one of the following agents: eribulin, ixabepilone, vinorelbine, gemcitabine, paclitaxel, docetaxel, or nab-paclitaxel. The primary objective of the study will be overall survival.[67]

Other chemotherapy compounds of interest. ANG1005 is a peptide-drug conjugate containing paclitaxel and covalently linked to Angiopep-2, using the LRP-1 transport system to cross the BBB.[59] This compound has shown interesting results in a phase II study in patients with metastatic breast cancer with recurrent BMs and achieved intracranial responses in 14% of the patients and 57% of the patients had stable disease[59] (Table 1). Extracranial responses were also observed. A randomized study is planned.[59]

TPI 287 is a third-generation taxane designed to overcome efflux pumps systems. Preclinical data suggest an activity on BMs from breast cancer cells.[68] TPI 287 was used in combination with bevacizumab in a phase I/II trial for the treatment of recurrent glioblastoma and showed a promising 60% overall response rate ($n = 23$),[69] further verifying its ability to cross the BBB. Studies in BMs for breast cancer are underway (e.g. ClinicalTrials.gov identifier: NCT01332630).[70]

Targeted therapies. In the setting of *HER2*-advanced breast cancer, neratinib is an oral, irreversible, tyrosine-kinase inhibitor of *HER1*, *HER2*, and *HER4* with demonstrated efficacy in metastatic breast cancer patients also in trastuzumab (anti-*HER2*) resistant disease.[71] Neratinib efficacy in preclinical models suggests good CNS

Table 1. Emerging systemic therapies in brain metastases from breast cancer.

Mechanism of action		Study name	Study design	Experimental drug	Tumor subtypes	Number of patients	CNS endpoint
Targeted therapy	Pan-HER inhibitor	NCT01494662[56,57]	Phase II	Neratinib monotherapy	*HER2*+ BCBM progression in the CNS after one or more line of CNS-directed therapy	40	ORR: 8%
				Neratinib (+ capecitabine)		39	VORR 49% RanoBM-ORR 24%
	CDK 4/6 inhibitor	NCT02308020[58]	Phase II	Abemaciclib	HR+, *HER2*- mBC who have ⩾1 measurable brain lesion	23	ORR: 8.2%
Chemotherapy	Peptide-paclitaxel conjugate	NCT02048059[59]	Phase II	Ang-1005	BCBM with or without LC	72	ORR: 14% SD 57%
	Long-acting topoisomerase-I inhibitor-polymer conjugate	NCT01492101[60,61]	Phase III	EP *versus* IC	mBC BM subgroup: stable BM locally pretreated	67 36 (treated with EP)	12-month survival rate (44% *versus* 20% IC)

BCBM, breast cancer brain metastases; BM, brain metastases; CNS, central nervous system; EP, etirinotecan pegol; IC, investigator's choice; LC, leptomeningeal carcinomatosis; mBC, metastatic breast cancer; ORR, objective response rate; SD, stable disease; VORR, volumetric objective response rate.

penetration.[72,73] In a randomized phase II trial, the neratinib-paclitaxel combination showed interestingly that the incidence of CNS recurrence was lower and that time to CNS metastases was longer compared with trastuzumab plus paclitaxel in previously untreated metastatic *HER2*-positive breast cancer.[74] More recently, the results of the TBCRC 022 trial showed encouraging data regarding neratinib in combination with capecitabine for the treatment of BMs from *HER2*-positive advanced breast cancer with no prior lapatinib or capecitabine treatment, with nearly half of the patients presenting a volumetric CNS ORR on progressive BMs.[56]

Abemaciclib is a selective cyclin-dependent kinase (CDK) 4/6 inhibitor that seems to cross the BBB and reaches concentrations that are 10-fold higher than palbociclib, another CDK 4/6 inhibitor. It is effective against BM in glioblastoma xenograft models.[75] Preliminary results of the I3Y-MC-JPBO study evaluating abemaciclib in patients with new or progressive BMs secondary to hormone receptor positive (HR+) metastatic breast cancer, NSCLC, or melanoma, provided evidence that abemaciclib had antitumor activity in HR+ breast cancer patients with BMs[58] (Table 1).

Also, findings from preclinical models suggest that PARP inhibitors might be of benefit for breast cancer BM treatment and certainly warrant further investigations.[12,76]

Immunotherapy. Patients with BMs have predominantly been excluded from immunotherapy clinical trials. Immune responses in the brain are highly regulated and BMs might also contain tumor infiltrating lymphocytes, challenging the use of immunotherapies for the treatment of CNS secondary tumors.[77] In melanoma and NSCLC, both anti-PD1 and anti-CTLA4 (immune checkpoint inhibitors) showed interesting CNS responses as monotherapy. The activity was even better in combination with up to 50% CNS responses in melanoma patients.[78–81] Escudier and colleagues reported preliminary results of the NIVOREN study, a prospective phase II study assessing safety and efficacy of nivolumab (anti-PD1), in patients with BMs from renal cell carcinoma. Among 44 patients eligible for assessment of CNS response, 23% had an intracranial ORR.[82] To date, immunotherapy has failed to improve the outcome of breast cancer patients. However, radiotherapy may increase the local efficacy of immunotherapy, as well as inducing an abscopal effect.[68] Innovative studies are needed to investigate the effects of radiation combined with immunotherapy and combinations with other systemic therapies on brain tumor control.[83]

Conclusions

Improving understanding of the biology of BMs is essential to identify optimal therapeutic targets in BMs from breast cancer and help overcoming the BBB challenges. Rethinking clinical research methodology, focusing on BMs prevention approaches and innovative treatment strategies will help improve outcome of patients and their QoL. These approaches should be implemented in a multidisciplinary manner in order to bring together the expertise needed to tackle the challenges in this area of unmet medical need in oncology.

Acknowledgements

The authors acknowledge the contribution of the AJE (American Journal Experts) Support Team and Ornella Martini for English-language editing of this manuscript.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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