Tumour Review

Central nervous system involvement in breast cancer patients: Is the therapeutic landscape changing too slowly?

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ABSTRACT

Central nervous system (CNS) involvement from breast cancer (BC) has been historically considered a relatively rare event. However, the development of new therapeutic strategies with a better control of extra-cranial disease and a longer overall survival (OS) has determined an increased incidence of brain metastases. Patients with HER2-positive or triple negative BC have higher occurrence of CNS involvement than patients with luminal-like disease. Moreover, after development of brain metastases, the prognosis is highly influenced by biological subtype. In patients with multiple brain metastases who experience important neurological symptoms, palliative treatment, with or without whole brain radiation therapy (WBRT), needs to be considered the first step of a multidisciplinary therapeutic approach. Patients with a good performance status and 1–3 brain lesions should be considered for radical surgery; patients technically inoperable with 4–5 metastases smaller than 3 cm may undergo stereotactic radiosurgery. The role of systemic therapy in the management of patients with brain metastases is controversial. Preliminary data suggest that systemic therapy after WBRT may improve survival in BC patients with brain lesions. In patients with HER2-positive disease, several retrospective or post hoc analyses showed a longer brain progression-free survival with trastuzumab in combination with or followed by other anti-HER2 drugs (such as pertuzumab, lapatinib, and T-DM1). Until now, no new strategies or drugs are available for triple-negative and luminal-like BC.

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Introduction

Breast cancer (BC) is the most frequently diagnosed tumor and the second leading cause of cancer death among women worldwide [1]. In 2007, the American Cancer Society reported that 160,000 women in the United States were living with metastatic breast cancer (mBC) with an estimated median survival of approximately 3 years [2]. The incidence of brain metastases is estimated between 140,000 and 170,000 per year [3] and BC is the second most common cancer to metastasize to the brain [4]. Autopsy studies have shown brain metastases in up to 36% of BC patients [5] and, accordingly, in the CEREBEL trial almost 20% of screened asymptomatic mBC patients presented with brain metastases [6]. However, the overall incidence of central nervous system (CNS) involvement in mBC patients reported in literature ranged from 10% to 16% [7]; this underestimation is probably due to the fact that in clinical practice CNS metastases are mostly being detected when symptomatic [8].

The two most important clinical factors related with the development of CNS lesions are the BC stage at diagnosis and the tumor biology. In facts, only 2.5% of patients diagnosed with early BC eventually develops brain metastases, compared to 7.6% in locally advanced disease and 13.4% in stage IV [7]. Moreover, patients with epidermal growth factor receptor 2 (HER2)-positive disease had the highest incidence of CNS involvement, followed by triple negative BC (TNBC; hormone receptor [HR]-negative and HER2-negative), luminal B-like (HR-positive, HER2-negative, and high proliferation rate), and luminal A-like (HR-positive, HER2-negative, and low proliferation rate) [9,10]. Extensive data suggests that young women with high proliferation rate, HR-negative, and/or HER2-positive tumor, may have the highest risk of developing brain involvement [8,11,12].

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Pathogenesis of CNS dissemination from breast cancer

The mechanism underlying brain dissemination is still unclear and many preclinical studies have been conducted to figure out the biological behavior of CNS metastasis in BC.

Brain metastasis formation entails several critical steps, such as cell migration, vascular spread, tumor cells extravasation and metastasis growth [13]. The major actors in the cell-to-cell and cell-to-extracellular matrix (ECM) interactions are the disintegrin and metalloproteinase domain-containing protein 8 (ADAM8) and the β1-integrin. ADAM8 is an enzyme that mediates cell-to-cell and cell-to-ECM interactions as well as ligand and receptor shedding. It is highly expressed in BC, especially in TNBC, and seems to mediate metastasis growth and to predict worse patient outcome [14]. Recently, an immunohistochemical analysis of 56 BC metastases revealed that more than 60% were positive for ADAM8 [14]. The β1-integrin has been identified as a potential mediator of invasion in glioma by promoting signal transduction at various receptors among which the tyrosine kinases receptors (TRKR) [15]. In addition, cell-to-ECM interaction, essential for cell migration through the blood–brain barrier (BBB), is also influenced by integrin activity [16].

The BBB represents a significant obstacle for tumor cells to gain access to the brain. However, it has been demonstrated by Lee and colleagues that endothelial expression of cyclooxygenase-2 (COX-2) raises metalloproteinases expression in BC cells, promoting their migration through the BBB [17]. The interaction between endothelial cells and BC cells is mediated by several factors, crucial for brain invasion. For example, the overexpression of the molecular chaperone αB-crystallin was shown to enhance BC cells adhesion to human brain microvascular endothelial cells [18] and a preclinical study in mice revealed that COX-2, the EGFR ligand HBEGF, and the alpha2, 6-sialyltransferase ST6GALNAC5 were also involved in BC extravasation into brain tissue [19].

Once tumor cells have migrated through the BBB, another crucial step for metastasis growth is provision of adequate supply of oxygen and nutrients through induction of proliferation of new blood vessels. Brain metastases are highly vascularized and vascular endothelial growth factor (VEGF)-driven angiogenesis is a common feature of CNS lesions. VEGF mediates endothelial cell retraction and increases permeability, vasodilation and new vessel formation. Of note, in a brain metastasis experimental model, anti-VEGF therapies were shown to decrease BBB permeability [13]. Moreover, the above mentioned study on BC cells showed that ADAM8 stimulates both transendothelial cell migration via β1-integrin activation and angiogenesis through VEGFA release.

Once across the BBB, BC cells are surrounded by reactive astrocytes which upregulate plasmin production, leading to paracrine secretion of death signals such as Fas ligand (FasL) [20]. In response to this insult, BC cells are able to produce anti-plasminogen activators, such as neuroserpin and serpin B2 to contrast astrocytes activity [21]. Besides preclinical data showed that BC cells co-cultured with brain tissue express many brain-specific genes [22], in particular BC survival genes [20].

An organ-specific brain metastasis gene expression profiling detected 37 crucial proteins with a differential expression between primary BC which develop brain metastases and which do not [23]. In this analysis, the overexpression of the glucose-regulated protein 94 (GRP94), the fibroblast growth factor-inducible14 (FN14), the tumor-necrosis factor (TNF) receptor-associated factor 2 (TRAF2), and HER2 were strongly associated with brain metastasis formation ($P < 0.001$). The overexpression of HER2 was the best predictor of subsequent development of brain metastasis, with a positive likelihood ratio (LR) of 6.7 ($P < 0.0001$), followed by FN14 (positive LR = 3.01; $P = 0.001$), GRP94 (positive LR = 1.89 $P = 0.003$), and TRAF2 (positive LR = 1.67; $P = 0.055$) [23].

Prognosis of breast cancer patients with brain metastases

In clinical practice, patients overall general condition is generally defined using either the Karnofsky performance status score (KPS) or the Eastern Cooperative Oncology Group (ECOG) system.

In the early 2000s, new prognostic tools have been approved for the prognostic stratification of patients with newly diagnosed brain metastases: the Radiation Therapy Oncology Group (RTOG) Recursive Partitioning Analysis (RPA), combining KPS, age, and disease extension (Table 1) [24] and the Graded Prognostic Assessment (GPA), combining age, KPS, number of central nervous system lesions and presence or absence of extra-cranial metastases [25].

A specific GPA for patients with BC has been developed in 2012 adding also the BC subtype to the prognostic factors [26]. Patients with a breast-GPA score of 0–1.0 have a median survival time (mST) of 3.4 months, patients with a score of 1.5–2.0 have a mST of 7.7 months, patients with a score of 2.5–3.0 have a mST of 15.1 months, and patients with a score of 3.5–4.0 have a mST of 25.3 months. In 2015, the breast-GPA was further modified by including the number of brain metastases into the prognostic factors (Table 2). The analysis was conducted in a cohort of 1552 patients with newly diagnosed brain involvement and showed concordance index between the observed OS and the OS estimated by the score was 0.78 (95% CI 0.77–0.80) for breast-GPA and 0.84 (95% CI 0.83–0.85) for modified breast-GPA ($P < 0.001$) [27].

Table 1
Recursive Partitioning Analysis (RPA) from Radiation Therapy Oncology Group (RTOG).

| RPA Stage	CHARACTERISTICS	MEDIAN SURVIVAL (months)
1	KPS ≥70 **and** Age < 65 years **and** Controlled systemic disease / metastases to brain only	7.1
2	KPS ≥70 **and** Age ≥65 years **or** Uncontrolled systemic disease	4.2
3	KPS <70	2.3

KPS: Karnofsky performance status.

Table 2
Graded Prognostic Assessment (GPA) to estimate survival from brain metastases from breast cancer. Adapted from Subbiah IM, et al. J Clin Oncol. 2015 [27].

FACTORS	SCORE (Points for each factors)				SUM	OS (months)
	0.0	0.5	1.0	1.5	0.0 - 1.0	3.1
KPS	≤ 50	60	70 to 80	90 to 100	1.5 - 2.0	6.3
BC subtypes	TNBC	HR-positive/ HER2-negative	HR- negative/ HER2- positive	HR-positive/ HER2- positive	2.5 - 3.0	15.5
Age (years)	> 50	≤ 50	-	-	3.5 - 4.0	26.0
Number of brain lesions	> 3	1 to 3				

KPS: Karnofsky performance status; BC: breast cancer; GPA: graded prognostic assessment; OS: overall survival; TNBC: triple negative breast cancer; HR: hormone receptor; HER2: human epidermal growth factor 2.
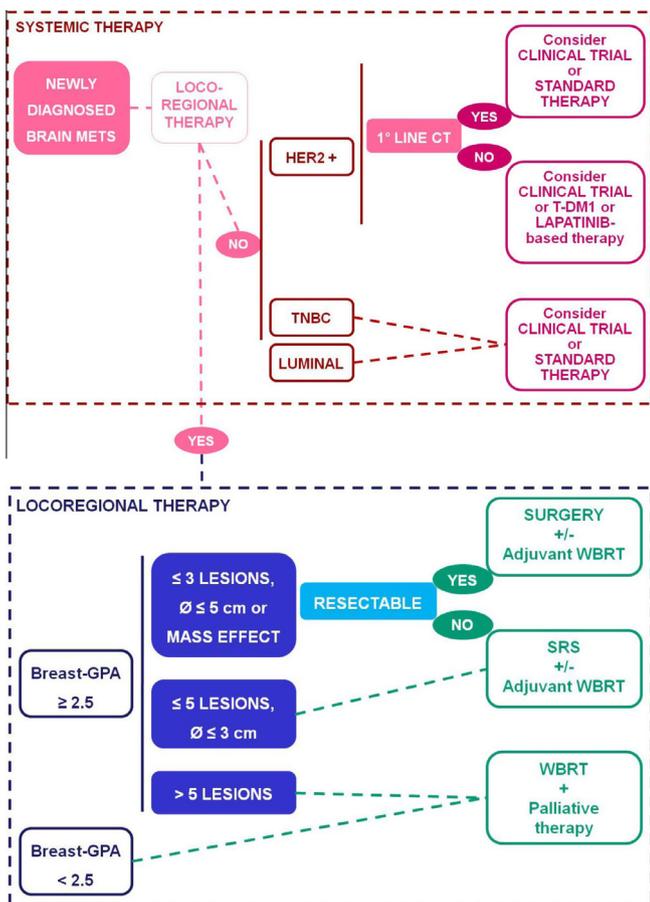
Fig. 1. Multidisciplinary approach for patients diagnosed with brain involvement from breast cancer: a possible therapeutic algorithm. Mets: metastasis; HER2: human epidermal growth factor 2; TNBC: triple negative breast cancer; CT: chemotherapy; GPA: graded prognostic assessment; Ø: diameter; SRS: stereotactic radio-surgery; WBRT: whole brain radiotherapy.

Loco-regional treatment

Even if the median survival of mBC has increased over the last decades, management of brain metastases continues to be challenging and requires a multidisciplinary team approach (Fig. 1) [28]. Historical data demonstrates that median survival after brain metastases diagnosis without any treatment is about 1 month and may increase to 2–3 months when corticosteroids and supportive treatment are added [29]. Notably, a number of loco-regional treatments have become available and overall survival (OS) of BC patients with brain metastatic lesions has remarkably increased.

Whole brain radiotherapy (WBRT)

The goals of radiation therapy are to alleviate neurological symptoms by lesion shrinkage and to prolong survival.

The first publication focusing on palliative radiation therapy in patients with symptomatic intracranial metastases referred a 63% reduction in symptoms [30] thus justifying the use of WBRT as the standard of therapy for brain metastases.

In recent years, the use of WBRT has considerably decreased due to growing concerns about late toxicity and thanks to advances in technology that have allowed for a more precise delivery of radiation. Nevertheless, WBRT remains the treatment of choice in patients with poor prognosis, widely disseminated brain metastases, lower performance status and uncontrolled systemic disease [31].

The use of WBRT is associated with a median survival of 4–6 months and an improvement in neurological symptoms, with clinical response rates ranging from 50% to 75% [32].

The most commonly used radiation dose is 30 Gy in 10 fractions of 3 Gy given over 2 weeks, a regimen that has emerged from a RTOG phase III trial demonstrating a benefit in outcome and tolerability compared to more rapid fractionation schedules [33]. Other RTOG trials investigated alternative approaches varying in terms of fractionation [34,35], dose escalation [36] and use of radiosensitizers [37,38]. However, no sufficient evidence is currently available to suggest higher efficacy or reduced toxicity of alternative dosing schedules over the standard WBRT protocol. Nevertheless, patients with a rapid progression of intracranial disease and/or short life expectancy can be approached with less frequent dosing, such as 20 Gy in 5 fractions [39].

Acute toxicity associated with WBRT is generally mild and self-limiting and includes fatigue, alopecia, dermatitis, nausea, vomiting, headache and decreased appetite; cerebral edema is relatively common, but is usually responsive to corticosteroids treatment.

Long-term side effects, that occur after 90 days of radiation treatment, are not self-limiting and may have severe consequences. The risk for late complications is related to the total radiation dose, fraction size, patient age, extent of disease and degree of neurological impairment. They include radiation necrosis,

neuroendocrine dysfunctions, cerebrovascular diseases and leukoencephalopathy, leading to neurocognitive deterioration and dementia.

Surgical resection

Patients with a favorable prognosis, RPA class 1 and even class 2 in selected cases, with a single brain lesion or oligometastatic disease should be assessed for suitability for radical surgery; in these cases aggressive treatment is indicated to achieve long-lasting control of CNS disease. For patients with a single, large metastasis in a surgically accessible location, resection may offer the best choice for rapid symptoms control. Surgery is also used in some patients with a limited number of metastases, particularly when there is one dominant, symptomatic lesion in an accessible position. The major risks associated with surgical resection include postoperative neurologic worsening, infection, intracranial hemorrhage and perioperative stroke.

Three randomized clinical trials have compared surgery plus WBRT to WBRT alone in patients with a single brain metastasis, demonstrating a survival benefit from the combined approach [40–42].

Patchell and colleagues randomized 48 patients with a single brain metastasis to either surgical resection followed by WBRT (36 Gy in 20 fractions) or WBRT alone. In this trial, patients who underwent surgery had significantly lower local recurrence rate (20 versus 52%; $P = 0.02$), longer OS (40 versus 15 weeks; $P = 0.01$) and better quality of life (QoL; 38 versus 8 weeks; $P = 0.005$) while no effect was noticed on the occurrence of distant brain metastases (20% in the surgical group versus 13% in the radiation group; $P = 0.52$) [40].

A similar trial confirmed a significantly longer OS with the combined approach (10 versus 6 months; $P = 0.04$), but it was only seen in patients that experienced stable disease [41]. Another study by Mintz and colleagues did not show improvement in outcomes from combined treatment (5.6 versus 6.3 months), although it might have been missed because of enrollment of patients with lower performance status and extracranial disease [42]. Recently, a retrospective study on breast cancer patients with solitary or limited number of brain metastases treated by surgical resection confirmed that this approach could be an effective treatment in selected patients [43]. Moreover, higher scores at the Mini Mental Status Examination, lower number of systemic metastases and the use of postoperative systemic treatment seemed to be significantly associated with better outcome. In contrast, HR status, HER2 status and molecular subtype were not significantly associated with survival.

Adjuvant WBRT

The rationale for the use of WBRT after surgery is to reduce recurrence rates, clearing residual cancer cells after surgery, and preventing the development of new metastases elsewhere in the brain. The impact of postoperative WBRT on OS is not clear. Results from randomized trials indicate that this approach reduces both local and regional intracranial recurrence but there is note evidence about improvement of OS.

As described above, for the treatment of a single brain metastasis, surgical resection combined with postoperative radiotherapy is more effective than radiotherapy alone. The efficacy of postoperative radiotherapy after complete surgical resection has been investigated in several trials. Patchell and colleagues compared the outcomes of patients with a single brain metastasis who underwent resection only with those who underwent surgery followed by adjuvant WBRT (50.4 Gy in 28 fractions), demonstrating increased local and regional recurrence rates with resection alone

(46% and 70% versus 10% and 18%), but no significant differences in OS [44]. According to these results, a large phase III trial conducted by the European Organization of Research and Treatment in Cancer (EORTC) enrolled 359 patients with one to three intracranial metastases randomly assigned to WBRT or observation following surgery or SRS. The trial demonstrated that the addition of WBRT fails to exert any substantial improvement on functional independence nor OS, although it reduces intracranial relapses and neurologic deaths [45]. Despite there is no consensus, postoperative WBRT continues to be used even if it is associated with potential late toxicities with not clear survival benefit.

Involved field radiotherapy (IFRT) is a radiation treatment technique that minimizes the radiation dose to uninvolved areas, delivering radiotherapy to the surgical bed only and limiting both short- and long-term toxicities associated with WBRT. A retrospective review of Connolly and colleagues investigated long-term outcomes in terms of local control, distant brain failure and OS in 33 patients (30% with BC) who underwent IFRT (40.5 Gy in 15 fractions) after surgical resection of a single brain metastasis. With the limits of retrospective collection of data, the study demonstrated that postoperative IFRT, at a median follow-up time of 16 months, obtained a local control rate of 85%, showing that it may be considered an alternative to WBRT. Local control rates at 12 and 24 months were 90.3% and 85.8%, respectively, while distant brain recurrence-free survival were 60.7% and 51.4%, respectively, and OS rates were 65.6% and 61.5%, respectively. On the whole, 15% of patients developed recurrence at the resection cavity and 39% at a new intracranial site [46].

Stereotactic radio-surgery

Stereotactic radio-surgery (SRS) is a non-surgical radiation therapy used to deliver precisely targeted high dose radiation in a single or few sessions. It allows maximum dose delivery within the target, minimizing the irradiation of healthy adjacent tissues and limiting the potential side effects of radiotherapy. There are three different types of radiation beams available for SRS: high energy X-rays produced by linear accelerators, gamma rays and charged particles such as protons produced by cyclotrons.

No prospectively randomized trials have been conducted to compare SRS (with or without WBRT) to surgery, but an observational study suggests that SRS is at least as effective as neurosurgery in selected patients, with local control rates of 80–90% when added to adjuvant WBRT [47]. In the absence of a direct comparison, the choice is usually based upon the size of the lesion, its surgical accessibility, symptoms and the functional status of the patient. For large lesions, surgery offers immediate decompression; moreover neurotoxicity and local failure after SRS increase with growing lesion size.

SRS is typically reserved to patients technically inoperable with 4–5 metastases at most, whose diameter is 3 cm or less, with few or no symptoms. When compared to surgery, SRS allows treating surgically inaccessible areas such as deep metastases, eloquent regions of the brain and multiple lesions. Additional advantages of SRS over surgery include short hospital stay, minimal risk of bleeding and infection, lower risk of complications, no need for general anesthesia, and fewer controindications.

The benefit of adding a SRS boost to patients who underwent WBRT has been investigated in a randomized trial by the RTOG [48]. In this trial 333 patients with one to three metastases (maximum diameter 4 cm) were randomly assigned to WBRT (37.5 Gy in 15 fractions) with or without SRS (15–24 Gy), demonstrating that the addition of SRS was able to obtain a better control of the treated lesion at one year (82% versus 71%; $P = 0.01$). When the entire group was considered, survival was similar with or without SRS, although for patients with only one lesion the OS

was significantly longer with SRS (median survival time 4.9–6.5 months; P = 0.04). Moreover, SRS significantly improved or maintained KPS at 6 months with a less steroid dose but there was a higher incidence of both acute and delayed grade 3 or 4 toxicity in the SRS arm. Therefore, for patients with single metastasis who undergo WBRT, SRS boost is considered standard of care. In an attempt to avoid the neurocognitive side effects of WBRT, several groups have studied whether WBRT can be omitted if SRS is performed and have demonstrated that the addition of WBRT to a definitive treatment with SRS improve loco-regional control, even if it does not impact on OS [45,49,50].

Systemic treatment

The role of systemic therapy in the management of patients with brain metastases is not settled and remains controversial. The development of new therapeutic strategies with a better control of extra-cranial BC disease has determined an increased incidence of brain metastases. To date, no systemic therapies have obtained a regulatory approval for the treatment of CNS metastases. Nevertheless, preliminary data supporting the efficacy of systemic therapies in the management of BC brain metastases are available from published trials, with the evidence that chemotherapy and targeted therapies after WBRT may improve survival in BC patients with brain lesions [51].

CNS relapse is still a critical turning point in the management of mBC treatment, so that the development of new therapeutic strategies active on brain metastases represents a major clinical challenge.

HER2-positive disease

As mentioned above, one of the main risk factors for the development of brain metastases from BC is represented by HER2 over-expression [52].

Several retrospective studies have shown a survival benefit of trastuzumab-based therapies for HER2-positive mBC patients with CNS metastases. Of note, the improvement of survival seems to be mainly due to the activity of active anti-HER2 treatments on extra-cranial disease rather than control of brain lesions [53,54]. To date, there is still a lack of clearly defined guidelines on systemic treatment in patients with brain metastases from HER2-positive BC.

Historically, the use of chemotherapy associated with trastuzumab was considered the standard of care for HER2-positive BC patients [55]. It has been reported that patients receiving trastuzumab in adjuvant setting are more likely to develop brain metastases [5,56,57], probably due to the increased survival, the onset of drug resistance and the poor ability of trastuzumab to cross adequately the BBB because of its large molecular size (185 kDa) [58]. Actually, due to the alteration in the BBB related with the WBRT, trastuzumab could still cross the BBB after radiotherapy [7,59]. In fact, higher levels of trastuzumab were found in cerebrospinal fluid of patients with BC after radiotherapy, compared to those who did not receive WBRT [58].

An exploratory analysis of the CLEOPATRA trial showed that mBC patients treated with pertuzumab, trastuzumab and docetaxel had a longer median time to development of CNS metastases as first site of disease progression compared to patients treated with trastuzumab and docetaxel (15.0 versus 11.9 months; HR 0.58; P = 0.0049) [60].

In 2012, a formal expert consensus-based process conducted by the American Society of Clinical Oncology (ASCO) recommended appropriate local–regional and systemic therapy for patients with HER2-positive BC with CNS lesions. The Panelists agreed that clinicians should have a low threshold for magnetic resonance imaging

(MRI) of the brain because of the high incidence of brain metastases [61].

To note, two phase I studies are evaluating the optimal dose as well as safety and efficacy of intrathecal trastuzumab (NCT01373710, NCT01325207).

Small molecules have also been investigated in HER2-positive BC with CNS involvement. Lapatinib is a tyrosine kinase inhibitor that crosses the BBB and targets both EGFR and HER2. In preclinical models, lapatinib levels in normal brain tissues were 1.3–2.8% of plasma concentrations, whereas the brain metastases-to-plasma concentration ratio reached 26% [62]. Furthermore, patients receiving lapatinib before surgical resection of brain lesions showed a 10-fold greater concentration of lapatinib in the brain than in the serum [63]. On the other hand, Gori and colleagues found low concentrations of lapatinib in the cerebrospinal fluid of two mBC patients treated with lapatinib, suggesting that drug concentration in cerebrospinal fluid may not be a surrogate of its distribution in CNS [64].

An increasing body of evidence shows that the combination of trastuzumab and lapatinib, either concomitantly or sequentially, leads to a longer survival in mBC patients with brain metastases. Patients treated with a sequential combination of a trastuzumab-based regimen followed by lapatinib plus capecitabine had about 10-months longer survival compared to patients treated with a trastuzumab-based regimen alone (27.9 versus 16.7 months; P = 0.01) [65]. Moreover, in two retrospective analyses the combination of trastuzumab and lapatinib (with or without chemotherapy) was shown to be associated with a longer OS compared with trastuzumab alone (HR 0.279; P = 0.012) [66,67]. The combination of lapatinib plus capecitabine seems also to be more effective than capecitabine single agent in reducing CNS as first site of progression (6% versus 2%; P = 0.045) [68]. The potential benefit of this combination was demonstrated also in the LANDSCAPE trial, in which patients with untreated CNS metastases received lapatinib plus capecitabine before WBRT, with a brain response rate of 66% and a 1-year survival of more than 70% [69].

More recently, a retrospective exploratory analysis of the EMILIA study showed a significant advantage in OS for patients with brain metastases treated with T-DM1 compared with patients treated with lapatinib and capecitabine (26.8 months versus 12.9 months) [70]. Therefore, these results support the association of lapatinib and capecitabine, but also the use of TDM-1 in monotherapy, for patients with HER2-positive BC with brain metastases.

Neratinib, an irreversible inhibitor of both EGFR and HER2, is under investigation as single agent or combined with capecitabine in BC patients with progressive brain metastases (NCT01494662). Preliminary data, presented at the 2014 ASCO annual meeting, suggested that this small molecule could help disease-control, even with a CNS overall response rate of only 7.5% [71]. In contrast, treatments with afatinib, an irreversible pan–HER inhibitor, was demonstrated not to improve patient outcome in a recent phase II trial [72].

Currently, other target agents are under evaluation and may hold promise for brain metastases treatment, such as everolimus [73] and bevacizumab [74].

Taken together, these data suggest that the utilization of chemotherapy after WBRT as well as the development of different formulations of anti-HER2 therapies could have a more favorable therapeutic profile.

Triple negative breast cancer (TNBC)

The systemic approach of patients with TNBC is represented by chemotherapy in both metastatic and early setting. Therefore, for patients diagnosed with TNBC the integrity of the BBB is crucial

and may limit the delivery of drugs to the site of brain metastases. In preclinical animal models, brain localizations were shown to be more permeable to drugs than normal brain tissue and 86% of metastases had an uptake of radiolabeled paclitaxel up to 50-fold greater than normal brain, although only 10% of lesions with the highest permeability showed an objective response to paclitaxel [75].

Several approaches have been proposed to increase BBB permeability, including BBB disruption using ultrasound, radiotherapy, or development of brain-specific vectors. ANG1005 is a novel formulation of paclitaxel conjugated to the angiopep-2 vector, which is supposed to facilitate the passage across the BBB [76]. In a phase II trial, patients with BC brain metastases were initially treated at a 650 mg/m^2 starting dose and then amended to 550 mg/m^2 due to exceeding toxicity, with an interim efficacy analysis showing a CNS response in one third of patients [77].

Brain objective response rate with conventional chemotherapy combinations ranges from 0% to 55% [78,79]. Over the last 15 years, cisplatin and carboplatin in combination with different drugs have shown response rates of 34–40%. In particular, a complete brain response of 13% and a partial response of 25% were achieved with the combination of cisplatin and etoposide in BC patients with brain lesions [80]. The response rate observed with topotecan for newly diagnosed brain metastases varied from 0% to 37% [78,81]; however, the drug showed an unfavorable hematologic safety profile with grade 3–4 neutropenia, grade 3–4 thrombocytopenia and grade 3–4 anemia in 37%, 31% and 16% of patients, respectively. Conversely, temozolomide showed no activity in mBC patients with brain lesions neither as a single agent nor in combination with vinorelbine, and only moderately in combination with cisplatin, despite its good BBB permeability [82–84]. Additional data, although limited to phase II studies not specific for TNBC, suggest that conventional chemotherapy such as cyclophosphamide/methotrexate/5-fluorouracil (CMF), 5-fluorouracil/doxorubicin/cyclophosphamide (FAC) or carboplatin-based regimens should be considered for chemotherapy naïve BC patients with brain lesions [85].

Even if highly vascularized metastatic lesions should theoretically have an important tumor shrinkage using antiangiogenic agents, patients with brain metastases have been routinely excluded from studies with antiangiogenic agents due to the concern of intracranial bleeding. However, preliminary results of two prospective phase II trials evaluating the combination of chemotherapy and bevacizumab, a humanized anti-VEGF monoclonal antibody, showed a CNS response rate higher than 60% and a favorable safety profile in patients with mBC [86,87]. Yen-Shen and colleagues showed that the administration of bevacizumab before etoposide and cisplatin appears highly effective in mBC patients with brain lesions refractory to WBRT. Moreover, both hematologic and non-hematologic toxicities was generally mild and manageable; in particular, only 1 patient experienced grade 3–4 hypertension and no grade 3–4 hemorrhage nor proteinuria were recorded [86].

Finally, sunitinib and sorafenib, two small molecule inhibitors of multiple kinases, were also evaluated in patients with brain metastases from various solid tumors. Sunitinib showed a significant reduction of CNS relapse in patients with metastatic renal cancer, but no data is available regarding treatment with sorafenib or sunitinib in BC patients with CNS lesions [88].

Luminal-like disease

Brain metastases in luminal-like BC are a relatively rare and late event, with a median time to development of CNS lesions of about 55 months [89]. In a retrospective series, patients with metastatic luminal-like subtype had a median survival from primary BC diagnosis consistently longer than patients with TNBC (72.7 months versus 39.6 months; $P < 0.01$), although the difference in median survival after brain metastasis diagnosis was less than 3 months (10.0 months versus 7.6 months, respectively; $P < 0.01$) [90].

Historical data demonstrates reliable activity of tamoxifen and megestrol acetate against brain metastases in luminal-like BC [91] and retrospective analysis proved that systemic treatment prolongs median OS after brain metastases in luminal-like BC patients (14.3 months with systemic chemotherapy with or without endocrine treatment versus 7.1 months without systemic treatment after whole brain irradiation; $P = 0.003$) [92]. In particular, tamoxifen has been reported to attain a 46-fold higher concentration in brain metastases and brain tissue when compared to serum concentration [93,94]. Moreover, brain lesions can be controlled also with aromatase inhibitors such as letrozole and anastrozole [95,96].

Palliation of neurological symptoms

As reported above, patients with brain metastases experience important and potentially invaliding symptoms [8], therefore palliation of neurological symptoms has to be considered the first step of a multidisciplinary therapeutic approach [97].

The majority of symptoms are due to growing CNS lesions squeezing the brain parenchyma and increasing intracranial pressure. The administration of corticosteroids has been routinely implemented in the management of intracranial hypertension, leading to BBB stabilization with a better cerebral blood flow. Generally, a starting dose of 4–8 mg daily dexamethasone should be considered in symptomatic patients; however, a 16 mg total daily dose or higher is recommended in patients with severe symptoms [97].

The use of osmotic-agent such as intravenous mannitol at a 20% solution, is also commonly used to treat severe neurological symptoms or when a rapid reduction of intracranial pressure is needed [98]. However, the optimal dose of mannitol is still unclear and a pooled analysis of 18 studies failed to found significant correspondence between change in intracranial pressure and mannitol dose [99].

Seizures are frequent manifestations of brain metastases, and symptomatic epilepsy should be treated as soon as possible with anticonvulsants. However, the choice of antiepileptic drugs is challenging for this patients because brain tumor-related epilepsy is often drug-resistant. New generation drugs, such as lacosamide and levetiracetam, are widely used because of their good safety profile and their limited drug interactions. In particular, levetiracetam showed to increase the seizure-control from 48% to 88% [100]. Notably, prophylaxis with anticonvulsants is useless in patients without history of seizures [101].

Conclusions

Over the last decade, some concrete improvements in the loco-regional treatment of mBC patients diagnosed with brain lesions have been achieved. However, systemic treatment options remain limited. Moreover, the number of clinical trials involving patients with CNS metastasis is very small and almost no prospective trial data are available regarding efficacy of systemic therapy in this subset of BC patients.

Only recently, some efforts have been made in the creation of national registries and tumor banks [102] with the aim to identify new biomarkers for predicting early brain metastasis occurrence and to increase our understanding of the biology of BC brain lesions. This translational researches will hopefully led to the development of new agents which actively cross the BBB and target the CNS metastatic lesions.

Author contributions

CF, EDC, MC, GP, and IV actively contributed to draft the manuscript. FP was involved in revising the manuscript critically for important intellectual content. All authors read and approved the final version of the manuscript.

Conflict of interest

None of the authors have relevant conflict of interest to declare.

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